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AN EXTENSIVE REVIEW OF EMULGEL A STIMULI RESPONSIVE SYSTEM

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ABSTRACT

The development of advanced drug delivery systems has gained significant attention for improving therapeutic efficacy and patient compliance. This study focuses on the formulation and evaluation of a ketoconazole-loaded emulgel with ph and thermosensitive stimuli-responsive properties. Ketoconazole, an antifungal agent, suffers from limited water solubility and bioavailability, which can hinder its therapeutic potential. To address these limitations, an emulgel formulation was designed using biocompatible polymers that respond to external stimuli, such as pH and temperature, to enhance drug release in targeted conditions. The formulation process involved optimizing the oil phase, emulsifiers, and gelling agents to ensure stability, ease of application, and controlled drug release. Comprehensive evaluation was performed, including physicochemical characterization, rheological analysis, in vitro drug release studies, and antifungal efficacy testings are to be caried out.

KEYWORD:- Ketoconazole, Emulgel, Stimuli responsive formulation, Controlled drug release, Ph and Temperature sensitive.

INTRODUCTION

The term “topical drug delivery” describes the process of a medicine to the skin. When alternative methods of medication delivery (such as the mouth, under the tongue, in the rectal cavity, or via the parenteral route) are ineffective or when a fungal infection develops on the skin, this approach is used. For both local and systemic issues, topical medication administration is a typical therapy option. The medicine is absorbed by the skin and then goes to the site of action to have a therapeutic effect in the topical administration system. A topical preparation’s medication release rate is directly impacted by the carrier’s physiological properties. Bypassing the first-pass metabolism is the main advantage of topical administration systems.[1] Particle size is the foundation of the word microemulsion. The tiny size of the medication particles makes it easy for them to diffuse through the skin and reach their target area. The gel’s ability to retain the microemulsion for an extended period of time will facilitate the drug’s prolonged release. An increasing number of fungal diseases are posing a serious threat to modern civilization. Tinea capitis, Tinea pedis, and Tinea corporis are fungal diseases that cause serious skin infections. The medicine may be more easily absorbed into the skin and its effects can be felt more quickly using a method like emulgel.[2]

Physiology of skin

Topical formulations are used to treat the skin. Designing topical dose formulations therefore requires an elementary familiarity with skin physiology and function.[3] 3A third of the blood flow in the body goes via the skin, which covers an area of around 2 square metres. The human skin has about 40–50 hair follicles and 200–300 sweat ducts per square centimetre. The pH of human skin may vary from 4.7 to 5.7.4

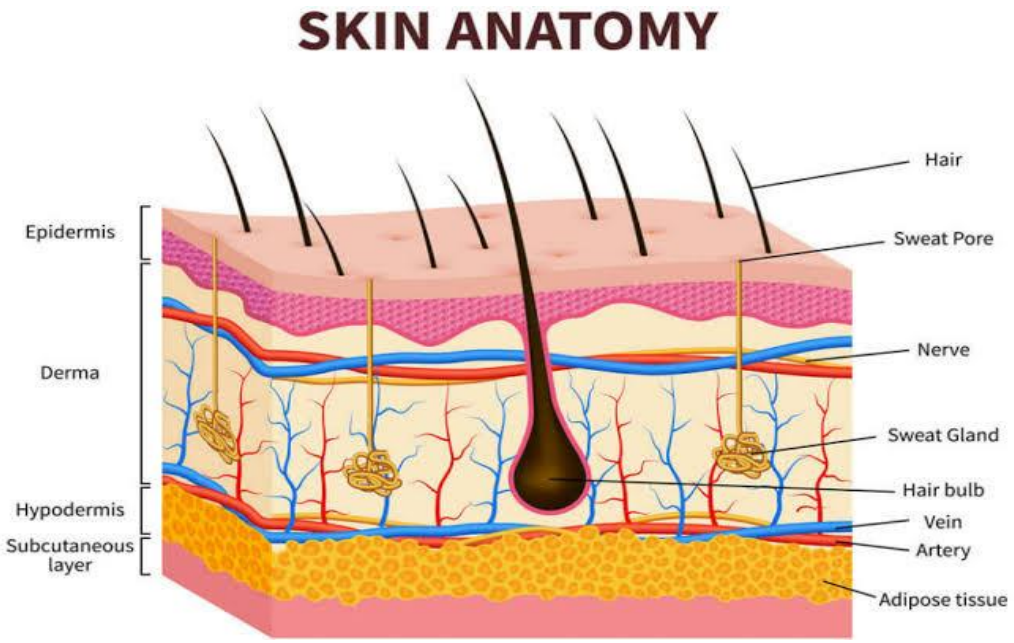


Figure 1: Physiology of skin.

