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# A COMPREHENSIVE REVIEW ON EMULGELS FOR NOVEL TOPICAL DRUG DELIVERY SYSTEM

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***Abstract:*** When compared with other routes of drug delivery systems, Topical Drug Delivery system is the simplest and effective way of drug administration which can be used to give local as well as systemic therapeutic effect. It provides patient compliance and is easy to discontinue the therapy at any time by removing the formulation from the application site. But the preparations have certain physiological and physicochemical limitations such as hydrophobic nature of the drug, partition coefficient etc. which affect the absorption of the drug through the skin. Some of these limitations can be overcome by formulation of Emulgel. Emulgel is a novel approach for topical drug delivery in which the emulsion preparation that may be oil in water or water in oil type is incorporated into the gel base. The Emulgel has properties such as being thixotropic, greaseless, easily spreadable, non-staining etc. which makes it better patient compliance and better therapeutic action. As the emulsion is incorporated into Gel, emulgel shows increase in bioavailability of the hydrophobic drugs also. Due to all these advantages, emulgel preparations are being popular choice for topical drug delivery for different kinds of therapeutic actions. This review article gives a comprehensive information about the advantages of emulgel over other topical preparations along with its formulation and evaluation methods.

***Keywords:*** Emulgel, Topical Drug Delivery System, Emulsion, Gel based Emulsion, Spreadability,

**Introduction:**

**Topical Drug Delivery System :-** Topical drug delivery system is the drug delivery system in which direct application of the formulation containing an active pharmaceutical ingredient applied to the skin to obtain the local as well as systemic effect of the drug[1].

The topical drug delivery system allows to deliver drug more specifically to the specific site. The main advantage of the topical drug delivery system is avoidance of first pass metabolism and prevention of the incompatibility associated with gastrointestinal region [2].Topical Drug Delivery, by avoiding first pass metabolism provides an increased bioavailability and consistent delivery for an extended period of time[3]. In topical drug delivery system, drug reaches to the target site via diffusion and their absorption takes place through the skin [4]. The release rates of the medications from topical preparations depend straight forwardly on various physical, chemical properties of the carrier and the medication used [5,6].

**Drug Delivery across the skin :**

The skin of an average adult body covers a surface area approximately $2m^2$ [7] and pH of skin is 4.5 to 6.5. The skin contains four layers: Non-viable epidermis (Stratum corneum), Viable epidermis, Viable dermis and Subcutaneous connective tissue [8].These are shown in the figure number 1.

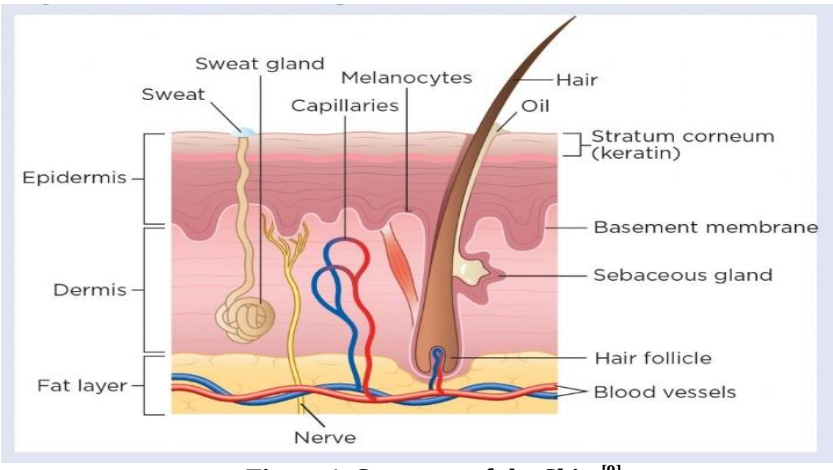


**Figure.1. Structure of the Skin [9]**

**Mechanism of Drug Permeation across the skin:**

There are three main mechanisms of drug absorption across the skin: Intercellular,Transcellular and Follicular [10].

The most common route is Intercellular mechanism. Transcellular mechanism is the short and well as direct route. The follicular mechanism (Transappendageal route) is through hair follicles and sweat glands [11].The penetration of drugs through the stratum corneum is by passive diffusion. The mechanism of drug permeation across the skin are shown in the Figure 2. The drug penetration can be enhanced by different ways : chemical (eg. surfactants, water, solvents), physical (eg. stripping, iontophoresis, ultrasound ), biochemical ( eg. peptides and metabolic inhibitors) and super saturation enhancement [12].

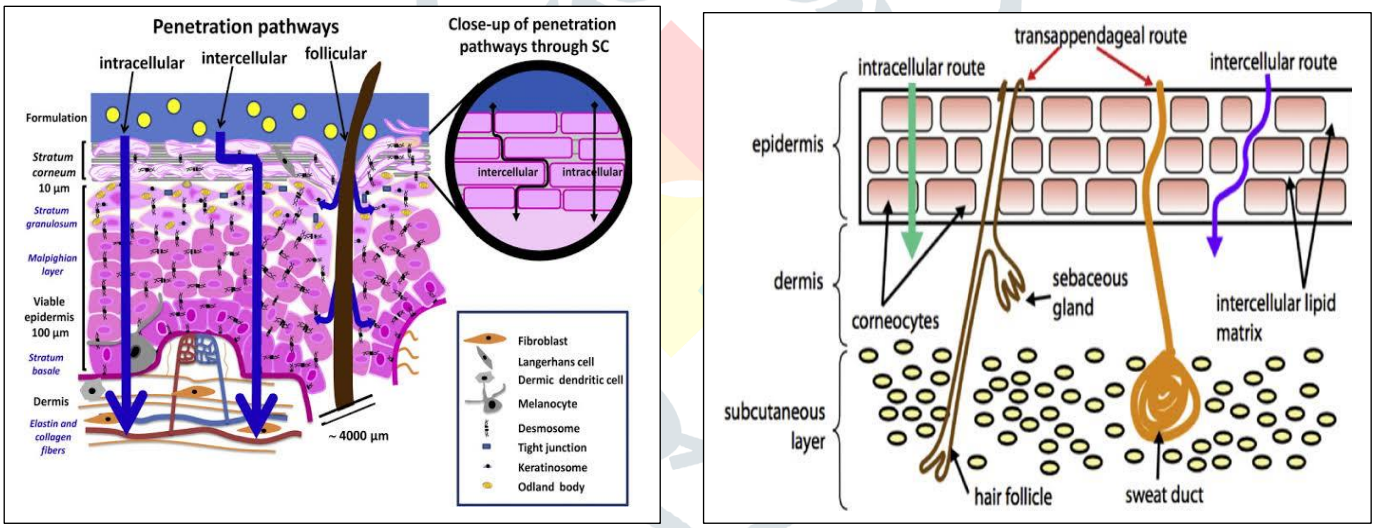


**Figure.2. Mechanisms of Drug Permeation across the skin [13, 14**

**Classification of Topical Drug Delivery System:-**

There are two types of Topical delivery products available, these are : External and Internal products [15]. As the name indicates, external products are applied by spreading or spraying and the internal products are applied orally, vaginally or rectally [16].

