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REVIEW ARTICLE ON SCIENTIFIC STUDY OF EMULGEL IN INDUSTRY

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ABSTRACT :

Drugs can be delivered topically by entering the body through the skin, vagina, eyes, or rectal tract. Medication might be used for systemic or localized effects. It is possible to create topical formulations with different physicochemical characteristics, such as solid, semisolid, or liquid. A medication emulsion is prepared and then added to an emulgel to generate the topical system. Emulgel is a low interfacial tension, thermodynamically stable formulation with numerous features, including good thermodynamic stability and improved permeability, that is created by mixing a surfactant and a co-surfactant. Emulgel offers a continuous release pattern with dual control. Emulgel increases patient compliance and bioavailability. The drug content, zeta potential, pH, viscosity, particle size, stability study, skin irritation test, and other.

KEY WORDS : Emulgel

TOPICAL DRUG DELIVERY SYSTEM :

Topical drug delivery system is the dosage form which is administered on the skin and other routes of drug delivery get failed or for skin disorders. The topical drug delivery system has the advantage of negotiating the first pass metabolism. It also helps to avoid the risk and inconvenience of i.v route therapy.

Topical formulations are prepared in different consistency such as solid, semisolid, and liquid. The topical delivery system is failed in the administration of hydrophobic drug.

EMULGEL

Emulgel is an emulsion that has been gelled using a gelling agent. It can be made either o/w or w/o type. Emulgel is a stable and superior system that incorporates poor water-soluble drugs. To put it simply, emulgel is a combination of emulsion and gel. Despite the many benefits of gels, one major drawback is the delivery of hydrophobic medications. To get around this limitation, an emulsion-based solution is being used, enabling even hydrophobic therapeutic moieties to benefit from the unique properties of the gel. Emulgel can deliver both hydrophilic and lipophilic drugs because of the presence of both aqueous and non-aqueous phases. In recent years, they have been used as a control release formulation. These are biphasic systems that have better drug delivery capabilities..

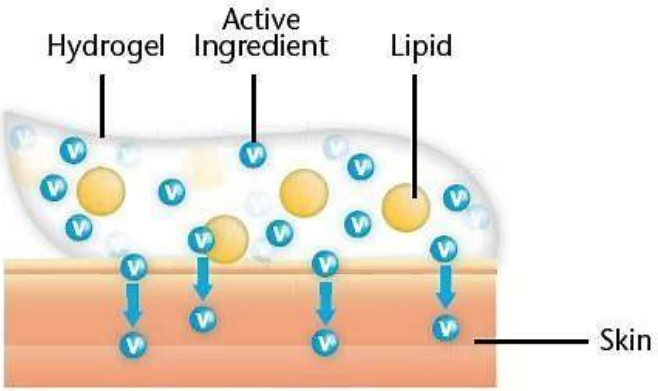

Fig no 01 Structure of Emulgel

TYPES OF EMULGEL

1. 1.MICROEMULSION
2. 2.NANOEMULGEL
3. 3.MACROEMULSION GEL

1.MICROEMULSION

Isotropic mixtures of a biphasic o/w systemic stabilized with an optically clear, thermodynamically stable surfactant constitute microemulsions. Droplets don't coalesce and range in size from 10 to 100 nm. It is composed of water, surfactant, co-surfactant, and oil in certain proportions. Extremely low interfacial tension, a wide interfacial region, and the capacity to dissolve both aqueous and oil-soluble substances are some of the distinctive characteristics that microemulsions may possess. By reducing the diffusion barrier in the stratum corneum, the components of the microemulsion may facilitate a faster rate of drug penetration.
Microemulsions have a low skin retention ability due to their low viscosity, which limits their use in the pharmaceutical industry. Gelling agents like HPMC K100M, Carbopol 940, and guar gum are added to address this limitation.

2.NANOEMULGEL

A nanoemulsion is a transparent (translucent) oil-water dispersion with globule sizes ranging from 1 to 100 nm that is thermodynamically stable because it contains surfactant and cosurfactant molecules. The term "Nanoemulgel" refers to the mixture of emulsion and gel. Compared to conventional formulations like emulsions and gels, many drugs exhibit greater transdermal penetration when applied as nanoemulsions. Both in vitro and in vivo, the nanoemulsion exhibits improved transdermal and dermal delivery capabilities. Due to its small globule size and high loading capacity, the drug enters the skin easily and has a short half-life of therapeutic effect.

