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Original Article

EMULGEL- AN INNOVATIVE APPROACH FOR DRUG DELIVERY

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Abstract:- Emulgels are used for a variety of drugs, including steroids, some antibiotics, analgesics, and antifungal agents. They address many of the disadvantages associated with other topical agents such as ointments, creams, and lotions. These traditional formulations can be sticky, cause discomfort for patients, have a limited spreading coefficient, and sometimes require vigorous rubbing for application. Moreover, they may encounter stability issues. One significant limitation of traditional gels, despite their benefits, is their ability to effectively deliver hydrophobic drugs.

Keywords- Skin, emulgel, skin barrier, topical formulation, half-life

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Introduction:

The skin, as the largest sensory organ in the human body, plays a pivotal role in several essential functions while serving as the first-line barrier against external influences. It accounts for approximately 10% of the total body mass and boasts an average surface area of 1.7 square meters(1). Beyond its protective function, the skin exhibits a remarkable capacity to absorb topically applied ingredients, making it an increasingly accepted and advantageous route for delivering a variety of pharmaceutical compounds(2). The structure of the skin facilitates the penetration of topically applied substances into various skin layers and, in some cases, into systemic circulation. Most substances penetrate the skin through three primary pathways: the stratum corneum, sweat ducts, and sebaceous follicles. In recent years, topical drug delivery has emerged as a novel and highly effective approach for managing a range of serious medical complications(3). This approach proves particularly valuable when conventional drug delivery routes fail to provide the desired therapeutic response. Furthermore, the topical route excels in targeting localized skin infections, such as fungal or bacterial skin conditions. The topical drug delivery system encompasses various dosage forms designed for application to the skin, offering an ideal alternative for addressing skin disorders and localized treatment. Notably, this system presents the distinct advantage of bypassing first-pass metabolism, which can significantly alter drug efficacy. Moreover, it mitigates the risks and inconveniences associated with intravenous route therapy (4). Topical formulations are available in diverse consistencies, including solid, semisolid, and liquid forms, further enhancing their adaptability and utility in healthcare and pharmaceutical applications (5).

1.1 Topical Drug Delivery

Topical drug delivery systems offer a versatile means of administering drugs to localized areas of the body, encompassing routes such as ophthalmic, vaginal, skin, and rectal application. These formulations span a wide spectrum, catering to cosmetic or dermatological purposes, as well as serving both healthy and afflicted skin(6). These formulations vary in physicochemical characteristics, ranging from solid to semisolid to liquid. Typically, drug substances are not administered in isolation but are incorporated into formulations alongside one or more non-medicated agents, each serving specific pharmaceutical functions(7). Enhanced drug absorption through the skin is achieved when the drug is in a solution form, possesses a favorable lipid-to-water partition coefficient, and is a nonelectrolyte. Often, pharmaceutical preparations applied to the skin are intended for local actions and are formulated to facilitate extended contact with minimal systemic drug absorption(8). Examples of drugs applied topically for their local effects include antiseptics, antifungal agents, skin emollients, anti-inflammatories, analgesics, and protectants. Topical drug delivery approaches are primarily categorized based on their consistency, which includes solid preparations, liquid preparations, semisolids, and miscellaneous preparations. The selection of the dosage form depends on the nature of the drug and the target site(9). Additionally, the drug's penetrability is influenced by various physiochemical factors such as skin thickness, pH, hydration, lipid content, blood flow, density of hair follicles, density of sweat glands, partition coefficients, and molecular weight, among others. Currently, one of the limitations of topical drug delivery systems is their ability to deliver hydrophobic drugs, posing a significant challenge(10). A recent development in this field is the emulgel, which addresses this limitation. Emulgels are closely related to gels and consist of a colloidal network that can hold a substantial amount of water or a hydroalcoholic solution. Emulgels enhance drug solubility, thus improving drug penetrability, making them an ideal approach for the topical delivery of drugs(10). While gels offer numerous benefits, they are typically unable to deliver lipophilic drugs, a limitation overcome by the development of Emulgels. Emulgels represent a combination of emulsion and gel, and the specific combination chosen depends on the nature of the drug to maximize bioavailability(11). The advantages of emulgels over traditional topical administration include thixotropy, lack of greasiness, improved spreadability, easy removal, biodegradability, emollient properties, and enhanced convenience. Furthermore, emulgels exhibit high stability and an extended shelf life, which has prompted researchers to explore the development of new products falling within this category(12).

Table-1: Classification of topical dosage forms

Liquid preparations	Semi-solid preparations	Solid preparations
Liniments	Ointments	Dusting powders
Lotions	Creams	Tablet
Paints	Pastes	Capsule
Solution	Gels	Poultices
Tinctures	Emulgels	Plaster
Syrup	Suppositories	Oral powders
Suspension		

1.2 Structure of Human Skin

The human skin is a complex organ composed of three main layers: the epidermis, the dermis, and the subcutaneous tissues (13).

a) Epidermis

The epidermis is the outermost layer of the skin and is the layer that directly interacts with topically applied substances. It lacks blood vessels and primarily serves as a protective barrier, forming a covering made up of stratified squamous epithelium cells. The epidermis is further divided into five layers(14):

Stratum Corneum: The outermost layer, which is also the thickest (comprising 20-30 cells).