The topical preparations can be classified according to their consistencies as follows: Solid preparation, Liquid preparation, Semi-solid preparation and Miscellaneous preparation as shown in the figure number 3 and 4 [17]

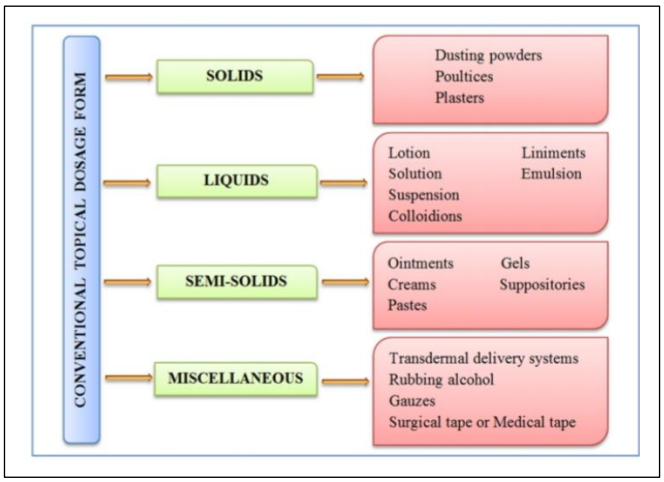


**Figure 3. Classification of Conventional Topical Dosage Forms.**

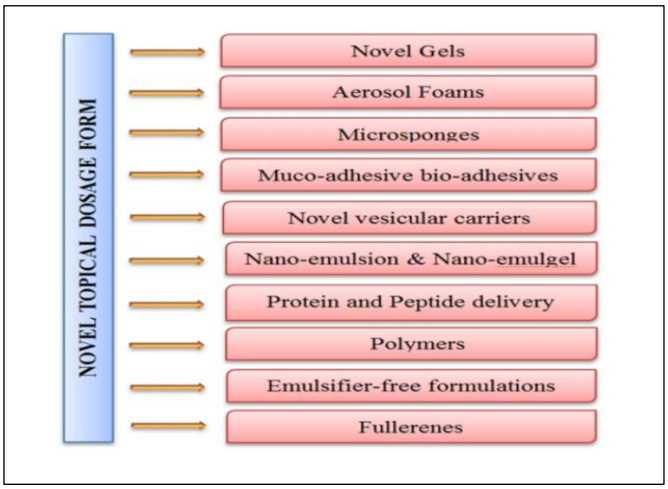


**Figure 4. Classification of Novel Topical Dosage Forms.**

**Factors**

Following are some factors which affect the drug absorption of any topical formulations:

**Physicochemical factors of the drug substance :** Partition coefficient, Molecular weight (<400 Dalton),Degree of ionisation ( Only unionised drugs get absorbed well), etc.

**Physiological factors**: Skin thickness ,Density of hair follicles, Density of sweat glands, Skin pH, etc.

**Effect of Vehicles**: Solubility, Polarity, Concentration, Distribution in a Stratum corneum, etc.

**Site of application:** Skin area dose, Total skin area in contact with vehicle, Duration of exposure etc.

The factors affecting topical absorption of the drug are given in the table number 1.

**Table 1: Factors affecting topical absorption of the drug [20]:**

| | | | |
|---|---|---|---|
| Physicochemical Factors of the Drug Substance | 1. Molecular weight (< 400 Dalton)<br>2. Diffusion coefficient<br>3. Water/Lipid partition coefficient<br>4. Permeability Coefficient<br>5. Ionization- Unionized drugs are well absobed<br>6. Protein binding capacity | Physiological Factors | 14. Skin thickness<br>15. Lipid content<br>16. Density of hair follicles<br>17. Density of sweat glands<br>18. Skin pH<br>19. Blood flow<br>20. Hydration of skin<br>21. Inflammation of skin. |
| Vehicle | 7. Solubility/Polarity<br>8. Volatility<br>9. Concentration<br>10. Distribution in a Stratum corneum<br>11. Excipients<br>12. Penetration enhancers<br>13. pH | Site of Application | 22. Skin area dose (Film thickness, Concentration)<br>23. Total skin area in contact with the vehicle<br>24. Duration of exposure |

**Rationale of Emulgel as Topical Drug Delivery System [21] :**

There are different types of topical dosage form preparations like Ointment, Cream, Lotion,etc. But they have many disadvantages and limitations for drug delivery such as they are very sticky , this may cause uneasiness to the patient when applied.They have lesser spreading coefficient also. Some of them need to apply with rubbing and some have the problem of stability also. Due to all these factors within the major group of semisolid preparation, the use of transparent gels has expanded both in cosmetics and pharmaceutical preparations. Though, there are many advantages of gels , a major limitation occurs during the delivery of hydrophobic drugs. This limitation is overcoming by emulgel. The Emulgels have many advantages like being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, bio-friendly, pleasing appearance, transparent and cosmetically acceptable, which also have a good skin penetration and long shelf life [22]. Emulgel have been picking up significance in Pharmaceutical topical semisolid preparations since the mid-1980s.

**Emulgel [22-30]:**

Emulgels are the emulsions, either of the Water in Oil (W/O) or Oil in Water (O/W) type, which are gelled by mixing with a gelling agent . Thus , **Emulsion+ Gel= Emulgel**. The schematic diagram of emulgel is shown in figure number 5.

Drug particles in emulgel formulation are entrapped within internal phase which go through the external phase (i.e. to the skin ) and slowly get absorbed. Thus it acts as controlled release drug delivery system. From internal phases which work as a reservoir ,the drug reaches the external phase (i.e.the skin) in a controlled manner.

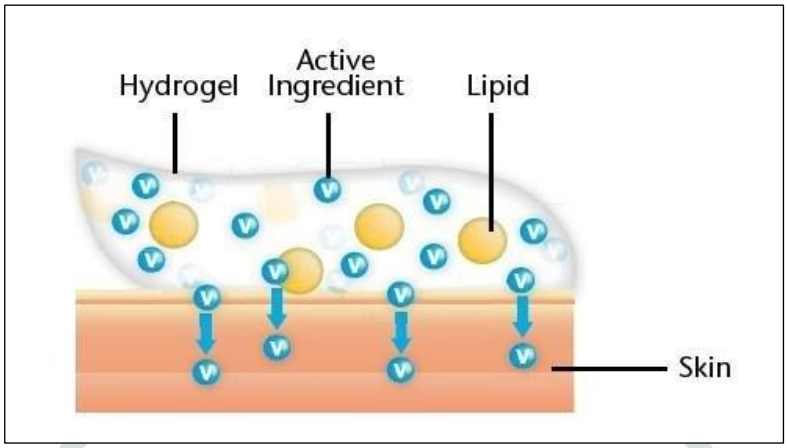


**Figure 5. Emulgel [30]**

Gel captures small drug particles and releases it in a controlled manner due to its mucoadhesive property .Since the emulgel possess the property of gel as well as emulsions, it works as dual control release system.

Water in oil emulsions are commonly used for the treatment of dry skin and emollient applications while Oil in water emulsions are most commonly used in general cosmetics acting as a water washable drug bases.

Oil-in-water systems are used to solublize lipophilic drugs whereas water-in-oil systems are used to encapsulate hydrophilic drugs.

**Advantages and Disadvantages of the Emulgel [30]:**

**Advantages :**

- Incorporation of hydrophobic drugs
- Better drug loading capacity
- Controlled release
- Avoiding first pass metabolism
- Avoiding gastrointestinal incompatibility
- More selective for specific site
- Convenient and easy to apply, therefore improved patient compliance
- Production feasibility and low preparation cost.

**Disadvantages of Emulgel:**

- Sometimes Skin irritation and allergic reaction may occur.
- Some drugs have poor permeability through the skin.
- Drugs having large particle size are not easy to absorb through the skin.
- The occurrence of bubbles during the formulation of Emulgel .