3.MACROEMULSION

Emulgel with emulsion droplet sizes larger than 400 nm. The individual droplets are clearly visible under a microscope, but they are physically invisible. Surface-active agents can help stabilize macroemulsions, which are thermodynamically unstable.

ADVANTAGES OF EMULGEL

- Using water/oil/water emulsions, hydrophobic drugs can be quickly implemented into the gel base.
- Improved stability and load capacity.
- Easy for production and a low-cost mechanism.
- The first metabolism is avoided.
- Avoid gastrointestinal incompatibility.
- Target drug delivery on the body.
- Improved patient compliance.
- Improved patient acceptability and suitability for self-medication.

DISADVANTAGES OF EMULGEL

- The drug and/or excipients can lead to skin irritation in people with contact dermatitis.
- Some medications have low permeability through the skin.
- Possibility of allergeic reactions.
- Larger-particle-size drugs are not easily incorporated into the skin

PREFORMULATION /STEPS IN FORMULATION DEVELOPMENT :

An important phase in the creation of emulgel formulations is preformulation. To acquire crucial data and knowledge regarding the mechanical, chemical, and physical characteristics of the ingredients and their compatibility, a number of experiments and studies are conducted. The preformulation steps in the formulation study of emulgels typically include the following:

IDENTIFICATION AND CHARECTERIZATION OF DRUG

1. **Organoleptic properties** : the drug, including its description, color, taste, odor, and appearance, were examined.
2. **Determination of Melting Point**: Using a capillary tube, the drug's melting point was ascertained. The capillary tube had a sealed end. After being filled, the sample was put inside the melting point device. It was noted what the drug's melting point was. The medication's melting point was discovered to be 200 0C, with a typical range of 198-202 0C. Drug was therefore appropriate for formulation. pH 7.4 phosphate buffer calibration curve [12–16] Making a pH 7.4 phosphate buffer Accurately weigh out 17.5 grams of sodium hydroxide, then

dissolve it in 500 milliliters of purified water using a volumetric flask. Identified it as option "A". In a volumetric flask, precisely weigh 13.8 grams of sodium dihydrogen phosphate and dissolve it in 500 milliliters of distilled water. Identified it as option "B". Consider 202.5

3. **Standard Calibration Curve**: Accurately weigh 100 mg of pure medication, then transfer it into a 100 ml volumetric flask. Add 7.4 mM phosphate buffer, labeled as stock solution I, to bring the volume up to 100 ml. (1000 µg/ml) Take 10 milliliters (by pipetting) out of stock solution I, transfer it to a second 100 milliliter volumetric flask, fill it up to the 100 milliliter mark, and label it as stock solution II. (100 µg/ml) Next, use a pipette to extract 2 ml, 4 ml, 6 ml, 8 ml, and 10 ml from stock solution 2, increasing the volume up to 10 ml. This will yield a final concentration that falls between 2, 4, 6, 8, and 10 µg/ml, accurately. 7.4 Phosphate buffer is used to make all dilutions. Measure the absorbance of each dilution using a UV Visible spectrophotometer at 242 nm.
4. **Compatibility Study of Drug and Excipient**: Prior to formulation, it is crucial to investigate the drug's and polymers' compatibility under experimental conditions. Therefore, it is essential to verify that, in experimental conditions, the drug does not react with the polymer and excipients and affect the product's shelf life.
5. **FTIR spectrum :**FT-IR spectra of pure Piroxicam and polymer at room temperature obtained in transmittance mode with an FT-IR spectrophotometer (FTIR8400S, Shimadzu, Japan). After being ground in a mortar and combined with Nujol, the samples were sandwiched between two KBr plates and compressed to create a thin layer. After inserting the sandwiched plates into the infrared spectrometer, the spectra were acquired. At a resolution of 2 cm-1, scanning was done between wave numbers 4000-400 cm-1.
6. **DSC (Differential Scanning Calorimetry):** In the DSC test, a milligram-sized sample of the material under investigation is heated slowly. The sample's heat evolution and consumption are monitored, and the exothermic and endothermic reactions that take place during this process are examined and quantified.