Physiological factors

1. Skin thickness: Varies from epidermis to subcutaneous layer. Epidermis has high thickness about 100–150 µm. Skin on the sole and palm has a high rate of diffusion.
2. Lipid content: It is an effective water barrier; percutaneous penetration increases when lipid weight in stratum corneum is low.
3. The density of hair follicles: Hair follicle infundibulum has a large storage capacity about 10 times more than the stratum corneum.
4. Skin pH: Sweat and fatty acid secreted from sebum influence the pH of the skin surface.
5. Blood flow.
6. Hydration of skin: Can enhance permeation of drug.
7. Inflammation of skin: That disrupts the continuity of stratum corneum increases permeability.
8. Skin temperature: Increase in temperature gives rise to increase in the rate of skin permeation

Physicochemical factors

1. Partition coefficient: More the value of log p more easily will be the percutaneous absorption of the drug.
2. The molecular weight (<400 Dalton).
3. The degree of ionization (only unionized drugs gets absorbed well).
4. Effect of vehicles.

Advantages and Disadvantages of emulgel

Advantages

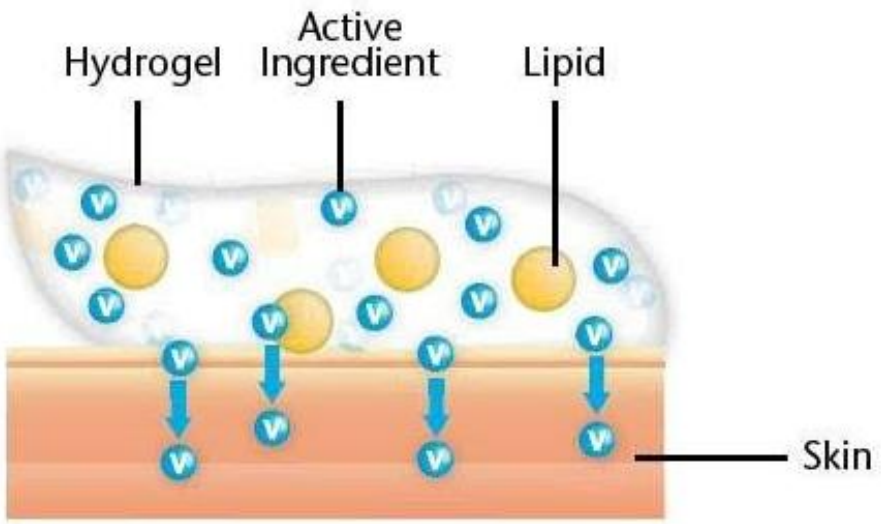
- Incorporation of hydrophobic drugs
- Better loading capacity
- Better stability
- Controlled release
- No intensive sonication
- Avoiding first pass metabolism
- Avoiding gastrointestinal incompatibility
- More selective for a specific site
- Improved patient compliance
- Convenient and easy to apply.[4]

Disadvantages

- Skin irritation on contact dermatitis
- The possibility of allergenic reactions
- The poor permeability of some drugs through the skin
- Drugs of large particle size are not easy to absorb through the skin
- The occurrence of the bubble during formulation of emulgel.[5]

Emulgel

Emulgel has been employed to overcome the issue of stability in cosmetics and pharmaceutical preparations. Emulgel has a number of beneficial features in dermatology, such as being thixotropic, greaseless, easily spreadable, efficiently removable, emollient, non-staining, water-disposable, longer time span of usability, bio-friendly, uncomplicated, and gratifying appearance.[6]



Methods of stimuli responsive emulgel

1) Thermosensitive emulgel
2) pH-sensitive emulgel

1) **Thermosensitive emulgel:** A thermosensitive emulgel is a semi-solid formulation that combines the properties of an emulsion and a gel, and it undergoes a phase transition from liquid to gel at body temperature. This makes it an excellent drug delivery system for topical, transdermal, and even injectable routes due to its improved drug release, retention, and ease of application.

Mechanism of thermosensitivity: The thermosensitive behavior is primarily attributed to the polymers. Poloxamer 407 exhibits reverse thermal gelation, where the sol-gel transition occurs as temperature increases. At lower temperatures, the formulation remains liquid for ease of application or injection, but at body temperature, it forms a gel for sustained drug release.