**Types of emulgel [31]:**

**i) Micro-emulgel:** These are visually transparent and thermodynamically stable with droplets size ranging from 10 nm to 100 nm.
**ii) Nano-emulgel:** Nanoemulgels are thermodynamically stable transparent (translucent) dispersions having droplet size 1 nm to 100 nm.
**iii) Macro-emulsion gel**: These are the emulgels in which particle size of droplets in emulsion is more than 400 nm. These are thermodynamically unstable but can be stabilized by using the surfactants. These are visually opaque but individual droplets can be easily seen with the help of microscope.

**Constituent used in Formulation of Emulgel [32-38]:**

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

**1. Drug Substances [33]:**

Mainly NSAIDs, antifungal agent, antibacterial agent, etc. are used for emulgel formulation. Proper choice of the drug for topical preparations is very important for successful development of a topical formulation. The important drug properties that affect its diffusion through the skin are as follows:

- **Physicochemical properties:**
  - Drug should have adequate lipophilicity for formulation of topical prepartions.
  - Drug should have Molecular weights less than 500 Daltons.
  - Highly acidic or alkaline drugs in solution are not suitable for topical product.
  - A pH of formulation for topical delivery should be between 4.5 and 6.5.
- **Biological properties:**
  - Any immune reaction should not be stimulated in the skin by the drug.
  - Irritation to the skin should not be caused by the drug.
  - Under near zero order release profile for topical delivery tolerance should not be developed.
  - Drugs, which undergo degradation in gastrointestinal tract or inactivated by hepatic first pass metabolism, are good candidate for topical delivery.

Ideal Properties of the Drug candidate to formulate as a Emulgel are given in the table number 2.

**Table 2: Ideal Properties of the Drug candidate to formulate as a Emulgel [33]:**

| | |
|---|---|
| Effective concentration (drug dose) | Less than 10 mg |
| T½ | ≤ 10 hr |
| Molecular mass | 800 Dalton or less; desirably 500 Dalton or less; limit could indeed more than this by a change in permeability of skin |
| Log p value | 0.8 to 5 |
| Skin permeability Coefficient | $\geq 0.5 \times 10^{-3}$ cm/hr |
| Irritation to Skin | Non irritating |
| Polarity | Less |
| Molecular size | Small |
| pKa | Higher |

**2. Vehicle [33] :**

Bioavailability of a drug at the target site is dependent upon the vehicle used for formulation. Following are some important consideration while choosing of a proper vehicle for formulation of topical prepartions:

The vehicle must:

- Deliver the drug at the target site directly.
- Release the drug from the formulation so it can freely goes towards the site of action.
- Deposit the drug efficiently on the skin and it's even distribution.
- Sustain a therapeutic drug level for a sufficient duration in the target tissue for providing of a pharmacological effect.
- Be appropriately formulated so that the target site be treated.

**A) Aqueous material [33]:**

This forms aqueous phase of the emulsion.The commonly used aqueous phases are water and alcohol.

**B) Oils [33]:**

These agents constitute the oily phase of the emulsion. Oily phase used in formulating emulgel are Mineral oils , Soft or Hard Paraffin are used either alone or in combination , Castor oil , Fish liver oil , Arachis oil , Cotton seed oil , Maize oil , Balsam oil, Birch oil, Myrrh oil, Wheat germ oil, Isopropyl myristate, Peanut oil , Coriandrum sativum seeds oil, etc. Various agents used as Oil phase and their quantity used are given in the table number 3.

**Table 3: Various agents used as Oil phase and their quantity used**

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

**3) Emulsifiers/Surfactants [34,35] :**

Emulsifiers are used for preparation of emulgel to promote emulsification and to control the stability during the self life. As the emulsion preparation are thermodynamically unstable, their stability can be increased by incorporating an appropriate emulsifying agent.

Surfactants having HLB values greater than 8 such as the Nonionic surfactants (Spans, Tweens) are used in the formulation of O/W emulsions whereas, Surfactants having HLB values less than 8 such as Mineral oils ( eg. Liquid Paraffin ) are used in the formulation of W/O type of emulsions.

Some examples of emulsifiers used in emulgel preparation are Sorbitan monolaurate (Span 20), Sorbitan monooleate (Span 80), Polyoxyethylene sorbitan monolaurate (Tween 20), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate, Polyethylene glycol stearate. In comparison to the individual system of Span and Tween, mixture of span 20 and tween 20 results greater stability of the emulsion.

**4) Co-surfactants [35]:**

Single chain surfactants are not capable for reducing o/w interfacial tension sufficiently to form emulsion in most of cases. A co-surfactant accumulates at interface layer because of its amphiphilic nature which results in increase in the fluidity of interfacial film by penetrating into the surfactant layer. Generally short to medium chain length alcohols are added as co-surfactants which help to increase the fluidity of interface.Ethanol is widely used as permeation enhancer, amongst short chain alkanols,. In medium chain alcohols Most effective enhancer reported in medium chain alcohols was 1-butanol. The ratio of surfactants and co-surfactant is the major factor for phase properties.

**5) Gelling agents [35]:**

Gelling agents are used to prepare gel base for Emulgel. They increase the thickness of Emulgel formulation and enhance the consistency of preparation by swelling in the aqueous phase and forming a gelly like structure. Incorporation of the gelling agent to the formulation makes it thixotropic. Some examples of gelling agent and their subtypes are given in table number 4.

**Table 4: Examples of Gelling agents [35] :**

| Gelling agents | Subtype | Examples |
|---|---|---|
| Polymeric gelling agents | Acrylic acid based | Carbomers (Carbopol 934 P, Carbopol 940P, Carbopol 974P etc.) |
| | Acrylic acid polymers | Pemulen1 polymeric emulsifiers |
| Cellulose-based gelling agent | | Hydroxipropyl methyl cellulose ((HPMC), Carboxymethyl cellulose, Hydroxyethyl cellulose (HEC) |
| Natural gelling agents | | Xanthum gum, Gellan gum, Guar gum, Pectin, Gelatin |

The gelling agents used to prepare emulgel are Carbopol 934, Carbopol 940, Carbopol 974, HPMC, HPMC 2910, Sodium CMC, Pemulen, Pluronic ® F127, HEC, etc.

HPMC based emulgel was found to be superior than Carbopol based Emulgel as it showed better drug release rate from the formulation. NaCMC based Emulgels showed higher mucoadhesivity, increased drug residence time as well as best in-vitro and in-vivo performance for vaginal application. Though HEC based Emulgel showed low mucoadhesion, it had good drug release profiles and rheological characteristics. Pemulen based Emulgel meant for buccal administration. Various gelling agents and their quantity used in the formation of Topical emulgel are given in table number 5.

**Table 5: Various gelling agents and their quantity used in the Formulation of Topical Emulgel [34] :**

| Sr. No | Gelling agent | Concentration used |
|---|---|---|
| **1** | Sodium CMC | **1-4%** |
| **2** | Carbopol 934 | **0.5-2%** |
| **3** | Carbopol 940 | **0.5-2%** |
| **4** | HPMC | **2.5-3.5%** |
| **5** | Combination of HPMC & Carbopol | **1.2%** |
| **6** | Pluronic ® F127 | **1-3%** |
| **7** | Pemulen | **0.1-0.4%** |

**6) pH adjusting agent/Neutralizer/(Buffering agents) [35]:**

The pH of the formulation should be adjusted as per the target area. As the topical emulgel formulation are applied to the skin, the pH of topical emulgel should be suitable for the skin (i.e.4.5 to 6.5 approximately). Commonly used pH adjusting agent in the emulgel formulation are NaOH, Triethanolamine, Potassium Hydroxide, Ammonium Hydroxide, Tromethamine, Aminomethyl Propanol etc.

**7) Penetration or Permeation Enhancers [36] :**

As the emulgel preparation are applied topically to the skin, the drug should penetrate through the skin to show it's pharmacological response. Penetration enhancers help to absorb drug through the skin. They interact with the skin constituent and induce temporarily and reversible increase in skin permeability.

