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A REVIEW ON EMULGEL: THE TOPICAL DRUG DELIVERY SYSTEM

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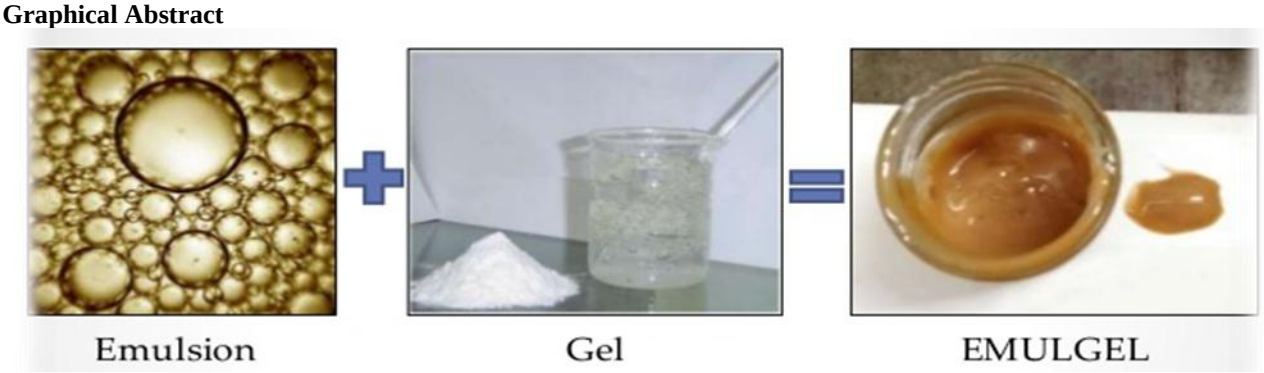
ABSTRACT

The purpose of this work was to optimize the emulgel formulation. When the gel and emulsion are used in the combined form, they are referred to as emulgel. And the use of gels has emerged both in cosmetics and pharmaceutical preparations, as compared to the other semisolid preparations. The use of emulgel can be extended in analgesics (aches and pains caused by colds, headaches, muscle aches, backaches, arthritis and other conditions & injuries) and antifungal drugs. The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. So emulgel can be used as better topical drug delivery systems over present systems. Emulgel is an interesting topical drug delivery system as it has a dual release control system, i.e., gel and emulsion. The review gives knowledge about emulgel including its properties, advantages, and formulation considerations.

KEYWORDS: Emulgel, Gelling agent, Topical drug delivery.

Graphical Abstract



1. INTRODUCTION

Drug delivery through skin is becoming gradually popular due to its convenience, effectiveness and its affordability. Stratum corneum forms a superior mechanical barrier to penetrate the drug substances and act as an ideal site, which deliver the drug (both locally and systemically) into the skin.[1] In topical drug delivery, the skin is one of the main and approachable organs on the human body.

Route of administration is depending on the sort and seriousness of the disease. For skin disorders, the topical route has been generally favored route of drug administration. Topical drug delivery systems are such type of system in which the direct application of formulation containing an active pharmaceutical ingredient to the skin to obtain the localizing effect of drug.[2]

Topical drug delivery system has several advantages such as the ability to deliver the drug more selectively to a specific site and prevention of incompatibility associated with gastro-intestinal.[3] Furthermore, topical deliveries by avoiding first pass metabolism provides increasement of bioavailability and consistent delivery for an extended period of time.[4,5] In topical drug delivery system, drug reaches to the site of action via diffuses out of the delivery system and their absorption takes the place on the skin.[6] Percutaneous absorption can be improved by increasing the release rate of the drug from the dosage form.[7] The release rate of medications from topical preparations depend directly on

various physical, chemical properties of the carrier and the medication utilized.[8,9]

Since the mid 1980s, the emulsion gels have been picking up significance in pharmaceutical topical semisolid dosage forms. There is wide usage as pharmaceutical dosage form originates from the huge use of emulsion systems, especially for dermatological formulae.

