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Emulgel: A Novel Approach for Topical Drug Delivery System

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Abstract
The use of topical drug delivery systems is expected to witness a significant rise in the future due to improved patient compliance. Emulgel have emerged as a popular choice among various options available in this domain. Emulgel possess several advantages, including excellent spreadability, adhesion, viscosity, and extrusion properties, which enhance their effectiveness as drug delivery systems. One notable advantage of emulgel is their ability to accommodate hydrophobic drugs within water-soluble gel bases. This characteristic is particularly valuable as many drugs exhibit hydrophobic properties and are not easily soluble in water. By formulating these drugs into emulgel, topical administration becomes more convenient and efficient. As a result, emulgel have the potential to revolutionize drug delivery, offering improved therapeutic outcomes and patient satisfaction. Continued research and development in this field are expected to lead to further advancements and applications of emulgel in delivering a wide range of therapeutic agents.

Keywords Topical drug delivery system, emulgel, transdermal, skin, gel

Introduction

In order to deliver drugs efficiently and effectively to the target site, other delivery methods besides oral and parenteral have been investigated by formulation scientists in response to advancements in pharmaceutical technology. Effective medication administration includes the prompt and efficient delivery of medicines to the site of action. The term "topical delivery system" refers to a technique for treating local ailments that involves applying the formulation to the skin, eyes, nose, and vagina. (1-3)
When a medicine is applied topically, it avoids the hepatic first pass metabolism, changes in gastric pH, and fluctuations in plasma levels that are typically experienced when a drug is delivered orally. (4)

Advantages of topical drug delivery system (5)

- Patient compliance and acceptance,

- Ease and convenience of application,
- Painless and noninvasive technique,
- Improvement in drug bioavailability,
- Better physiological and pharmacological response
- Minimum systemic toxicity and exposure of drug to non-infectious tissue/sites.

The skin is one of the body sections that is easiest to administer substances topically. Molecules enter the skin primarily through the intact stratum corneum, sweat ducts, and sebaceous follicle. Topical channels such as the skin, rectal, vaginal, and ophthalmic are utilised to deliver drugs for localised action on the body. The topical drug delivery technique, such as emulgel (gellified emulsion), is typically employed when other drug administration methods fall short in treating cutaneous problems such fungal infections, acne, psoriasis, and other conditions directly. Emulsion gels have become more significant in the area of pharmaceutical semisolid dosage forms since the mid-1980s. (6)

Drug delivery across the skin

The epidermis, which is the skin's topmost layer, is made up of stratified, keratinized squamous epithelium, and its thickness varies from area to area of the body. With elastic filaments, it is thickest there. The deeper and more fragile structures are shielded by the skin, which creates a barrier that is essentially waterproof. Under the skin, blood vessels are widely dispersed. A continuous venous plexus that is nourished by blood entering from skin capillaries is crucial. Through extremely muscular arteriovenous anastomoses, blood is also given to the plexus directly from the tiny arteries in the body's most exposed regions, including the hands, feet, and ears. The direct access to the skin as a target organ for diagnostic and treatment is a distinctive feature of dermatological pharmacology. Water and electrolytes cannot be absorbed or lost because the skin serves as a two-way barrier. Topical medication absorption mostly occurs through three mechanisms: transcellular, intercellular, and follicular. Most medications travel over the tortuous route that skirts corneocytes and through the lipid bilayer to reach the skin's viable layers. The pilosebaceous route is the next most popular administration method (and maybe one that goes unnoticed in the clinical context). The barrier is found in the stratum corneum, the epidermis' outermost layer, as shown by the roughly similar rates at which substances can pass through either the stratum corneum alone or the entire skin. Since many years ago, painkillers and anti-infection medications have been applied topically to the skin in the form of creams and gels. Among these are topical creams for skin infections, gels and creams for vaginal yeast infections, and creams to relieve arthritis pain. Other medications can now be absorbed transdermally (through the skin) (7)