**Ideal Properties of penetration enhancers**:

1) They should be pharmacologically inert, non irritating, non toxic and compatible with the drug and excipients.
2) They should be colourless, odourless, tasteless.
3) They should be inexpensive and have good solvent properties.
4) Loss of body fluids, electrolytes or any other endogenous material should not be caused by the penetration enhancers and skin should regain its barrier function immediately after removing of the formulation applied.

**Mechanism of Penetration enhancers [37]:**

Penetration enhancers may act by following mechanisms:

a) By Disruption of the structure of stratum corneum lipid.
b) By Interacting with intercellular protein.
c) By improving partition of the drug, solvent or co-enhancer through the stratum corneum.

The penetration enhancers may act by altering any of the three pathways. The polar pathway is altered by causing conformational change in protein or solvent swelling. The fatty acid enhancers increase the fluidity of the lipid-protein portion of the stratum corneum. By altering the multi-laminate pathway for penetration, certain enhancers act on both polar as well as non polar pathway. Penetration enhancers can increase the drug diffusivity through skin proteins. The type of penetration enhancer used has a significant impact on the design and development of the topical formulation. Commonly used penetration enhancers are Oleic acid, Clove oil, Menthol, Eucalyptus oil, Tulsi oil etc.

Various penetration enhancers and their quantity used in Formulation of Topical emulgel are given in the table number 6.

**Table 6: Various penetration enhancers and their quantity used in Formulation of Topical emulgel [37] :**

| Penetration Enhancer | Quantity | Dosage form |
|---|---|---|
| Oleic acid | 1% | Gel |
| Lecithin | 5% | Gel |
| Urea | 10% | Gel |
| Isopropyl myristate | 5% | Gel |
| Linoleic acid | 5% | Gel |
| Clove oil | 8% | Emulgel |
| Menthol | 5% | Emulgel |
| Cinnamon | 8% | Emulgel |

**8) Preservatives [38] :**

Preservatives are the chemical substances used to improve or amplify shelf life of drugs by lowering the oxidation of emulgel and by inhibiting microbial production. The Commonly used preservatives are Parabens like Methyl paraben, Propyl paraben ; other preservatives used are Potassium sorbate, Sodium benzoate etc.

**9) Antioxidants [38] :**

Antioxidants are used to inhibit the oxidation of the emulgel by inhibiting formation of free radicals in the formulation. Thus they decreases the degradation of the Emulgel formulation and increases the shelf life.

The antioxidants used are Butylatedhydroxy anisole, Butylatedhydroxy toluene.

❖ **Method of preparation of emulgel :**

Emulgel are prepared by incorporation of gel and emulsion.

The emulsion and gel are formulated separately and are mixed together.

For formulation of emulsion, aqueous phase and oil phase are taken separately and are mixed together. Then the gel is prepared by using gelling agent.

After prepartion of Gel and Emulsion, both are mixed together with gentle stirring.

**Steps involved in preparation of Emulgel:**

**Step 1:** Preparation of gel with gelling agent

By dispersing the gelling agent in the distilled water and with constant stirring at the moderate speed, the gel formulation is prepared. Then the pH is adjusted as per the need (i.e. about 6 to 6.5) using pH adjusting agent (eg. Triethanolamine, NaOH).

**Step 2:** Preparation of emulsion:

Emulsion is formulated depending upon whether oil in water or water in oil type of emulsion is to be formulated. The oil soluble excipients are mixed with oil phase whereas the water soluble excipients are mixed with aqueous phase, later both the Oil and Aqueous phases are mixed with the help of suitable amount of surfactant and co-surfactant to form a stable emulgel.

**Step 3:** Addition of the emulsion into gel base :

Finally the formulated emulsion is incorporated in gel base to form emulgel.

The schematic diagram of steps involved in emulgel prepartion is shown in figure number 6.

**Method of Emulgel Preparation:**

Mohammed [39] suggested a method for preparing emulgel. The gel in formulations is prepared by dispersing Carbopol 934 and Carbopol 940 in purified water with constant stirring at a moderate speed. pH is adjusted to 6-6.5 using triethanolamine (TEA). By dissolving Span 20 in light liquid paraffin, the oil phase of the emulsion is prepared while the aqueous phase is made by dissolving Tween 20 in purified water. Methyl and Propyl paraben are dissolved in Propylene glycol whereas drug is dissolved in ethanol followed by mixing of both solutions in the aqueous phase. Both the oily and aqueous phases are separately heated at 70°C to 80°C; then the oily phase is added to the aqueous phase with continuous stirring and cooled to room temperature.

Gel and emulsion are mixed in 1:1 ratio with the help of Glutaraldehyde to obtain the emulgel.