Emulgel are emulsions, either of the water-in-oil type or oil-in-water type, which are gelled in form by mixing with a gelling agent.[10] The emulsion is also acts as controlled release drug delivery system in which the drug particles entrapped in internal phase and go through the external phase to the skin, and slowly get absorbed. In the external phase of the skin, the drug reaches in a controlled manner through the internal phases which act as a reservoir of the drug. Gel captures small drug particles in it and provides its release in a controlled manner because of a cross-linked network. It prolongs the contact period of medication over the skin because of its mucoadhesive property.[11] Since emulgel possesses the property of both gel and emulsions it acts as dual control release system.[12] Water-in-oil type emulsions are employed more extensively for emollient actions and for the treatment of dry skin and emollient applications while oil-in-water type emulsions are most useful in general cosmetic acts as a water washable drug bases.[13-15]

When the emulsion possess the property of thixotropic then the process of penetration into the skin are simplified. Therefore, to improve emulsion penetration and stability, it is incorporated into the gel. Therefore, gels for dermatological use have more positive properties, for example, being emollient,[16,17] greaseless, thixotropic, easily removable, non-staining, and it is compatible with various excipients. Release rate, as well as the stability of incorporated drugs, can be affected by the type and concentration of the polymer which forms the gel. Emulgel, have a good patient acceptability. In comparison to the other topical formulations, emulgel can be suitably applied to the skin due to its non-greasy nature such as ointments, creams etc., which are so thick and require excess rubbing.[18-21] Emulgel, may serve as a better option when one is concerned with the topical delivery of poorly water soluble drug, it has also proven better and a stable vehicle for poorly water-soluble or hydrophobic drugs.[22-24]

2. Topical Drug Delivery System

In the tropical drug delivery, there is local delivery of therapeutic agents via skin for treating cutaneous disorders. This type of system is generally used for local skin infection. Topical gel formulation provides a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. Here are several forms available for this i.e. solid to semisolid and to liquid also. Local skin infections are generally treated by this system.[25]

3. Anatomy of Skin[26]

Skin covers almost 15% of an adult body weight. It's a largest organ of the human body. Skin is such an important part of a human body playing super beneficial role that includes protection against many agents such as physical, chemical and biological. There is another important role of skin i.e. thermoregulation.

Going on deep there are several layers of skin categorized below:

- The Epidermis
- The non-viable Epidermis
- A viable Epidermis (Stratum corneum)
- Overlying dermis
- Hypodermis

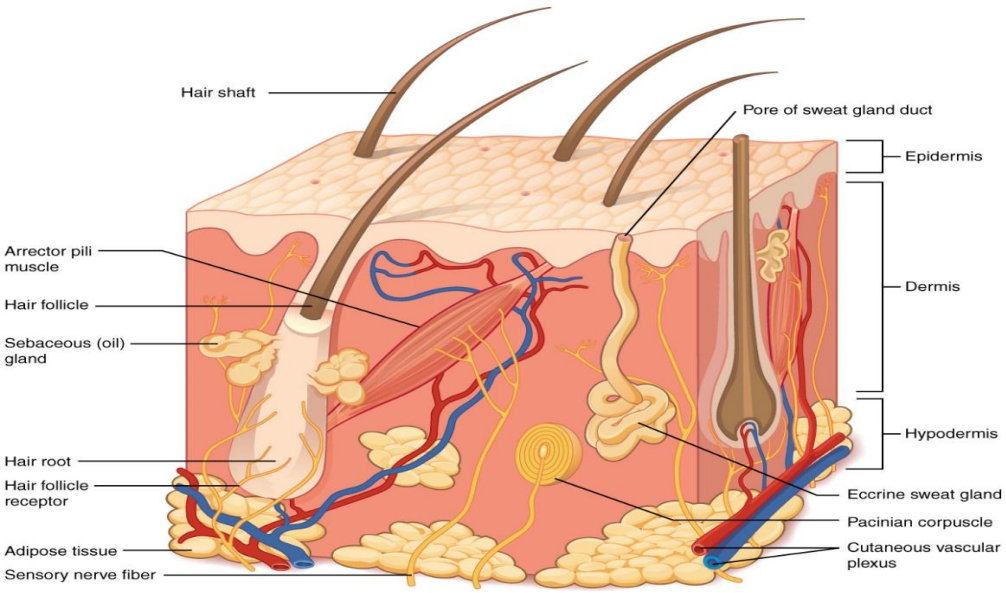


Fig. 1: Anatomy of skin.