2) **pH-sensitive emulgel:** A pH-sensitive emulgel formulation is designed to release the drug in response to changes in pH, making it suitable for targeted drug delivery (e.g., gastrointestinal tract, wound healing, or vaginal drug delivery). It combines the structural advantages of emulsions and gels while responding to environmental pH variations for controlled or site-specific drug release.

Mechanism of pH Sensitivity: The pH-sensitive polymer in the emulgel matrix changes its properties (e.g., swelling, solubility, or gelation) depending on environmental pH:

Carbopol: Swells at pH > 5 due to ionization of carboxyl groups, forming a gel.

Chitosan: Gels in acidic conditions as its amine groups are protonated.

Eudragit®: Swells or dissolves at specific pH ranges based on its type (e.g., Eudragit L dissolves above pH 6). This allows the formulation to release drugs selectively at specific sites or conditions.

Component of emulgel

For the preparation of emulgel some constituents are used including drug, which are:

- **Vehicle:** Oily and watery carriers are used in the emulgel formulation, along with hydrophobic and hydrophilic medications. Aqueous phase emulsions employ carriers like water, alcohol, and other aqueous compounds.[7]

- **Aqueous material:** These are the watery agents that make up the formulation and are hydrophilic; examples of these agents include water, polyethylene glycols, propylene glycols, alcohols, glycerine, and many more.

- **Oil:** One way to get an emulsion ready is to employ oils as an oil phase. Emulsions made of mineral oil and either soft or hard paraffin are often used for topical applications. For instance, the majority of oral and topical remedies include laxative-effecting oils, such as castor and mineral oils.[8]

- **Emulsifiers:** By increasing the emulsification of the preparation, an emulsifier is used to enhance the shelf-life stability. Span80, Tween 20, Tween 80, stearic acid, and other similar compounds are emulsifying agents.[9]

- **Gelling agents:** Any dosage form may be gelled with the use of a gelling agent. Any formulation benefits from its improved uniformity. Carbopol 940, Carbopol 934, HPMC-2910, and others are examples of gelling agents.[10]

- **Penetration enhancers:** Chemical compounds called permeability enhancers are used to make medicine molecules permeability through the skin much more robust. The skin's chemical structure is changed by the interaction of permeability enhancer with the skin's components. Skin permeability

changes, albeit brief and reversible, are a result of this shift in the skin's chemical composition.

- **pH adjusting agent:** The formulation's pH is controlled using these substances. Such compounds include triethylamine and sodium hydroxide, among others.