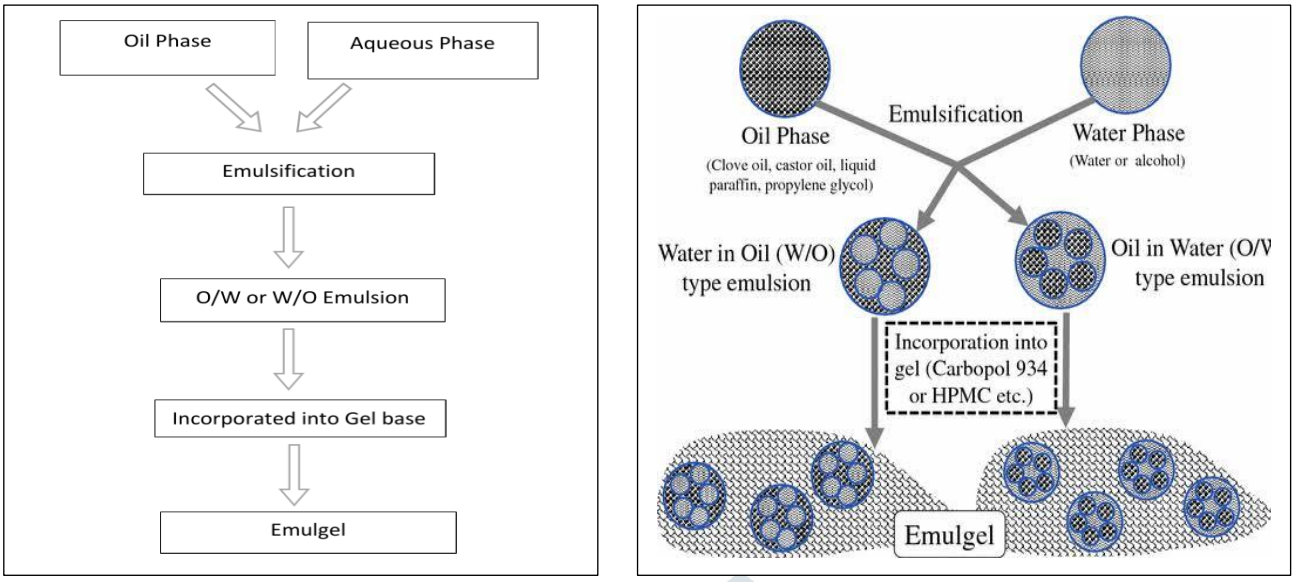


**Figure 6. Schematic diagram of Steps Involved in Emulgel Prepartion [40]**

**Optimization of Emulgel [41]:**

Optimization is a technique of searching the best composition or experimental conditions. Optimization can be defined as the implementation of systemic approaches to obtain the best combination of product and/or processes characteristics under a given set of conditions or it can also be said as choosing the best element from some set of available alternatives. The term optimization has been derived from optimize, that means to make as perfect, functional or effective as possible. In pharmacy, the word optimized was earlier used to suggest that a product has been improved to obtain the desired objectives of a development scientist, in pharmaceutical preparations or pharmaceutical processes; The main aim of designing quality formulations is achieved by implementing various Optimization techniques like Experimental Design (ED), the terms Formulation by Design (FBD) and Quality by Design (QBD) indicates that quality in the product can be developed by using various techniques of experimental design. It is important to design an optimised formulation of emulgel with a desired drug release and minimum number of trials. Earlier, any new pharmaceutical formulation was designed by studying the influence of composition and process variables on dosage form characteristics, changing one single or separate factor at a time while keeping others constant, this technique was also called as changing one variable at a time or one factor at a time. By this technique, problem may be solved but it does not guarantee the true optimum concentration or process and the product obtained may be suboptimal. Some of the limitations of traditional methods are: unpredictable, uneconomical, time-consuming, energy utilizing, unsuitable to plug errors, yielding only workable solutions, non-suitable to reveal interactions, energy utilizing etc. In order to overcome all these errors Many statistical designs have been recognised as useful techniques to optimise the process variables, that involves systematic experimental design.

There are various types of Experimental Designs for optimization of emulgel Formulation as follows:

1) Factorial designs

2) Fractional factorial design

3) Full factorial design (FFD)

4) Plackett-burman designs (Hadamard designs)

5) Central composite design (Box-Wilson design)

6) Box-behnken designs (BBD)

7) Taguchi design (TD)

8) Mixture design (MD)

9) Screening designs (SD)

10) Response surface designs (RSD)

11) Star design

12) Box design (BD)

13) Doehiert hexagon or uniform shell design (USD)

14) Simplex lattice design (SLD)

15) Extreme vertices design (EVD)

16) D-optimal design (DOD)

17) Sequential optimization design (SOD)

There are various software used for optimization of Emulgel Formulation like,

**Design Expert, DE Pro XL and DE KISS, Mini Tab, MATREX, OPTIMA, OMEGA, FACTOP, GRG2** etc.

**Evaluation of the Emulgel:**

**1) Physical Examination [42]:**

The Emulgel is visually inspected for its different physical parameters like Colour, Appearance, Homogeneity, Phase separation, Odour, Taste, Grittiness.

- **Colour:** Colour is checked against white and black background.
- **Appearance and Homogeneity**: Appearance and Homogeneity is checked by direct observation with naked eye or under the microscope.
- **Odour:** The odour is checked by mixing the Emulgel in water and smelling it.
- **Consistency:** The consistency of Emulgel is checked by applying it to the skin.
- **Phase Separation Study:** Phase separation study is carried out by Centrifugation method. The Emulgel is centrifuged at an ambient temperature (Room temperature i.e. 25°C ) and 3500 RPM for 30 min [64] or 6000 RPM for 10 min [65] to evaluate the system for creaming or phase separation. The Emulgel is observed by visual inspection. If there is no phase separation or creaming observed during this test, it indicates that the formulation is stable.

**2) Globule Size and it's distribution in Emulgel [43]:**

Globule Size and it's distribution is determined by Malvern Zeta Sizer. A 1 gm of sample is dissolved in purified water and agitated to get homogeneous dispersion. The sample is injected into the Photocell of the Zeta Sizer. Mean globule diameter and distribution is calculated.

**3) Rheological Characterization [44, 45] :**

The Emulgel contains aqueous phase, oil, surfactants and gelling agent as formulation components.The rheological properties of a dosage form like Viscosity and Flowability can be greatly affected by a small change in the physiological properties of the formulation components.The change in viscosity affect the stability factors , drug release and other biological functions.Taking these factors into consideration, it is very essential to understand the rheological properties of Emulgel. Viscosity measurement can be carried out with different kinds of viscometers. Eg. Brookfield Viscometer, Cone and Plate viscometer.

In Cone and Plate viscometer, the viscosity of the Emulgel is determined at 25°c using Cone and Plate viscometer with spindle connected to a thermostatically controlled circulating waterbath.

**4) pH Determination [45]:**

The pH of the Emulgel is determined using Digital pH meter. 1% aqueous solution of Emulgel (1 gm of emulgel in 100 ml distilled water) is prepared and subjected to measure the pH by the Calibrated Digital pH meter. The test is performed in triplicate and the average pH value is calculated [46, 47].

**5) Drug-Excipient Compatibility study [46] :**

**Fourier Transform Infrared (FTIR) Spectroscopy Study:**

The study carried out by FTIR Spectroscopy is to verify whether the drug and excipients are compatible with each other or not. In this study, spectrum of the Drug sample and the Excipients used is determined separately and then also in combined form in the same operating conditions. In comparison with pure drug, the absorbance peak spectra of Drug in combination with the different excipients is observed.

If the spectra shows no shift and no overlapping found over the peaks (i.e. no disappearance of the characteristic peaks), it suggests that there is no interactions between the pure drug and the excipients.

**6) Swelling Index [47, 48]:**

To determine the swelling Index of the prepared topical emulgel, 1 gm of Topical Emulgel is taken on the porous Aluminum foil which is then placed in a 50 ml Beaker containing 10 ml of 0.1N NaOH. The sample is removed from Beaker at different time intervals and put on a dry place for some time, then it is re-weighed. The Swelling Index is calculated by using the following formula:

**Swelling Index (SW%)= [(Wt-$W_0$)/$W_0$ ×100]**

Where,

SW% = Percent Swelling Index

Wt= Weight of Swollen Emulgel after time t,

$W_0$= Initial weight of Emulgel at zero time,

**7) Extrudability Study [48]:**

As emulgel is a semisolid preparation, extrudability test is important to know whether the prepared emulgel formulation is easily extrudable from the packaging tube or not.

The pressure required to extrude semisolid preparation is dependent upon the viscosity and consistency of the formulation. More quantity of Emulgel extruded at little applied pressure on tube which may result in better patient compliance. Extrudability of the Emulgel is dependent on the viscosity of the formulation as well as smooth texture of the formulation.

For extrudability study, The Emulgel formulation is filled in the Lacquered Aluminium Collapsible Tube and sealed by crimping to the end. The weight of tube filled with Emulgel is recorded. The tubes are placed between two glass slides and are clamped. The known quantity of weight (in grams) is placed over the slides to extrude at least 0.5 cm ribbon of emulgel in 10 seconds. The amount of extruded emulgel is collected and weighed. The test is performed in triplicate and the average values are calculated. The extrudability is then calculated by using following formula:

**Extrudability= Weight applied to extrude Emulgel from the tube (in grams) / Area ($Cm^2$)**

More the quantity of Emulgel extruded, more is the extrudability.

**Alternative methods to used determine the Extrudability :**

**i)** The alternative method to determine the Extrudability of prepared emulgel can be done using hardness tester. In this method Aluminium tube is filled with 15 gm of emulgel. The plunger is adjusted to hold the tube suitably. 1kg/cm weight is applied for 30 second. The quantity of emulgel extruded is weighed. The process is repeated thrice at equidistance of the tubes[30].

**ii)** Hardik A. Lakkad et al.[75] used another different method to determine the extrudability of the emulgel formulation as follows:

Emulgel formulation was filled within a clean, lacquered aluminum collapsible tube with a 5 mm opening nasal tip. Extrudability was then determined by measuring the emulgel extruded through the tip when a constant load of 1 kg was placed over the pan. The extrudability of emulgel formulation was calculated by using the following formula,

**Extrudability=(Amount of emulgel extruaded from the tube ×100)/(Total amount of emulgel filled in the tube).**

**8) Spreadability/ Spreading Coefficient [49-51]:**

For topical preparations spreadability is one of the important parameters.