3.1. Epidermis: The epidermis consists of four or five epithelial cells which depends on its location on the body. It is a vascular tissue that does not have any blood vessels.

3.2. Non-Viable Epidermis: It is the outermost layer of epidermis, there is a belief in the field of dermatology that this layer consists of dead cells. But now it is believed that it performs various protective functions such as impact resistant, initiation of inflammation through cytokine activity, dendritic cell activity. It has no nuclei and behaves as a selectively permeable membrane for some toxins and allergens.

3.3. Viable Epidermis: This layer is situated below the non-viable epidermis and responsible for various barriers of skin. It contains melanocytes and merkel cells also consist of the cells which are at various stages of differentiation.

3.4. Dermis: The dermis is the layer between epidermis and subcutaneous tissues and consists of many irregular connective tissues and relieves the body from stress. It is divided into two layers, the superficial area and deep thicker area. The superficial area is known as the papillary region and the deep thicker region is known as the reticular region. Structural components of dermis are collagen, elastic fibers and extrafibiliar matrices. Addition to all this it also contains some receptors like mechano receptor for sense of touch and thermoreceptor for sense of heat. Some hair follicles sweat glands are present in the dermis. These provide nourishment and waste removal for both dermal and epidermal cells.

3.5. Hypodermis: It is a layer between dermis and underlying tissue and organs. It consists of adipose tissue that works as a storage site for body fat. It serves to fasten the skin to the underlying surface, providing thermals.

4. Rationale for Topical Preparation[27]

With the purpose to formulate an efficient and effective topical preparation, considerations are mainly concerned with the site of action of the drugs and its effect. Topical preparations may be used produce:

5. Action and Effects of Drugs

The topical preparation includes various effects and action that are as follows:

5.1. Effect on Surface

- The cleansing effect of removing germs and dirt.
- Improves cosmetic appearance.
- Protective action against moisture.
- Produce an antimicrobial effect.

5.2. Effect on stratum corneum

- Moisturizing effect.
- Keratolytic effects.
- Anesthetic effects, inflammatory effects, antihistamine etc. are the major classes of drugs that penetrate viable epidermis and dermis.

6. Advantages of Topical Drug Delivery System[28]

- Avoidance of primary pass metabolism.
- Easily to terminate the medication.
- Easy to use and apply.
- Drugs delivered to specific sites.
- The gastro intestinal incompatibility will be avoided.
- Self-medication.
- Better patient compliance.
- Avoids fluctuation in drug levels and risks.

7. Disadvantage of Topical Drug Delivery System[28]

- Possibility of skin irritation at the site of application.
- Some drugs with poor permeability do not penetrate via skin.
- Contact dermatitis due to some drug may occur.
- Possibility of allergic reactions.
- Drugs with larger particle sizes are difficult to penetrate.

8. Factors Affecting Topical Drug Adsorption[29]

8.1. Physiological factors

1. Thickness of skin.
2. pH of skin.
3. Temperature of skin.
4. Lipid content.
5. Blood flow.
6. Density of sweat gland.
7. Density of hair follicles.
8. Hydration of skin.
9. Inflammation of skin.

8.2. Physiochemical factors

- Molecular weight of drug.
- Partition coefficient.
- Vehicle effect.
- Degree of ionization.