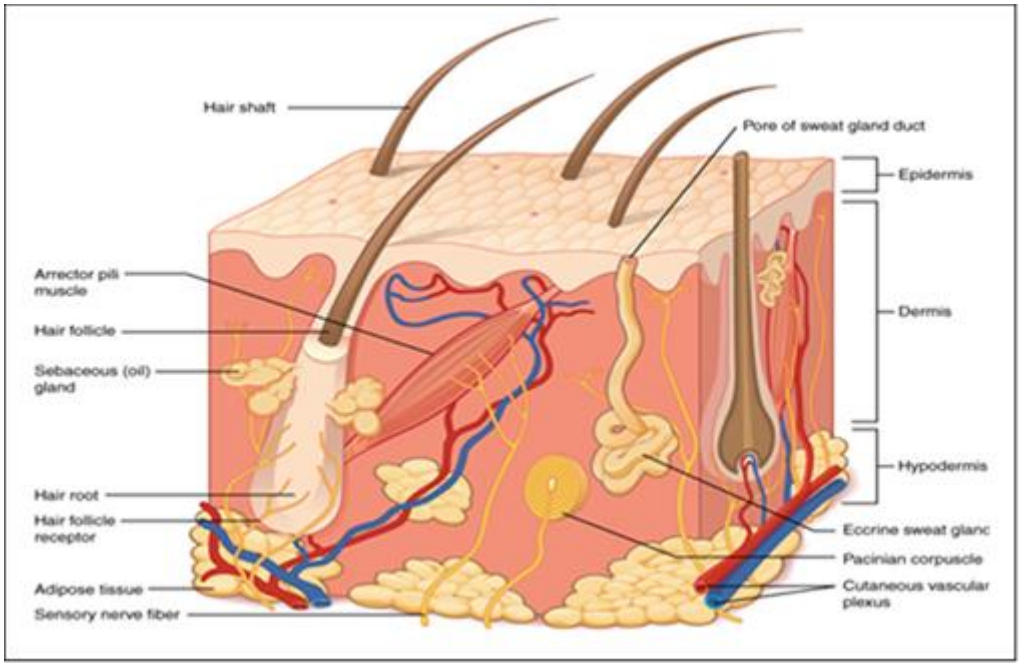

Fig. 1 structure of skin

Physiology of skin (8,9)

The majority of topical treatments are designed to be administered directly to skin. In order to construct topical dose forms, it is crucial to have a fundamental understanding of how the skin functions physiologically. About one-third of the blood that circulates through an average adult's body is received by the skin, which has a surface area of about 2m2. On average, there are 200–300 sweat ducts and 40–70 hair follicles per square cm on the surface of an ordinary human skin. The pH range of the skin is 4 to 5.6. The pH of the skin's surface is influenced by sweat and sebum-secreted fatty acids. Four separate layers of tissue can be thought of as making up the skin.

- **Non-viable epidermis**

The skin's top layer, known as the stratum corneum, serves as a physical barrier to the majority of substances that come into contact with the skin. Most of the body is covered in a stratum corneum that is 10 to 20 cell layers thick. Each cell is a flat, plate-like structure that is between 34 and 44 m long, 25 and 36 m broad, and 0.5 and 0.20 m thick, with a surface area between 750 and 1200 m stacked up to one another in a brick-like pattern. The stratum corneum is composed of protein (75-85%), which is primarily keratin, and lipid (5-15%), comprising phospholipids, glycosphingolipids, cholesterol sulphate, and a neutral lipid.

- **Viable epidermis**

The thickness of this skin layer, which lies between the stratum corneum and the dermis, ranges from 50 to 100 m. The cells in the healthy epidermis have physicochemical similarities to other biological tissues. Tonofibrils keep cells connected. This area's density is not much different from that of water. About 90% of the substance is water.

- **Dermis**

Dermis is located directly below the viable epidermis. It is a structural fibrin, and histologically speaking, only a very small number of cells in normal tissue resemble it. The dermis has a thickness of 2000 to 3000 m and is made up of a loose connective tissue matrix made of fibrous protein embedded in an amorphous ground material.

- **Subcutaneous connective tissue**

The subcutaneous tissue, also known as the hypodermis, is not actually regarded as a true component of the structured connective tissue, which is made up of loose-textured, white, fibrous connective tissue that houses cutaneous nerves, the pores of the sweat glands, and blood and lymph veins. The majority of researchers believe that the medicine enters the bloodstream before it reaches the hypodermis, despite the possibility that the fatty tissue could act as a drug depot.