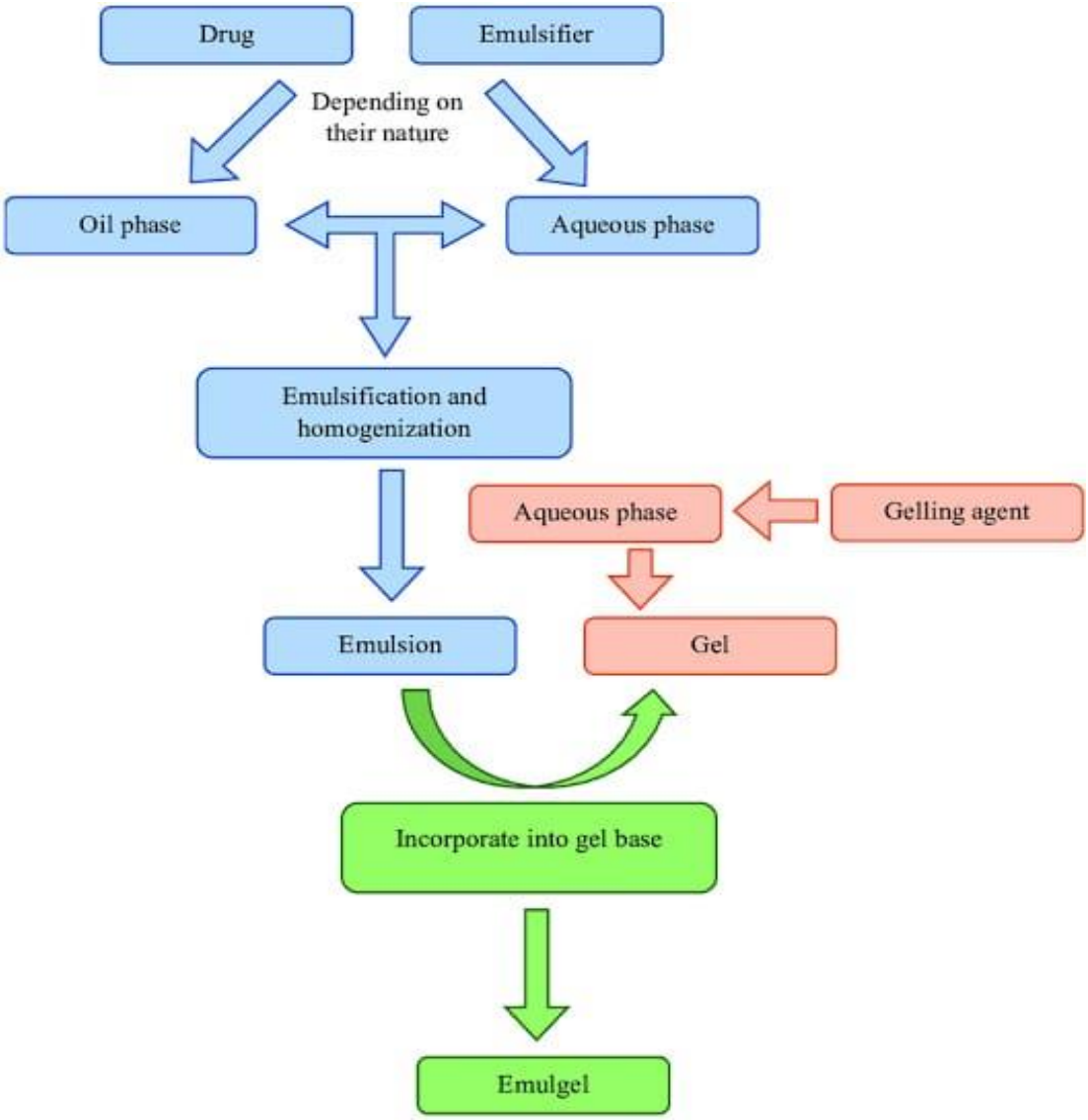
- **Preservatives:** Preservatives are chemical substances, either synthetic or non-synthetic, that extend the shelf life of drugs, excipients, and formulations by inhibiting the development of microorganisms. The antibacterial activity of each preservative falls within the range that has been provided. The antibacterial activity within a certain pH range should be considered when choosing preservatives. The final product needs a preservative that can ward off bacteria and other microbes, whether they are Gram-positive or Gram-negative. The most optimal medium for microbial development is purified water, which comprises 50.0-80.0% of the topical solution. Therefore, topical compositions cannot be complete without preservatives.

Preparation of emulgel

Step 1: Formulation of gel base: For the gel base, dissolve a certain amount of polymer in dilute dimethyl urea (DME), mix well with a magnetic stirrer set at moderate speed, and then adjust the pH to between 5.5 and 6.5 using a combination of triethanolamine and sodium hydroxide.[11]

Step 2: Formulation of O/W or W/O type of emulsion: Using a magnetic stirrer, combine the ingredients of Smix according to the recipe. To make a transparent emulsion, slowly pour the Smix into the oil phase while swirling constantly.[12]

Step 3: Formulation of emulgel: To make emulgel, slowly pour the created emulsion into the gel base while stirring constantly with a homogenizer.[13]



Evaluation of emulgel

1. **Physical appearance:** The prepared Emulgel is checked visually for their color, homogeneity, consistency and phase separation. The color of formulation was checked against white and black background. The consistency of emulgel was checked by applying on skin.

2. **pH Evaluation:** pH evaluation is the important criteria especially for the topical formulation. The pH of emulgel should be between 5.8 – 6 to mimic the skin condition. If the pH of the prepared emulgel is acidic or basic, it may cause irritation to the patient. pH of the prepared emulgel was measured using digital pH meter by dipping the glass electrode into an emulgel. The measurement of pH of each formulation was done in triplicate and average values were calculated.

3. **Viscosity:** "Brookfield Viscometer was used to determine viscosity of prepared Emulgel formulation. For the determination of viscosity, prepared Emulgel formulation was added to the beaker and settled it for 30 minutes at 25-30 °C. Adjust the spindal in that way that spindal does not touch the bottom of the jar and rotate at a moderate speed 100 RPM for 10 minutes. The viscosity reading was noted".