EXCIPIENT DRUG COMPATABILITY STUDY :

1. Physical compatibility tests evaluate the mixture's physical characteristics, such as:
- Solubility Studies: Analyze the API's solubility in the excipient or excipient mixture. Poor medication distribution within the proniosomal vesicles may result from the API's insolubility in the excipient.
- Melting Point and Thermal Analysis: Examine the thermal behavior of the API and excipients using thermogravimetric analysis (TGA) or differential scanning calorimetry (DSC) to look for interactions or decomposition..
- Particle Size and Morphology: Monitor the proniosomal vesicles' particle size and morphology after excipients are added to make sure they stay within the intended range.
2. Chemical Compatibility Tests:
- Fourier Transform Infrared Spectroscopy (FTIR): To find possible chemical interactions, use FTIR to examine the functional groups and chemical structures of the excipients and API.
- Nuclear Magnetic Resonance (NMR): Use NMR spectroscopy to investigate chemical reactions and confirm the existence of particular chemical groups.
- X-ray Diffraction (XRD): In order to identify any modifications in the solid-state form, look at the crystallinity and polymorphism of the excipients and API.
- High-Performance Liquid Chromatography (HPLC): Examine the API's and its degradation products' chemical stability in the presence of excipients.
3. Bioavailability Studies: If at all feasible, conduct bioavailability studies on humans or animals to evaluate how excipients affect the systemic absorption of the API. Variations in bioavailability may be a sign of compatibility problems.

CRITERIA FOR EXICIPIENT SELECTION :

7. Biocompatibility:
- Make sure excipients are safe to use on skin or mucous membranes, and that they don't irritate or sensitize skin or have any negative effects when applied to the intended site.

8. Rheological Properties:

- Choose excipients that will enable the proniosomal gel to exhibit the appropriate rheological properties, including spreadability, shear-thinning behavior, and viscosity.

9. Dosage Form and Route of Administration:

- Excipients ought to be compatible with the particular dosage form (gel) and the intended administration route (topical or transdermal).

10. Patient Acceptance:

- The texture, smell, or appearance of the excipients should not adversely affect the patient's experience. This is crucial for topical gels in particular.

11. Manufacturability and Process Compatibility:

- To guarantee dependable and effective production, take into account the excipients' compatibility with manufacturing procedures and ease of incorporation into the formulation.

FORMULATION :

An emulgel is made by following a set of steps that combine the characteristics of a gel and an emulsion, such as water in oil or oil in water, to produce a stable and functional product. Emulgels are frequently utilized in cosmetics and pharmaceuticals. An overview of the formulation process is provided below:

Ingredients Needed:

1. Oil Phase:
- Lipophilic substances (e.g., oils or active ingredients in oil form)
- Lipophilic emulsifiers (e.g., Span or Montanox series)

2. Aqueous Phase:
- Hydrophilic substances (e.g., water)
- Hydrophilic emulsifiers (e.g., Tween or Montanox series)
- Active ingredients in water-soluble form

3. Gelling Agent:
- Carbomer, HPMC, sodium carboxymethylcellulose, or other suitable gelling agents

4. Preservatives: (as required for microbial stability)
- Methylparaben, propylparaben, or any other approved preservative

5. Co-solvents: (optional, for enhancing solubility or texture)
- Propylene glycol, glycerin, etc.

6. Neutralizing Agent: (to adjust the pH)
- Triethanolamine or sodium hydroxide (for carbomer-based gels)

7. Colorants and Fragrance: (optional, for aesthetic appeal)

Procedure:

1. Prepare the Oil Phase:
- a.In a heat-resistant container, weigh the lipophilic ingredients and lipophilic emulsifiers, then heat them until they melt.
- b. Fully combine to guarantee even distribution.

2. Prepare the Aqueous Phase:
- a.In a different container, weigh, warm up, and combine the hydrophilic ingredients, hydrophilic emulsifiers, and co-solvents (if applicable).
- b. Raise the temperature to match the oil phase's.