9. Factors to be considered while choosing a topical preparation[30,31]

1. Effect of a vehicle e.g. an occlusive vehicle enhances penetration of the active ingredient and improves efficacy. The vehicle by itself has a cooling, drying emollient or protective action.
2. Match the type of preparation with the type of lesions. For e.g. avoid greasy ointments for acute weeping dermatitis.
3. Match the type of preparation with the site e.g. gel or lotion for hairy areas.
4. Irritation or sensitization potential. Generally, 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.

10. Drug delivery across the skin

The two important layers in the skin are: the epidermis and the other one is dermis. Blood vessels are distributed profusely beneath the skin in the subcutaneous layer. There are three primary mechanisms for drug absorption via skin: intercellular, trans-cellular and follicular. The other, 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 barriers for drugs.[32] 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, fluidizing the crystalline structure of the stratum corneum.[33] 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.[34]

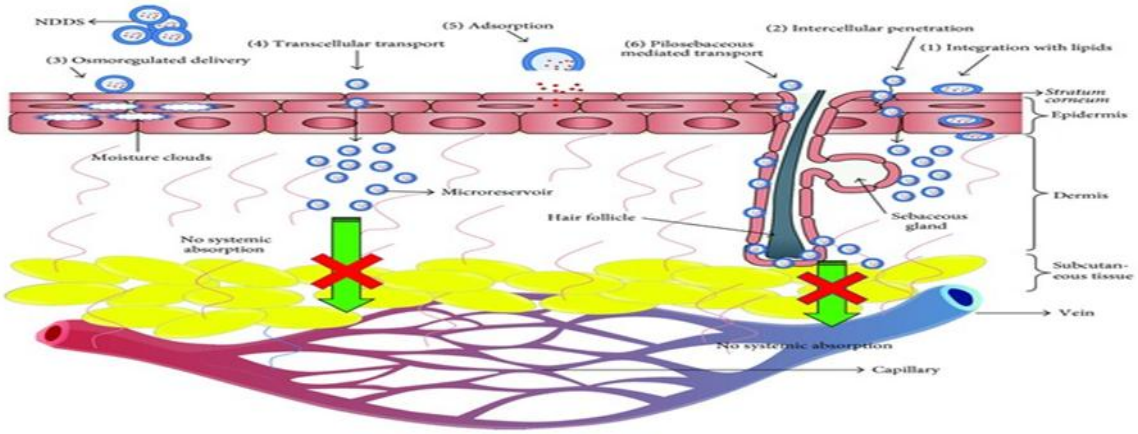


Fig. 2: Drug permeation through skin

11. Emulgel[35,36]

Emulgel are the combination of gel and emulsion. Both oil-in-water type and water-in-oil type of emulsion is used as a vehicle to deliver the various drugs to the skin. They have a high ability to penetrate the skin. The presence of the gelling agent in the water phase converts emulsion into an emulgel. It has several favorable properties for dermatological use such as thixotropic, greaseless, easily spreadable, easily removable, water-soluble, emollient, non-staining, transparent, bio-friendly, pleasing appearance and longer shelf life.

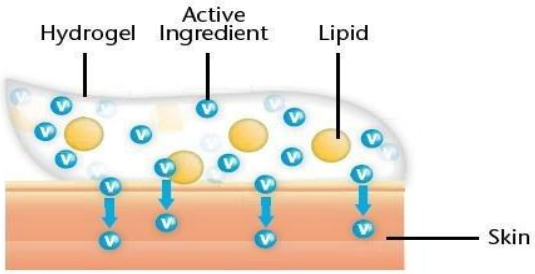


Fig. 3: The structure of Emulgel.

11.1. The ideal properties of emulgel

- Being greaseless.
- Easily spreadable.
- Easily removable.
- Emollient.
- Non-staining.
- Longer shelf life, bio-friendly.
- Pleasing appearance.