4. **Spreadability:** Spreadability is determined by apparatus which is suitably modified in the laboratory and used for the study. Spreadability was measured by two glass slides and a wooden block, which was provided by a pulley at one end on the basis of Slip and Drag characteristics of gels. A ground glass slide was fixed on this block. "A 1 gm of gel of different formulations were placed on the ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide. Excess of the gel was scrapped off from the edges. The top plate was subjected to pull of 50gms. If time taken for the separation of two slides is less then better the spreadability".[14]

Spreadability is calculated by using the following formula:

S = M ×L/T

Where, S is the spreadability,

M is the weight in the pan (Weight tied to the upper slide),

L = is the length moved by the glass slide

T = time taken to separate the slide completely from each

5. **Drug content determination:** Emulgel is mixed in a suitable solvent. Filter it to obtain clear solution. Determine its absorbance using UV spectrophotometer. From the standard equation by putting the absorbance value concentration and drug content can be obtained. Drug content was calculated using the slope and the intercept obtained by linear regression analysis of standard calibration curve.

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

6. **In-vitro drug diffusion study:** Release from emulgel formulation was measured through dialysis membrane by using Franz diffusion cell. Dialysis membrane was soaked in diffusion media for overnight and then placed on support screen of diffusion cell assembly. Phosphate buffer at pH 5.5 was used as the receptor medium and 1g of gel was placed on the donor side. At predetermined time interval, 2ml of sample was withdrawn from the receptor compartment and replaced with same volume of phosphate buffer at pH 5.5. The aliquots were analyzed by UV spectrophotometer at 226 nm.

7. **Stability study:** "Emulgel was packed in aluminium collapsible tubes (5gm) and subjected to stability study at 5°C, 25°C/60% RH, 30°C/65%RH for 1 month. Samples are withdrawn at each 10days as per ICH guidelines and analyzed for their physical appearance, pH, drug content, drug release profile etc."[15]

8. **Microbiological assay:** For this method Ditch plate technique is used. Through this method the bacteriostastic or fungiststic activity is evaluated.

9. **Accelerated stability studies:** It is performed by ICH guidelines. The stability test is done in hot air oven at 37 ± 2 ºC, 45 ± 2 ºC and 60 ± 2 ºC for 3 months.[17]

10. **Skin irritation test:** This test is very important because the preparation is a topical formulation. The test is carried out on the animal skin. The emulgel is applied to the animal skin, and then the animals are returned in to their cages. After 24 hr the animals are tested. Then the emulgel are removed from the site and wiped with tap water.

Packaging of emulgels

Packaging of emulgels are usually done in membrane sealed lacquered aluminum tube with inner coating of a phenoxy-epoxy based lacquer closed with propylene screw cap or an aluminum laminated tubes closed by a moulded seal, with a propylene screw cap.

Material for laminates tubes

1. **Foil laminates:** It provides light, air and moisture barrier.
2. **All plastic laminates:** It has a chemical resistant barrier.

SUMMARY

In topical drug delivery system, a large number of formulations are used, but they also have their own

disadvantages. Most of these disadvantages are overcome by emulgel preparation. The emulgel have proven as most convenient, better, and effective delivery system through the project. Incorporation of emulsion into gel makes it a dual control release system to further solve the problems such as phase separation, creaming associated with emulsion, and improvement of stability. Emulgel needs constituents as like the emulsion and gel preparation. The preparation of emulgel is done with three steps; preparation of emulsion, preparation of gel and incorporation of these two preparation. Every formulation needs a proper evaluation. So, here also there are nearly twenty five types of evaluation methods, such as photo microscopy, Spreadability, rheological study, In-vitro drug release study, etc. Nowadays, the emulgel is widely used. The most commonly used emulgels are Miconaz-H-emulgel, Isofen emulgel, Diclon emulgel, etc. Normally the emulgels are used as anti-inflammatory drugs.

CONCLUSION

Topical drug delivery will be extensively applied in the coming years to improve patient compliance. Since it is also capable in enhancing spreadibility, adhesion, viscosity and extrusion. They will become a popular drug delivery system. Moreover, they will become a solution for loading hydrophobic drugs in a water soluble gel base. Emulgel has already shown to be the best delivery technique in terms of efficiency, effectiveness, and ease of use. Its gel-like qualities and superior drug release compared to traditional topical administration methods are a result of its non-greasy nature and absence of oily bases. Emulgel is an effective medication delivery vehicle with a high drug loading capacity. Because of their little size, drugs are able to effectively penetrate the skin. Emulgel offers a dual control release effect and is created by mixing an emulsion with a gel basis. Creaming, phase separation, and improved stability are just a few of the issues that the emulgel process helps to resolve. Emulgel allows for the delivery of hydrophobic medicines by combining them with the oil phase of an emulsion.

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Authors contributions

All the authors have contributed equally.

Conflict of interests

Declared none.

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