3.Add the Gelling Agent
- Sprinkle the gelling agent (e.g., carbomer) into the aqueous phase while stirring continuously.
- Allow the gelling agent to hydrate and thicken the mixture. This may take some time, and additional mixing might be needed.

4. Combine the Phases:
- Slowly pour the oil phase into the aqueous phase while stirring continuously.
- Ensure a uniform mixture by thorough mixing.

5.Neutralize and Adjust pH:
- If carbomer is being used, neutralize the mixture with a neutralizing agent (triethanolamine, for example) while keeping an eye on the pH. Preheat to the appropriate pH (usually between 6.0 and 7.0).
- For other gelling agents, adhere to the particular guidelines regarding pH correction or neutralization.

6. Add Preservatives:
- Make sure the selected preservatives are evenly distributed throughout the emulgel formulation.

7. Add Colorants and Fragrance
- To improve the formulation's appearance, add colorants and fragrance if preferred.

8. Homogenize:
- To further guarantee even distribution of all ingredients and, if required, to reduce particle size, use a high-shear mixer or homogenizer.

9. Cool and Package:
- Before putting the emulgel into appropriate packaging containers, let it cool to room temperature.

10. Check for Stability:
- To make sure the product will remain stable over time, perform stability tests such as temperature cycling and microbiological testing.

EVALUATION OF EMULGEL :

Physical Examinations

physical characteristics such as texture, color, homogeneity, and consistency. A digital pH meter is used to measure the pH of a 1% solution in emulgel water. Measurement of spreadability On a glass slide, 0.5 g of emulgel is placed, and a circle is drawn around it. After that, a second slide is positioned over it, and for a predetermined amount of time, a predetermined weight is applied to it. The diameter's increase Test for Syneresis Measurement Gel contracts while at rest, pushing out a tiny amount of liquid known as syneresis.

Spreadability

A spreadability test apparatus proposed by Mutimer et al. (1956) was modified in a laboratory and employed for the study. A wooden block with a pulley on one end is used to construct it. 'Slip' and 'Drag' properties of the emulgel are used to calculate spreadability using this method. A fixed ground glass slide is located on this block. There is an excess of Emulgel (about 2 gm) on this ground slide that is being observed. Next, a second glass slide the same size as the fixed ground slide and a hook are positioned between this slide and the emulgel. A 1 kg weight is positioned on top of each of the two slides for five minutes in order to force out air and create a uniform layer of emulgel between the slides. The edges are scraped clean of any extra emulgel. Next, the top plate is pulled with an 80-gram force. Using a piece of string fastened to the hook, determine how long it takes the top slide to travel 7.5 cm (measured in seconds). The better the spreadability, the shorter the interval The formula was used to calculate spreadability.

$S = M.L/T$

Where,

S = spreadability.

M = Weight tied to upper slide.

L = Length of glass slides.

T = Time taken to detach the slides.

Extrudability study

The amount of force needed to extrude material from a tube is often determined empirically. The process for figuring out how much applied shear in the rheogram zone causes plug flow when the shear rate exceeds the yield value. The percentage of emulgel and emulgel extruded from a lacquered aluminum collapsible using the gramme weight necessary to extrude at least a 0.5 cm emulgel ribbon in 10 seconds is the method used in this study to evaluate emulgel formulations for extrudability. As the amount extruded rises, extrudability gets better. The extrudability of each formulation is measured three times, with the average results being published.. After that, the extrudability is computed using the formula:

Extrudability = Weight used to extrude emulgel from tube (in gm) / Area (in cm2).

Rheological studies

A Brookfield viscometer with spindle no.18 at 100 rpm is used to determine the rheological properties of the various emulgel compositions at 25° C.

Swelling Index

The swelling index was calculated by weighing one gramme of prepared topical emulgel on porous aluminum foil and depositing it separately, undisturbed, in a glass beaker with a 50 ml capacity and 10 ml of 0.1 N NaOH. After being taken out of the beakers at different intervals, the samples are left in a dry area for a while before being weighed again. The swelling index was calculated by using the equation:

$SW\ \% = [Wt - Wo / Wo] \times 100$

Where,

SW % = Equilibrium percent swelling,

Wt = Swollen Weight emulgel after time t,

Wo = Initial weight of emulgel at time zero.