The delivery of the correct dose of drug highly dependent on the spreadability of emulgel formulation. The spreadability is important for the ease of application of topical preparation and better patient compliance. It indicates whether the emulgel is easily spreadable by small amount of shear or not. The spreadability of the formulation is dependent on the viscosity of the formulation. Higher the viscosity of the formulation, lower will be the spreadability of the formulation.

For the determination of Spreadability of the Emulgel, the spreadability test apparatus (as shown in figure number 7) suggested by Mutimer et al (1956) is used. It consists of a wooden block or glass having a pulley on the opposite end. With the help of this apparatus, spreadability is measured by 'Slip' and 'Drag' characteristic of the emulgel formulation.

Two glass slides of 6×2 cm are used for this purpose. On the wooden block, a ground glass slide is fixed. An emulgel (about 1-2 gm) is placed on this ground slide. The emulgel is then sandwiched by putting another glass slide of same dimensions on it. Weight of 100 gm is placed on the top of these two slides for about 5 minutes to expel the excess of air and to produce a uniform film of the emulgel between these two slides. Excess of the Emulgel is scrapped off from the edges of these slides. The hook is provided with the second glass slide. A string is tied to the hook. Measured quantity of load (about 20gm) is placed in the pan attached to the pulley with the help of the string tied to the hook. The time in seconds required by the top slide to separate away from the ground slide and to cover a distance of 7.5 cm is noted. A shorter interval

indicates better spreadability. The experiment is repeated in triplicate (n=3) and the average of such determinations is calculated for each formulation.

Spreadability is calculated by using the following formula: **S= M.L/ T**

Where, S= Spreadability, M= Mass (weight) which is tied to upper slide (20gm)

L= Length of glass slide (6 cm) , T= Time taken to separate the upper slide and cover a distance of 7.5 cm.(in seconds).

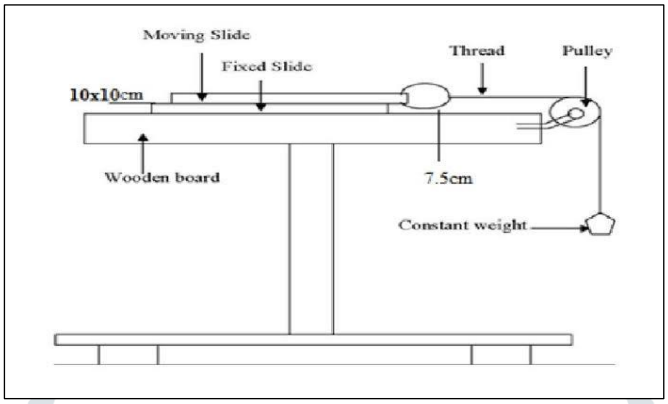


**Figure 7. Spreadability Test Apparatus [50]**

**Alternative method of calculating Spreadability [51]:**

A weighed quantity of emulgel ( 1- 2 gm) is placed on one glass plate. The diameter of the emulgel placed is measured, another glass plate is placed upon it and thus the emulgel is sandwiched between two glass plates. The spread in emulgel diameter is noted down.

**9) Ex-vivo Bio-adhesive Strength Measurement of topical emulgel (Mice shaven skin) [52]:**

The modified method is used for bio-adhesive strength measurement. The fresh skin from mice is cut into pieces and washed with 0.1 N NaOH. Two pieces of skin are tied to the two glass slides separately from that one piece is attached on the slide which is fixed on the wooden block, and another piece is tied with the balance on the right-hand side. The right and left pans are then balanced by adding extra weight on the left-hand pan. 1 g of topical emulgel is placed between these two slides containing hairless skin pieces, and extra weight from the left pan is removed to sandwich the two pieces of skin, and some pressure is applied to remove the presence of air. The balance is kept in this position for 5 min. Weight is added slowly at 200 mg/min to the left-hand pan until the patch detached from the skin surface. The weight in grams required to detach the emulgel from the skin surface gave the measure of bio-adhesive strength.

The bio-adhesive strength is calculated using the following formula:

**Bio-adhesive strength =** Weight required (in g)/Area (cm2).

**Alternative method used for Ex-vivo Bio-adhesive strength measurement [53]:**

Another method can be used for Bio-adhesive strength measurement by modification in physical balance as shown in figure number 8. In this method the two pans of physical balance are removed. A glass slide is hanged on the left side of the pan whereas a beaker ( about 100 ml) is used at right side of the pan. On the left side a weight (About 20 gm) is hanged for balancing the assembly. Below the hanged slide, another glass slide is placed. Hairless, fresh rat skin portions are attached on both the slides. Between two rat skin portions, emulgel formulation (about 1 gram) is placed. A little pressure is applied for the formation of Bio-adhesion bond and then water is added slowly to right side beaker, until the slides get separated from each other. The weight in grams of water required for separation of the two slides is noted.

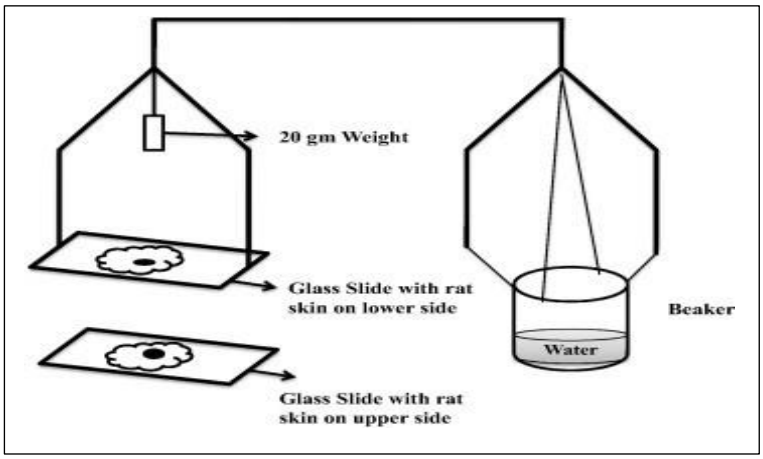


**Figure 8. Bio-adhesive strength measurement apparatus**

**10) In vitro drug release study [54-56]:**

For the In vitro drug release study, the modified Franz diffusion cell or Keshary-chien Cell

with effective diffusion area 3.14cm² and 15.5ml cell volume is used. It is shown in figure number 9. A standard Cellophane dialysis membrane is used as the separation membrane for receptor and donor compartments. The dialysis membrane separating the two compartments can also be obtained from egg shell membrane. Like human stratum corneum, egg shell is mainly made up of keratin. The content of the egg is detached by making a small hole to egg and the outer shell of the egg is dissolved by putting it in the concentrated hydrochloric acid for about 15 minutes. Then the membrane is put into the fresh water and washed gently prior use.