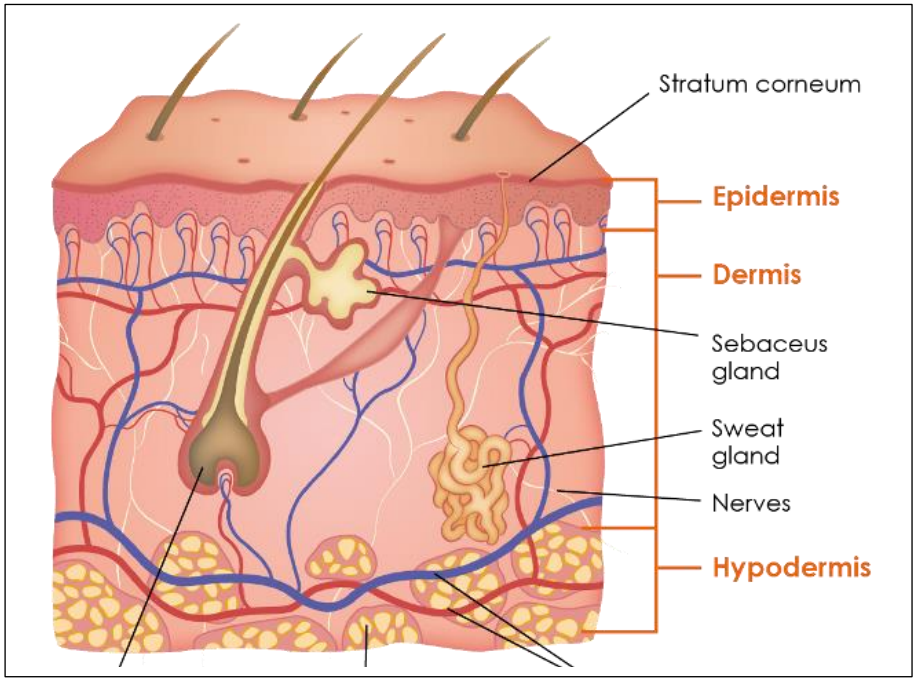

Fig. Physiology of skin

Factors affecting topical absorption of drug [10,11]

Physiological factors

1. Thickness of skin
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
3. The degree of ionisation (only unionised drugs gets absorbed well).
4. Effect of vehicles

Emulgel

Emulgel is the amalgam of an emulsion and a gel, as their name suggests. Different medications are delivered to the skin using emulsions of the water-in-oil and oil-in-water types. They are highly capable of penetrating the skin. A traditional emulsion becomes an emulgel when the gelling ingredient is present in the water phase. Emulgel for dermatological usage offers a number of beneficial characteristics, including being thixotropic, greaseless, readily spreadable, easily removable, emollient, non-staining, water-soluble, prolonged shelf life, bio-friendly, clear, and pleasant look.

The three main ways that molecules can enter the skin are through the intact stratum corneum, sweat ducts, and sebaceous follicles. More than 99% of the total skin area that is open to percutaneous medication absorption is found on the stratum corneum surface. The rate-limiting stage for percutaneous absorption is passage through this outermost layer. The main processes in percutaneous absorption involve creating a concentration gradient, which acts as a propellant for drug release from the vehicle (partition coefficient), drug release from the skin (diffusion coefficient), and drug diffusion across the skin's layers.

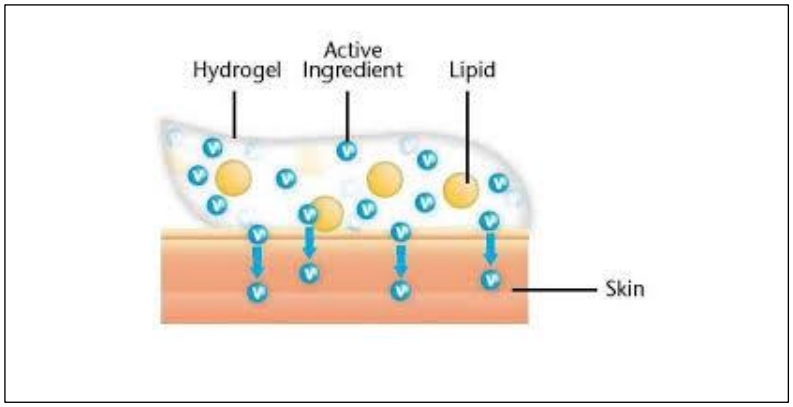

Fig. 3 Structure of Emulgel

Rationale of emulgel as a topical drug delivery system

Ointments, creams, and lotions—many commonly used topical agents—have numerous drawbacks. When used, they are extremely sticky and give patients a headache. They must also be applied with rubbing because they have a lower spreading coefficient. Additionally, they display the stability issue. The usage of translucent gels in cosmetics and medicinal preparations has increased as a result of all these aspects within the main group of semisolid preparation. The definition