Skin irritation study

In the formulation, 0.5 g of each is uniformly placed over a 4 cm2 area on the hairless skin of rabbits. After 24, 48, and 72 hours of application of the formulation, the skin surface is examined for any obvious changes such as erythema (redness).

The following are the erythemal scores: no erythema=0, minimal erythema (barely perceptible-light pink) =1, moderate erythema (dark pink) =2, moderate to severe erythema (light red) =3, and severe erythema (dark red) =4 (extreme redness).

Stability study

The emulgels are tested for three months at 50°C, 250°C/60% relative humidity, 300°C/65% relative humidity, and 400°C/75 % relative humidity. They are packaged in aluminum collapsible tubes (15 gramme). Samples are collected and analyzed monthly in accordance with ICH guidelines for a variety of factors, including drug content, release profile, pH, physical appearance, and rheological characteristics.

Dilution test

Phase separation and clarity were visually confirmed by adding Continuous phase to an emulgel dilution that was 50–100 times aqueous.

Determination of pH

To find the formulation's pH, a digital pH meter was utilized. To measure pH three times, the pH meter electrode was cleaned in distilled water before being added to the mixture.

Drug Content Determination

It takes one gramme of emulgel. It needs to be combined with an appropriate solvent. Filter it to obtain a clear solution. Find its absorbance with a UV spectrophotometer. One makes a standard drug plot in the same solvent. By entering the absorbance value into the standard plot equation, one can calculate the concentration and drug content using the same standard plot.
Drug Content = (Concentration × Dilution Factor× Volume taken) × Conversion Factor.

Zeta potential

The zeta potential of the emulgel formulation is determined using the Zetasizer (Malvern Zetasizer). The result is computed when the formulation is placed in a transparent, disposable zeta cell. Cuvettes are soaked in methanol before being filled with the experiment's sample.

In Vitro release study

The Franz diffusion cell is used in the drug release experiments. Apply emulgel uniformly to the egg membrane's surface. The egg membrane is clamped between the donor and the receptor chamber of the diffusion cell. Next, freshly prepared PBS (pH 5.5) solution is added to the receptor chamber in order to solubilize the medication. The receptor chamber is stirred using a magnetic stirrer. The emulgels' 1.0 ml aliquots must be taken at the proper intervals, and a UV visible spectrophotometer must be used to determine the drug content of the appropriately diluted samples. For each time period, the total amount of medication released is calculated using cumulative adjustments. The total amount of medication released across time is determined using time as a function.

Centrifugation study

The stability of the emulgel is ascertained through this process. It's finished after a week of preparation. The experiment was run for 30 minutes at 3000 rpm in a minicentrifuge.

STABILITY STUDIES :

The duration of a pharmaceutical product's physical, chemical, microbiological, and pharmacokinetic properties and characteristics over the course of its shelf life after manufacture is referred to as the stability study of the product. The product's shelf life is determined by the substance's reduction to 90% of its initial concentration. The term "shelf life" refers to the product's stability and is commonly used interchangeably with "expiration date." Every pharmaceutical preparation has a different expiration date**.**

IMPORTANCE OF STABILITY STUDIES

1. Product instability of active drug may lead to under medication due to the lowering of the drug in dosage form.
2. During the decomposition of the drug or product it may lead to toxic products.
3. During the marketing from one place to another during the transportation the drug has the compatibility to change its physical properties.
4. In stability ma due to the changing in physical appearance through the principles of kinetics are used in predicting the stability of drug there different between kinetics and stability study.

TYPES OF STABILITY STUDIES ON DRUG SUBSTANCES

1. Physical stability: The original physical properties such as appearance, color, dissolution, palatability, suspendability are retained. The physical stability may affect the uniformity and release rate; hence it is important for the efficacy and safety of the product.
2. Chemical stability: It is the tendency to resist its change or decomposition due to the reactions that occur due to air, atmosphere, temperature, etc.
3. Microbiological stability: The microbiological stability of the drugs is the tendency to resistance to the sterility and microbial growth. The antimicrobial agents used in the preparation retain the effectiveness within specified limits.
4. Therapeutic stability: The therapeutic effect (Drug Action) remains unchanged.