11.2. Advantages of Emulgel[37,38]

- Avoidance of first pass metabolism.
- Avoidance of gastrointestinal incompatibility.
- More selective to a specific site.
- Improve patient compliance.
- Suitability for self-medication.
- Providing utilization of drug with short biological half-life and narrow therapeutic window.
- Ability to easily terminate medication when needed.
- Convenient and easy to apply.
- Incorporation of hydrophobic drugs
- Better loading capacity.
- Better stability.
- Production feasibility and low preparation cost.
- Controlled release.
- No intensive sonication.

11.3. Disadvantages of Emulgel

- Skin irritation on contact dermatitis.
- The possibility of allergic reactions.
- The poor permeability of some drug through the skin.

- Drugs of large particle size are not easy to absorb through the skin.
- The occurrence of the bubble during formation of emulgel.

12. Rationale of Emulgel as Topical Drug Delivery

To develop topical formulation incorporating hydrophobic drugs which is not possible by simple hydrogel i.e. only possible by formulating emulgel (gel + emulsion).

To improve patient compliance, many widely used topical agents like ointments, creams, lotions have many disadvantages like they are very sticky in nature which is causing uneasiness to the patient when applied. Moreover, they also have a lesser spreading coefficient and need to be applied with rubbing. And they exhibit the problem of stability also.

13. Various ingredients of Emulgel formulation

13.1. Aqueous material: In this, it forms aqueous phase of the emulsion. And water is generally used.[39]

13.2. Oils: They are responsible for the oily phase of the emulsion. The oil phase has a great importance in the formulation of the emulsion /microemulsion/ nano-emulsion as physicochemical properties of oil (e.g., polarity, viscosity and molecular volume) significantly govern the spontaneity of the emulsification /micro-emulsification / nano emulsification process, the droplet size of the respective emulsion, drug solubility. Usually, the oil, which has the maximum solubilizing potential for the selected drug candidate, is preferred as an oily phase for the formulation of emulsion/ microemulsion/ nano-emulsion. This helps to attain the maximal drug loading. Hence, the choice of the oily phase is often a compromise between its tendency to solubilize the drug and its capability to facilitate the formation of the respective emulsion with desired characteristics. Oil phases which are used in development of emulgel are balsam oil, birch oil, castor oil, isopropyl myristate, myrrh oil, rose hip oil, wheat germ oil.[40-41]

Table 1: Use of oils.

Chemical	Quantity	Dosage form
Light Liquid Paraffin	7.5%	Emulsion and Emulgel
Isopropylmyristate	7-7.5%	Emulsion
Isopropyl stearate	77.5%	Emulsion
Isopropyl palmitate	7-7.5%	Emulsion
Propylene glycol	3-5%	Gel

13.3. Emulsifier: Emulsifiers are used to control emulsification process and stability. By incorporating an appropriate emulsifying agent stability of emulsion can be increased because these are thermodynamically unstable. Surfactants having HLB values greater than 8 such as the nonionic surfactant (spans, tweens) are used in the formulation of o/w emulsions whereas mineral oils such as liquid paraffin have HLB value less than 8 and therefore are used in the formulation of water in oil emulsions. In comparison to the individual system of span or tween, mixtures of span 20 and tween 20 results greater stability of the emulsion.[42]

13.4. Permeation enhancer: These are the agents that partition into and interact with skin constituent to induces a temporary and reversible increase in skin permeability.[43]

13.5. Gelling agent: These are the agents used to increase the consistency of any dosage form can also be used as thickening agent.[44,45]

14. Formulation of Emulgel[46,47]

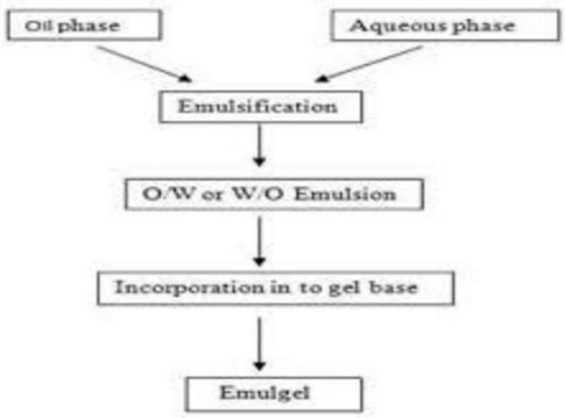


Fig. 4: Flow chart of emulgel preparation.