of a gel is a colloid, which is normally 99 percent liquid and is immobilized by surface tension with a minor quantity of a gelatin component present. Gels have several benefits, but delivering hydrophobic medicines is one of their main drawbacks. Therefore, an emulsion-based strategy is being employed to get around this restriction such that even a hydrophobic medicinal moiety can be successfully integrated and delivered through gels [7]. Numerous medicinal items are applied to the skin or mucous membrane in an effort to either improve or restore a basic skin function or pharmacologically modify the action of the tissues highlighted. Topical or dermatological products are the terms used to describe such items. Many commonly used topical medications, such as creams, lotions, and ointments, have a number of drawbacks. When applied, they are uncomfortable for the patient because they are sticky, have a low spreading coefficient, and must be rubbed in. They also have a stability issue. The usage of transparent gels in pharmaceutical and cosmetic preparations has increased as a result of all these elements within the main category of semisolid preparations. Gels have several benefits, but delivering hydrophobic medicines is one of their main drawbacks. (12)

Advantages (13,14)

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.

Materials Use for Preparation of Emulgel

Aqueous material

This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols (15)

Oils

The oily phase of the emulsion is formed by these substances. Mineral oils are frequently employed in topically applied emulsions as the medication carrier and for their occlusive and sensory properties. They can be used alone or in combination with soft or hard paraffin. Non-biodegradable mineral and castor oils that have a local laxative action are frequently employed in oral preparations, along with fish liver oils and various fixed oils of vegetable origin (such as Arachis, cottonseed, and maize oils) as nutritional supplements (16,17).

Table 1 Oils used in formulation of emulgel

Oils	Quantity	Role
Light Liquid Paraffin	7.5%	Oil base
Isopropyl myristate	7-7.5%	Oil base
Isopropyl stearate	7-7.5%	Oil base
Isopropyl palmitate	7-7.5%	Oil base
Propylene glycol	3-5%	Oil and gel base

Emulsifying agents

Emulsifying chemicals are used to both encourage emulsification during manufacturing and to regulate stability over the course of a shelf life that can range from days for impromptu emulsions to months or years for commercial preparations. For instance, sorbitan monooleate (span 80), polyoxyethylene sorbitan monooleate (tween 80), stearic acid, and sodium stearate are just a few examples. (18-22)

Gelling agent

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent (23, 24)

Table 2 Gelling agents use

Gelling agent	Quantity	Role
Carbopol-934	0.5%-2%	Gel based
Carbopol-940	0.5%-2%	Gel based
HPMC-2910	2.5%	Gel based
HPMC	3.5%	Gel based
Sodium CMC	1%	Gel based

Penetration enhancers

These are substances that enter the skin and interact with its components to increase skin permeability temporarily and irreversibly [25].

Table 3 Penetration enhancers

Penetration enhancers	Quantity
Oleic acid	1%
Lecithin	5%
Urea	10%
Isopropyl myristate	5%
Linoleic acid	5%
Clove oil	8%
Menthol	5%
Cinnamon	8%

Preparation Of Emulgel (26)

1. **Preparation of gel:**
   The Carbopol 940 is dispersed in distilled water with constant stirring at moderate speed by using a mechanical stirrer. Then pH is adjusted to 6-6.5 by using triethanolamine.

2. **Oil phase preparation:**
   The oil phase is prepared by mixing span 20 in oil then the oil phase was sonicated for 10 min and heat it on a water bath to 70^0c

3. **Aqueous phase preparation:**
   The aqueous phase is prepared by dissolving tween 20 in purified water (aqueous phase) and methyl paraben and propyl paraben dissolved in propylene glycol then drug is dissolve in ethanol, then mix both the solution with the aqueous phase

4. **Preparation of Emulgel**
   Both the oil and aqueous phases are heated to 70-80^0 C, add the oil phase to the aqueous phase with continuous stirring until it got cooled to room temperature

then the emulsion is mixed with gel in a 1:1 ratio with gentle stirring to obtain emulgel.