5. Toxicological stability: Toxicological stability has no significant increase in the toxicity occurs

STABILITY TESTING METHODS

Stability testing is a procedure performed for all the pharmaceutical products at various stages of the product development. In the early stages, the stability testing is performed by the accelerated stability studies which mainly are performed at high temperature/ humidity. Depending upon the aim, steps followed, the stability testing procedures have been categorized into four types and they are :-

1. Real-time stability testing
2. Accelerated stability testing
3. Retained sample stability testing
4. Cyclic temperature stress testing.

REAL TIME STABILITY TESTING

It is normally performed for a long duration of time to allow significant degradation of the product under the storage conditions recommended. The period of time for the test of the product depends on the stability of the product.

ACCELERATED STABILITY TESTING

It is done at higher temperatures and that decomposition the product is determined. The information is used to predict the shelf life or used to compare the relative stability of alternative formulations The accelerated stability studies are easily predicted by the Arrhenius equation:

K=Ae-Ea./RT K= Specific rate constant

A= Frequency factor or Arrhenius factor

Ea= Energy of activation

R= Real gas constant 4.184 j/mol. K

T= Absolute temperature,

In this method the drugs are stored at different temperatures such as 40°C, 60°C, 70°C, 80°C, 100°C etc. These studies are to be done at room temperature and at refrigerator temperatures. During different intervals the samples are collected and examined for the stability. The sampling is done at 3 months in the first year and 6 months interval the next year and yearly thereafter.

RETAINED SAMPLE STABILITY TESTING

In this type of testing, the stability is done by selecting one batch for a year. The samples stability studies help to predict the shelf life. The maximum shelf life of every product predicted could be 5 years which is conventional to the test samples at 3, 6. 9, 12, 18, 24, 36, 48 and 60 months**.**

CYCLIC TEMPERATURE STRESS TESTING

In this method, cyclic temperature stress tests are designed knowledge of the product so as to mimic likely conditions in the market place storage. In this testing the sampling is considered to be conducted by a cycle of 24 hours which is known as the rhythm of the earth is 24 hours

PACKAGING AND LABELLING OF TABLETS PACKAGING: -

➢ A Pharmaceutical Package container is an article or device which contains the Pharmaceutical Product and the container may or may not in direct contact with the product. The container which is designed for pharmaceutical purpose must be stable.

➢ The packaging of medicines is equally important as producing it with no errors in their composition. Medicine may become lethal if it comes to a constant contact of external components like heat, air and water. With innovation and technology, various types and categories of packaging machines are evolved and are widely used across the globe.

TYPES OF PACKAGES

1.PRIMARY PACKAGING

• Primary packaging is those packages which are in direct contact with the pharmaceutical formulation. The main aim of primary package is to protect the formulation from environmental, chemical, mechanical and/or other hazards

2.SECONDARY PACKAGING

♦ Secondary package refers to the package that is external to the primary package. In addition to offering extra security during storage, this package contains information about pharmaceutical products, such as leaflets.

3.TERTIARY PACKAGING

♦ It shields the products from damage and is the outer package of secondary packaging. It is employed in shipping and bulk handling. Barrel, crate, container, pallets, and slip sheet are a few examples.

Fig no 03 levels of packaging

LABELLING :

Label means a display of written, printed or graphic matter upon immediate container or the wrapper of a drug package.

TYPES OF LABELS

I. Manufacturer label
II. Dispensing label

Fig no 04 image of voveran lable

MANUFACTURER LABEL

A label provided by the drug's manufacturer, packer, or distributor that includes drug information intended for use by physicians, pharmacists, or nurses (FDA).

LEGAL REQUIRMENTS OF A MANUFACTURER LABEL

➢ The name of preparation
➢ Strength and dosage form.
➢ Quantity.
➢ Instructions for the use.
➢ Precautions & warnings.
➢ Registration number.
➢ Batch number.
➢ Manufacturing & Expiry date.
➢ Price
➢ The name and address of pharmaceutical industry

DISPENSING LABEL

A dispensing label is a label that is used to dispense medication and includes the patient's name, the date of dispensing, the supplier's name and address, the medication's nature, and any additional instructions that may be required.

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