Step1: Preparation of gel using the gelling agent: Sufficient quantity of Carbopol 940 (1% w/w) was weighed and sprinkled onto warm distilled water with continuous stirring. The dispersion was allowed to hydrate for 1-2 hours. Other ingredients like propylene glycol (10% w/w) and glycerol (10% w/w) were added subsequently to the aqueous dispersion with continuous stirring. A required quantity of drug (1% w/w) was added and properly dispersed. The dispersion was neutralized to pH 6 using triethanolamine and the final weight was adjusted with distilled water. The gel was

sonicated for 15 minutes and kept overnight to remove air bubbles.

Step 2: Preparation of Emulsion: Depending upon whether oil in water or water in oil emulsion was formulated.

Step 3: Incorporation of the emulsion into gel base: Hence, the emulsion was incorporated in gel base to form emulgel.

15. Evaluation parameters of Emulgel

15.1. Physical appearance: The prepared emulgel is inspected for the color, homogeneity, consistency.[48]

15.2. pH: The pH values of 1% aqueous solutions of the prepared gels were measured by a digital pH meter. Electrodes were completely dipped into the semisolid formulations and pH was noted.[49]

15.3. Spreadability: To study the spreadability of formulations, special apparatus was designed. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from formulations, placed between, under the application of a certain load lesser the time taken for the separation of the two slides, better spreadability. Two glass slides of 6x2 cm each were selected. The formulation was placed over one of the slides whose spreadability had to be determined (500mg). This slide was placed over the other slide in such a way such that formulation was sandwiched between the two slides. The formulation between the two slides was squeezed consistently to frame a slight layer, for this reason, weight (100 gm) was set upon the upper slide. The excess of the formulation adhering to the slides was scrapped off after the weight was removed. The lower slide was fixed on the surface of the apparatus and the upper slide was tied to a string. To this sting load (20 gm) could be applied with the help of a simple pulley. Under the direction of weight applied the time taken for the upper slide to move the distance i.e. of 6cm and separate away from the other slide(lower) was noted. The experiment was repeated (n=3) and the average of such determinations was calculated for each formulation
Where, M= Weight which is tied to the upper slide (20gm)
L= Length taken of glass slide (6cm)
T= Time taken (seconds)
The delivery of the correct dose of the drug depends highly on the spreadability of the formulation.[50]

15.4. Swelling Index: For determination of swelling index of formulated emulgel following procedure adopted, 1gm of the gel is taken on porous aluminum foil and then placed separately in a beaker of 50ml containing 10ml 0.1 N NaOH. Then samples were taken from beakers at different time points and put it on a dry place for some time after it reweighed. Swelling index is calculated as follows:
Where,
Wo = Initial weight of emulgel at zero time
Wt = Weight of swollen emulgel after time (t)
(SW)% = Percent swelling Index.[51]

15.5. Extrudability study of topical emulgel (Tube Test): It is a typical experimental test to measure the force required to expel the material from the tube. The formulation, whose extrudability checked, filled in clean, lacquered aluminum collapsible metal tubes. The tubes were pressed with the help of a finger to extrude the material. In the present study, the method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in the percentage of emulgel. Emulgel extruded from lacquered aluminum collapsible tube on the application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds.[52] The experiment was repeated (n=3) and the average of such determinations was calculated for each formulation.