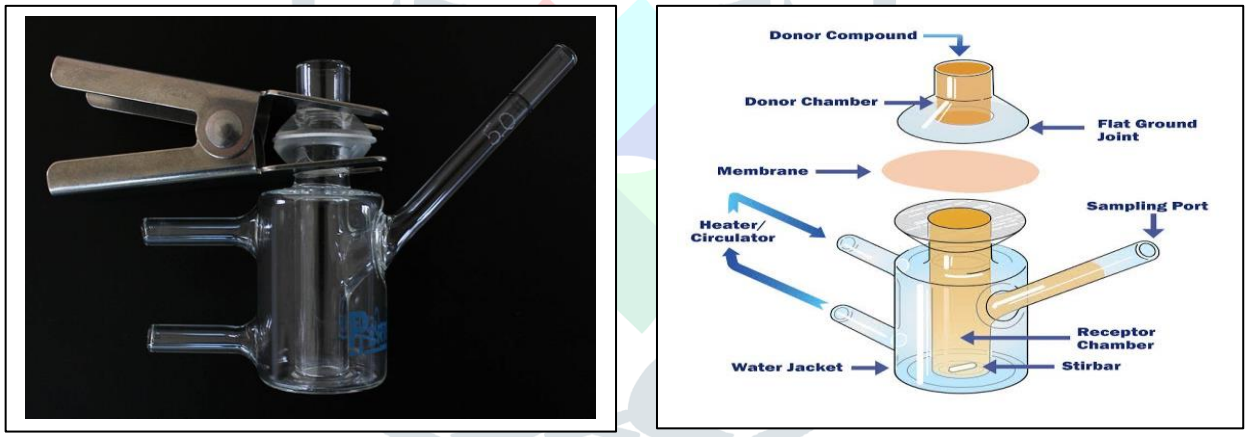


**Figure 9. Franz Diffusion Cell apparatus [55]**

Emulgel (1 mg) is applied onto the 9.8 cm² area surface of the dialysis membrane separating the donor and receptor compartments of the diffusion cell. A freshly prepared phosphate buffer (pH 6.8 - 7.4) is filled in the receptor chamber to solubilize the drug. The fluid in the receptor chamber is continuously stirred at 100 RPM by using a magnetic stirrer. The temperature of the receptor chamber is maintained at 37˚ C with the help of circulating water jacket. The sample from the receptor chamber is collected at suitable time interval from the sampling port and it is replaced with equal amount of fresh buffer. The collected samples are analyzed for drug content with the help of UV-visible spectrophotometer after appropriate dilutions. To obtain the total amount of drug released at each time interval, Cumulative corrections are made. The cumulative amount of drug release across the membrane is determined as a function of time. The cumulative percentage drug release is calculated using standard calibration curve. The best batches showing high percentage of drug release are selected for ex-vivo studies using rat skin.

**11) Ex-vivo skin permeation and retention Studies [56, 57 ]:**

The freshly excised skin of rat is placed in Aluminum foil. The dermal side of the skin is delicately teased off for any following fat and/or subcutaneous tissue. With the help of a magnifying glass the skin is then precisely checked to guarantee that specimens are free from any surface inconsistencies like small openings or cervices in the part that is utilized for transdermal permeation studies. The skin is washed with physiological saline buffer.

The ex-vivo skin permeation of drug from different formulations is studied using Keshary-chien cell (shown in figure number 10). The effective permeation area of the diffusion cell is 9.8 cm2. The receptor compartment has a volume of 37.5 ml.

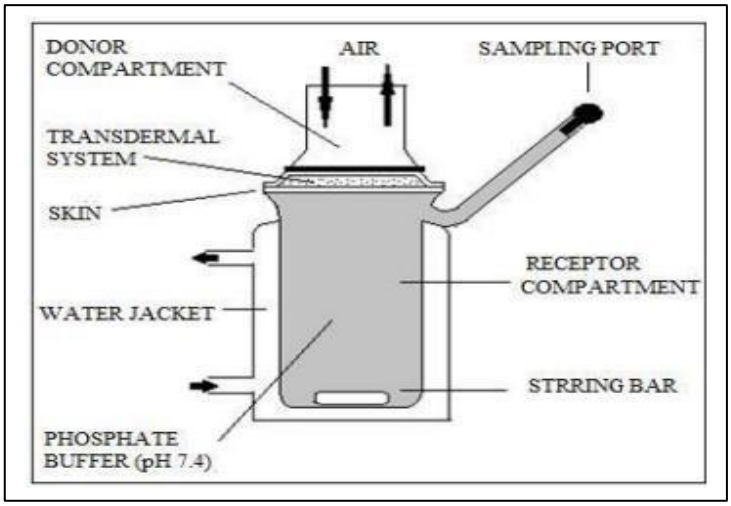


**Figure 10. Keshary-chien cell apparatus [57]**

The rat skin is sandwiched securely between donor and receptor compartment with the donor compartment having epidermis site. The emulgel formulation is applied to the epidermal surface of the rat skin. A freshly prepared phosphate buffer (pH 6.8 - 7.4) is filled in the receptor chamber to solubilize the drug. The fluid of the receptor chamber is continuously stirred with the help of magnetic stirrer. The temperature of receptor compartment is maintained at 37±1°C with the help of circulating water jacket. About 3 ml Aliquots (samples) are withdrawn at different time interval for 24 hr (0.5hr, 1hr, 2hr, 4hr, 6hr, 8hr, and 24 hr) and are replaced with an equal volume of phosphate buffer to ensure sink condition. The cumulative percentage drug diffused across the skin is calculated at each sampling point. All the determinations are carried out in triplicate and the data is compared by ANOVA. The ex-vivo permeation study of emulgel is compared with the marketed emulgel for permeation characteristics.

**12) Drug Content Determination [58] :**

Drug concentration in emulgel is measured by using spectrophotometer. A known quantity of emulgel (1gm) is dissolved in a suitable solvent (methanol , saline phosphate buffer pH 6.8). Sonication is done for 2 hrs if the drug is not soluble after gentle shaking.Filter it to obtain a clear solution. The absorbance of the resulting solution is analysed using UV visible spectroscopy. The Drug Content is determined with the help of calibration curve of drug. Following formula is used for drug content determination,

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

**13) Drug Release Kinetic Study [59]:**

For analysis of drug release kinetics from the topical Emulgel, the release data is fitted to following equations.

**A) Zero order equation, $Q = K_0 t$**

Where Q is the amount of drug released at time t and $K_0$ is the zero – order release rate.

**B) First – order equation, $\ln (100 - Q) = \ln 100 - K_1 t$**

Where Q is the percentage of drug release at time t and $K_1$ is the first – order release rate constant.

**C) Higuchi's equation, $Q = K_2 t^{1/2}$**

Where Q is the percentage of drug release at time t and $K_2$ is the diffusion rate constant.

**D) Hixson-Crowell:**

The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles of formulation.

**$Q_0^{1/3} - Q_t^{1/3} = KHC\ t$**

Where, Qt is the amount of drug released in time t, $Q_0$ is the initial amount of the drug in emulgel and KHC is the rate constant for Hixson-Crowell rate equation.

When this model is used, it is assumed that the release is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix.

**E) Korsmeyer-Peppas Model:**

Korsmeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data is fitted in Korsmeyer–Peppas model: **$M_t/M_\infty = Kt^n$**

Where $M_t/M_\infty$ are fraction of drug released at time t, k is the rate constant and

" n " is the release exponent. The " n " value is used to characterize different release mechanisms as given in the table number 7.

**Table 7: Diffusion exponent and Release Mechanism:**

| Diffusion exponent (n) | Diffusion Mechanism |
|---|---|
| <0.5 | Fickian diffusion (Higuchi matrix) |
| 0.5 < n < 1 | Anamolous (non fickian diffusion |
| 1 | Case-II transport (zero order release) |
| N>1 | Super case-II Transport |

**14) Skin Irritation Study [60]:**

The skin irritation test is very important as the Emulgel formulation is a topical preparation and Various preparation when applied to skin might cause skin irritation. Therefore for assessment of the skin sensitising potential of the formulation, the formulated Emulgel is applied to the dorsal skin of laboratory animals. The animal used may be rats or rabbit. This test is conducted in accordance with the approval of Animal Ethical Committee. The animals are kept under standard laboratory conditions with temperature of 25±1°C and relative humidity of 55±5%. The animals are housed in polypropylene cages with free access to standard laboratory diet and water. The animals are acclimatized for at least seven days before experimentation. The hair on the dorsal side of the rats is removed with an electric hair clipper on previous day of experiment. 0.5gm of Emulgel formulation is applied on the properly shaven area of the skin (approximately 1 $inch^2$ i.e. 2.54 $Cm^2$) of rat. The Emulgel is removed from the application site and wiped with distilled water to remove any remaining test Emulgel residue after 24 hours. The rats are tested for any undesirable skin changes i.e. Change in Colour, Change in the skin morphology is checked for a period of 24 hours.