Evaluation Of Emulgel

- **Organoleptic properties**

Organoleptic qualities encompass the study of things like colour, homogeneity, regularity, texture, and appearance. Colour was observed visually and recorded. The homogeneity of the emulgel was checked by rubbing it between fingertips. The appearance of the emulgel was evaluated visually. After they had been placed in the container immediately and on a regular basis for a period of 15 days, phase separation was examined and the skin was exposed to Emulgel to assess its consistency. (27)

- **pH**

Using a digital pH metre, the pH of the batches of prepared emulgel was determined. An electrode was dipped into 0.5 grammes of dissolved material in 10 ml of distilled water to determine the pH. (26)

- **Globule size and its distribution**

By using the Malvern zeta sizer, globule size and distribution are assessed. A homogenous dispersion is achieved by dissolving a 1.0 g sample in filtered water and stirring it. The zeta sizer's photocell received the sample injection. It is determined the mean globule diameter and distribution. (28)

- **Measurement of viscosity**

A Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 63 is used to calculate the viscosity of the form batches. Before taking the measurement, the formulation whose viscosity needed to be assess is poured to the beaker and given 30 min. to settle at the assay temperature (25 1 °C). In order to prevent the spindle from touching the jar's bottom, it is lowered perpendicularly into the center of the emulgel and revolved for 10 minutes at a speed of 50 rpm. Take the reading. (29)

- **Spreadability**

Two glass slides with standard dimensions are choose in order to assess the spreadability of the gel compositions. The formulation whose spreadability is to be assess spread over one slide, and the other slide is placed on top, sandwiching the gel in between them. After pressing the slides together to remove any air, the gel that is sticking to them remove it. The upper slide is linked to a weight, which caused it to slide off by force, allowing only the lower slide to be held firmly by the opposing fangs of the clamp. Carefully connect to the upper slide a 20 g weight The time it took for the upper slide to fully separate from the bottom slide record it. (29)

- **Drug content**

Weight the Emulgel and placed in a 100 ml volumetric flask with 15 ml of ethanol and agitated for 30 minutes. The remaining volume is then made up of phosphate

buffer, and the necessary dilutions are made. The final product is filtered via a 0.45 m filter. A spectrophotometric measurement was made at selected wavelength to determine the solution's absorbance. (30)

- **In vitro drug release study**

Studies on the Emulgel's in vitro drug release are conducted utilising diffusion cells and egg membrane. This is delicately clamped to one end of the dialysis cell's hollow glass tube. On the egg membrane dialysis membrane surface, emulgel (1g) is applied. Freshly made PBS solution (pH 7.4) is poured into the receptor chamber to solubilize the medication. An electromagnetic stirrer stirs the receptor chamber. The samples (1 ml aliquots) were collected at appropriate intervals, and following the proper dilutions, the samples were examined for drug content by UV-visible spectrophotometer. The overall amount of medication released at each time period is calculated using cumulative adjustments. A function of time is used to calculate the total amount of medication released across the egg membrane. Using a standard calibration curve, the cumulative% drug release is estimated. (29)

- **Microbiological assay**

It employed the ditch plate method. It is a method for determining whether a chemical has bacteriostatic or fungal action. It is mostly used for formulations of semisolids. We utilised Sabouraud's agar dried plates that had already been produced. Three grammes of the gellified emulsion are added to the plate's ditch. From the ditch to the edge of the plate, freshly made culture loops are scattered across the agar at an angle. (31)

- **Skin irritation test**

By introducing a 0.5 g sample of the test substance under a double layer of gauze to a skin area that is approximately 1" x 1" (2.54 x 2.54 cm2) in size, the test substance is applied to each site (two sites per rabbit). On a rabbit's skin, the gellified emulsion is applied. The animals were placed back in their cages. The gelled emulsion is removed 24 hours after exposure. To eliminate any leftover test item residue, tap water is applied to the test locations (32).

- **Stability studies**

The prepared emulgel is packed in aluminum 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 are withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles (33)

Conclusion

The use of topical drug delivery systems is expected to increase significantly in the future, primarily due to improved patient compliance. Among the various options available, emulgels offer several advantages that make them a popular choice. Emulgels excel in terms of spreadibility, adhesion, viscosity, and extrusion, which contribute to their effectiveness as drug delivery systems.One notable advantage

of emulgels is their ability to load hydrophobic drugs in water-soluble gel bases. This characteristic is particularly valuable because many drugs have hydrophobic properties, meaning they are not easily soluble in water. By incorporating these drugs into emulgels, it becomes possible to administer them topically in a more convenient and effective manner.