15.6. Bio-adhesive strength measurement: A modified balance method was used for bioadhesion measurement. The two pans were removed from physical balance. On the left side, a glass slide was hanged and a 100 ml beaker was used in place of the side pan. A weight of 20 g was hanged on the left side, for balancing the assembly. Another glass slide was placed below the hanging slide. On both slides, portions of hairless fresh rat skin were attached. One gram of gel was placed between two rat skin faces. To form a bioadhesion bond, a little pressure was applied, and then slowly water was added to the right side beaker, till the gel was separated from one face of rat skin attached. The volume of water added was converted to mass. This gave the bioadhesive strength of gel in grams.[53]

15.7. Drug Content Determination: Gel formulation (1 gram) was dissolved in suitable solvent. Filtered it to obtain a clear solution. The resulting solution absorbance was noted using UV Visible spectrophotometer. Drug content was determined from calibration curve for drug.[54]

15.8. In-vitro drug release studies: In-vitro releasing behavior of the drug from emulgel formulations were investigated using egg shell membrane. An interesting investigation used egg membranes which, like human stratum corneum, consists mainly of keratin.[55] By using 0.5M hydrochloric outer shells the whole egg was dissolved which resulted in a membrane. Thereafter, the contents of the egg may be detached and the membrane washed and refrigerated or soaked in isopropyl myristate under vacuum to impregnate the keratin matrix. The replacement of water in the membrane with this lipid is assumed to increase its likeness to stratum corneum biochemistry. The Keshary-chien cell was used for release and permeation study. One gram of gel was applied on the 0.8 cm^2 area of the surface of the egg membrane tied to the lower end of the donor compartment. The volume of the receptor fluid was reserved 37.5 ml.

The temperature condition of the receptor fluid was maintained at 37˚ C and stirred continuously at 100 rpm on a magnetic stirrer. Aliquots of 3.0 ml were withdrawn and analyzed for the drug content after suitable dilutions by spectrophotometric method. The volume of fluid which was withdrawn for analysis is replaced with the same volume of the fresh buffer after each sampling. The cumulative amount released across the egg membrane was calculated and plotted against time. The best batches showing high percent release were selected further for *ex-vivo* studies using rat skin.

15.9. Ex-vivo skin permeation and retention studies: Albino rat 10-12 weeks old weighing 200-250 g was used. The excised skin was placed in aluminum foil and the dermal side of the skin was delicately teased off for any following fat and/or subcutaneous tissue. The skin was then precisely checked through a magnifying glass to guarantee that specimens were free from any surface inconsistencies, for example, small openings or services in the part that was utilized for transdermal permeation studies. The skin was washed with physiological buffer saline and freshly obtained skin was used in all experiments.

The ex-vivo skin permeation of drugs from different formulations was studied using Keshary-chien cells. The effective permeation area of the diffusion cell was 9.8 cm^2. The receptor compartment has a volume of 37.5 ml. Albino rat skin was sandwiched securely between donor and receptor compartment with the donor compartment having epidermis site. The donor compartment was maintained at 37±1^oC with constant stirring. The emulgel formulation was applied to the epidermal surface of the rat skin. At a predetermined time interval for 24 hrs. (0.5hr, 1hr, 2hr, 4hr, 6hr, 8hr, and 24hr), 3.0 ml of aliquots were withdrawn and were replaced with an equal volume of fresh receptor compartment solvent to ensure sink condition. The cumulative percentage drug diffused across the skin was calculated at each sampling point.

The amount of free drug content in the receptor compartment and the amount of drug remained on the epidermal surface of the skin on subtraction from the initial drug content of the formulation applied resulted in the amount of drug content in the skin. The ex-vivo permeation study of emulgel is compared with the marketed emulgel for permeation characteristics. All the determinations were carried out in triplicate and the data were compared by ANOVA.

CONCLUSION

After thorough literature survey, we reached into a conclusion that emulgel have proven as very convenient, better and effective delivery systems. Due to its non-greasy, gel-like property, it provides and lacks oily bases, and it provides better release of the drug as compared to other topical drug delivery systems.

Many drugs that have utility in the treatment of skin disorders are hydrophobic in nature. Such drugs can be delivered in the form of emulgel where they can be incorporated in the oil phase of the emulsion and combined with Gel.

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