Allergic symptoms like edema (inflammation), erythrema (redness), Irritation (rashes) is observed for 24 hours. If no allergic symptoms observed, then the test is passed. If the allergic symptoms occurrs in more than 2 rats , the study is repeated.

**15) Microbiological assay/ Microbial test [61] :**

As the Emulgel formulation may be contaminated with microorganisms. The microbiologal assay of emulgel Formulation is carried out using any of the methods for microbial test. Commonly Ditch plate technique is used for microbial test of semisolid formulations. By using this method Bacteriostatic or fungistatic activity of a formulation is evaluated. Sabouraud's agar dried plates are prepared before the use. About 2-3 grams of the emulgel is 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 plates are observed after incubation for 18-24 hr at 25°c for any microbial growth, and the percentage of inhibition is measured using following formula:

**Percentage inhibition = L2/L1 × 100**,

Where, L1 = Total length of the streaked culture, and L2 = Length of inhibition.

**16) Accelerated Stability Study [62-63]:**

Accelerated stability study is carried out as per the ICH Guidelines (given in table number 8) to assess the stability of the Emulgel after storage. For this study Stability Chamber/ Hot air oven is used.

**Table 8: ICH Guidelines for Stability Study [63]**

| Study | Storage Condition | Time Period |
|---|---|---|
| **Long Term** | 25°c ± 2°c/ 60%RH±5 **or**<br>30°c ±2°c /65% RH± 5% RH | **12 months** |
| **Intermediate** | 30°c ± 2°c /65% RH± 5% RH | **6 Months** |
| **Accelerated** | 40°c ±2°c /75% RH± 5% RH | **6 Months** |

A Sufficient quantity of Emulgel formulation is sealed in 10gm of Collapsible Aluminium Tube in triplicate, and stored under accelerated condition of 40°C±2°C/75%±2%RH for a period of 3 months. The Samples are withdrawn at an interval of 1, 2 and 3 months for Accelerated Stability Conditions. The collected samples are evaluated for it's physical appearance (visually inspected for any change in colour, odour and appearance) , pH, Rheological Properties (Viscosity, Flow behaviour), Drug content and Microbial test.

**Packaging of Emulgels [64] :**

For packaging of emulgel formulations Lacquered Aluminium Collapsible tubes are used. The tubes used are provided with inner coating of phenoxy-epoxy based lacquer which is with propylene screw cap.

Materials used for laminates tubes are foil laminates and plastic laminates. Foil laminate act as barrier for moisture, air and light whereas Plastic laminates act as barrier for chemical resistance.

**Marketed preparation of Emulgel and their applications [64,65] :**

Examples of Marketed formulations of emulgel with their Pharmaceutical application are given in the table number 9.

**Table 9: Marketed prepartion of emulgel and their applications [64,65]:**

| Drug Name | Brand Name | Category | Company |
|---|---|---|---|
| Diclofenac diethyl ammonium | Voltaren Emulgel | Anti-inflammatory | Novartis |
| Diclofenac Sodium | Diclomax emulgel | Anti-inflammatory | Torrent Pharma |
| Miconazole nitrate, Hydrocortisone | Miconazole-H-emulgel | Topical Corticosteroid and Antifungal | Medical Union Pharmaceuticals |
| Clindamycin Phosphate | Denacine emulgel | Anti-acne | Beit jala Pharmaceutical Company |
| Diclofenac Potassium | Cataflam emulgel | Anti-inflammatory | Novartis |
| Azithromycin | Avindo gel | Antibiotic | Cosme Pharma Laboratories |
| Metronidazole | Lupigyl gel | Antibiotic | Lupin Pharma |
| Clobetasol Propionate | Topinate gel | Corticosteroid | Systopic Pharma |
| Benzoyl peroxide | Pernox gel | Anti-acne | Cosme Remedies. Ltd |

Current Elevations in Development of Emulgel for Various Drugs is shown in table number 10

**Table 10: Current Elevations in Development of Emulgel for Various Drugs:**

| Drug | Aim | Use | Reference number |
|---|---|---|---|
| **Ocimum basilicum extract** | Formulation and evaluation of Ocimum basilicum-based emulgel forwound healing using animal model. | Wound healing | [ 66 ] |
| **Metronidazole** | Modulating the properties of sunflower oil based novel emulgels using castor oil fatty acid ester: Prospects for topical antimicrobial drug delivery | Topical Antimicrobial | [ 67 ] |
| **Curcumin** | Mucoadhesive emulgel systems containing curcumin for oral squamous cell carcinoma treatment: From pre-formulation to cytotoxicity in tissue- engineering oral mucosa. | oral squamous cell carcinoma | [ 68 ] |
| **Ciprofloxacin HCl** | Synthesis and characterization of novel tamarind gum and rice bran oil-based emulgels for the ocular delivery of antibiotics | Antibiotic | [ 69 ] |
| **Levofloxacin and Betamethasone** | Formulation and evaluation of Levofloxacin and Betamethasone Ophthalmic emulgel | Treatment of ocular tissues. | [ 70 ] |
| **Insulin** | Vesicular emulgel based system for transdermal delivery of Insulin: Factorial design and in vivo evaluation | Antidiabetic effect | [ 71 ] |
| **Calcipotriol** (Synthetic analogue of vitamin D) | Topical emulgel formulation containing inclusion complex of Calcipotriol with Cyclodextrin | For treatment of psoriasis | [ 72 ] |
| **Rice bran extract** | Ethanol extract emulgel 96% Brokatul Rice (Oryza Sativa L.) as antioxidant | For inhibiting tissue oxidation (anti-ageing effect) | [ 73 ] |
| **Mupirocin** | Development of emulgel delivery of Mupirocin for treatment of skin Infection | For treatment of skin Infection | [ 74 ] |
| **Mupirocin** | The Design, Development and Characterisation Of Mupirocin Loaded Emulsion Based Gel For Diabetics Wound Healing | Antimicrobial for Diabetics Wound Healing | [ 75 ] |
| **Piroxicam** | Formulation and in vitro Evaluation of Piroxicam Emulgel | Anti-inflammatory effect | [ 76 ] |

**Conclusion :**

Emulgel is a significant novel drug delivery system in which both the hydrophobic and hydrophilic drugs can by incorporated in the gel by formulating emulsions. Emulgel is a recent technique to formulate topical dosage form for both local and systemic pharmacological treatment. Because of its properties like spreadability, viscosity, extrusion and adhesion, Emulgel become a popular choice of drug delivery with increased patient compliance.

**Future Perspectives:**

In the formulation and development process for the Pharmaceutical drugs the major problem arises due to hydrophobic nature of the drugs. Due to the hydrophobic nature, the drug has poor solubility and bioavailability in the body. This drawback can be overcome with formulation of Emulgel, as the emulgel provides the aqueous environment for solubility of drug with presence of the gel in the formulation. Thus hydrophobic drugs can be incorporated into Oily base and delivered to the skin by formation of Emulgel. Due to all these favorable things, emulgel can more effective and profitable way for formulating topical dosage form for hydrophobic drugs.

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