References

[1] Chen HY, Fang JY. Therapeutic patents for topical and transdermal drug delivery systems. Expert Opinion on Therapeutic Patents 2000;10:1035-43
[2] Tripathi KD. Essentials of Medical Pharmacology. JP Medical Ltd., 2013
[3] Mycek MJ, Harvey RA, Champe RC. Lippincott's Illustrated Reviews Pharmacology. Philadelphia: Lippincott-Raven, 2009
[4] TorinHuzil J, Sivaloganathan S, Kohandel M, Foldvari, M. Drug delivery through the skin: molecular simulations of barrier lipids to design more effective noninvasive dermal and transdermal delivery systems for small molecules, biologics, and cosmetics. Wiley Interdiscip Rev: Nanomed Nanobiotechnol 2011;3:449-62
[5] Joshi M, Butola BS, Saha K. advances in topical drug delivery system: micro to nanofibrous structures. J NanosciNanotechnol 2014;14:853-67
[6] 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.
[7] Panwar AS, Gandhi S, Sharma N, Emulgel: A review Asian Journal of Pharmacy and Life Science, 2011; 335
[8] Tortora GJ, Derrickson B. Principles of anatomy and physiology. 11th ed. John Wiley and Sons; 2007. p. 144-70.
[9] Ranade VV, Hollinger MA. Drug delivery system. 2nd ed. CRC Press; 2010. p. 207-27.
[10] Kalia YN, Guy RH. Modeling transdermal drug release. Adv Drug Delivery Rev 2001;48:159-72.
[11] 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.
[12] 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.
[13] Mishra AN. Controlled and novel drug delivery. 4 th ed. CBS Publisher and Distributers, Delhi; 1997. p. 107-9.
[14] Swarbrick J. Encyclopedia of pharmaceutical technology. 3 rd ed. Vol. 1. Informa Healthcare; 2007. p. 1311-23.
[15] Lachman L, Lieberman HA. The Theory and Practice of Industrial Pharmacy. 3 rd ed. Varghese Publishing house; 1990. p. 534.

[16] Vyas SP, Khar RK. Controlled drug delivery. 1 st ed. Vallabh Prakashan; 2002. p. 416-7.
[17] Bonacucina G, Cespi M, Palmieri GF. Characterization and stability of emulsion gels based on acrylamide/sodium acryloyldimethyltaurate copolymer. AAPS PharmSciTech 2009;10:368-75.
[18] Benson HA. Transdermal drug delivery: penetration enhancement techniques. Curr Drug Delivery 2005;2:23-33.
[19] Rutter N. Drug absorption through the skin: a mixed blessing. Arch Dis Child 1987;62:220-1.
[20] 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.
[21] Swarbrick J. Encyclopedia of Pharmaceutical Technology. 3 rd ed.; 2006. p. 1551.
[22] Gibson M. Pharmaceutical Preformulation and Formulation, Interpharm; 2004.
[23] 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.
[24] Kumar L, Verma R. In vitro evaluation of topical gel prepared using natural polymer. Int J Drug Delivery 2010;2:58-63.
[25] Jacob SW, Francone CA. Structure and function of man. WB Saunders Co. Philadelphia; 1970. p. 55-60.
[26] Khullar R, Kumar D, Seth N, Saini S. Formulation and evaluation of mefenamic acid emulgel for topical delivery. Saudi Pharm J 2012;20(1):63-67
[27] Amar Muragi, Sheetal Samant, Patil MB, Formulation and Evaluation of Herbal Emulgel Loaded with Extract of Cedrus deodara for its In-Vitro Anti-Inflammatory Activity, International Journal of Ayurvedic Medicine, Vol 13 (3), 2022; 749-753
[28] Singla V, Saini S, Rana AC, Singh G. Development and evaluation of topical emulgel of lornoxicam using different polymer bases. Int Pharm Sci 2012;2:36-44
[29] Ranga PM, Sellakumar V, Natarajan R, Mohan KK. Formulation and In-vitro evaluation of ciprofloxacin-loaded topical emulgel. Int J Pharm Chem Sci 2012;1:237-42
[30] A. Susmitha, Dr. A. Seetha Devi, formulation and evaluation of herbal emulgel of ocimum tenuiflorum and mentha arevensis leaves extract for anti-acne activity, Indo American Journal of Pharmaceutical Research, 2018, 1374-1376.
[31] Narendran H, Koorapati S, Mamidibathula L. Formulation and evaluation of aceclofenac-lycopene transemulgel. World J Pharm Res 2013;2:1036-45.

[32] Chaudhari P, Ajab A, Malpure P, Kolsure P, Sanap D. Development and in vitro evaluation of thermoreversible nasal gel formulations of rizatriptan benzoate. Indian J Pharm Educ Res 2009;43:55-62
[33] Jones DS, Woolfson AD, Brown AF. Textural, viscoelastic and mucoadhesive properties of pharmaceutical gels composed of cellulose polymers. Int J Pharm 1997;151:223-33.