• Stratum Lucidum

• Stratum Granulosum

• Stratum Spinosum

Stratum Basale: The innermost layer of the epidermis.

b) Dermis

The dermis is located beneath the epidermis and serves as a structural framework for the skin. It is composed of loose connective tissue and has a thickness ranging from 2000 to 3000 micrometers. The dermis plays a critical role in providing physical support to the epidermis and nourishing its cells. It consists of two main layers(14):

• Papillary Layer

• Reticular Layer

Both layers contain important structural components, such as elastin, fibrillin, and collagen. The dermis is also home to essential glands like sebaceous glands and sweat glands, along with hair follicles, blood vessels, and nerve endings. Additionally, smaller blood vessels within the dermis supply nourishment, maintain elasticity and deliver oxygen to the epidermis(14).

c) Subcutaneous Layer

The subcutaneous layer is considered a genuine connective tissue layer with a loose texture. It contains fibrous connective tissue, blood vessels, and lymph vessels. Comprising fatty cells and tissues, the subcutaneous layer provides cushion-like protection to the body and serves as an insulating layer. This layer is vital for temperature regulation and protection. Understanding the distinct roles and compositions of these skin layers is crucial when considering drug delivery through the skin, as each layer presents unique challenges and opportunities for topical drug administration(15).

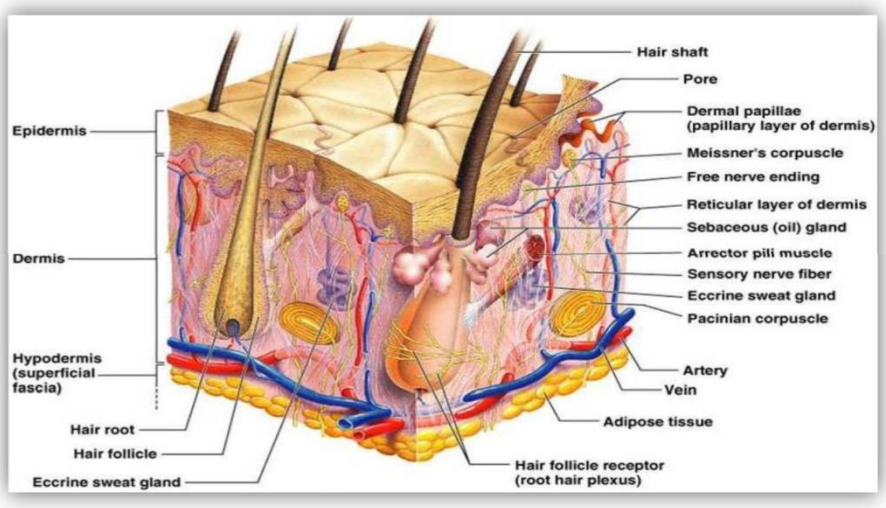

Fig-1: Structure of Human Skin

1.2.1 Penetrability of Skin

To achieve systemic circulation or provide localized effects, topically applied active ingredients must traverse various layers of the skin. The major pathways for crossing the skin involve intercellular penetration, transcellular penetration, and follicular penetration(15):

1. Intercellular Penetration: Intercellular penetration entails the transport of drugs through the junctions between the epithelial cells that make up the skin. This mechanism allows drugs to move through the spaces between these cells to reach their target.

2. Transcellular Penetration: Transcellular penetration is defined as the transport of drugs across the epithelial cells themselves. In this process, the active ingredients navigate through the individual skin cells to make their way from the outermost layer to deeper layers and potentially into the systemic circulation.

3. Follicular Penetration: In the case of follicular penetration, the drug follows the path of the hair follicles to cross the skin barriers. Skin contains a substantial number of hair follicles, with an average of 40-70 hair follicles per square centimeter of the human skin surface. Active ingredients can enter the skin through these follicular pathways.

It's important to note that the skin surface is slightly acidic, with a pH that typically ranges from 4 to 5.6. This pH can be influenced by the secretions of sweat and fatty acids. The skin's pH, along with its various penetration mechanisms, plays a significant role in determining how topically applied substances are absorbed and distributed within the skin and the body(16).

1.2.2 Factor Affecting Penetrability & Absorption of Topically Applied Products

1.2.2.1 Skin Hydration

1.2.2.2 Vascularity

1.2.2.3 Lipid Content

1.2.2.4 pH of Skin

1.2.2.5 Density of Hair Follicles

1.2.2.6 Density of Sweat Glands

1.2.2.7 Inflammation of Skin

1.2.2.8 Lipid Contents

1.2.2.9 Partition Coefficients

1.2.2.10 Molecular Weight

1.2.2.11 Degree of Ionization

1.2.2.12 Type of Vehicles

1.2.2.13 Allergies or hypersensitivity

1.2.3 Pathway of Transdermal Permeation

Permeation through the skin can occur by diffusion via multiple routes, including(17):

a) Transdermal Permeation: This mechanism involves the passage of substances through the stratum corneum, which is the outermost layer of the epidermis. Transdermal permeation is a common route for drug delivery through the skin, particularly for transdermal patches(18).

b) Intercellular Permeation: Intercellular permeation refers to the movement of substances between cells of the stratum corneum, which is the topmost layer of the epidermis. This intercellular route allows molecules to travel through the spaces between these cells(19).

c) Transappendage Permeation: Transappendage permeation involves the passage of substances through structures such as hair follicles, sebaceous glands, and sweat glands. These structures can serve as pathways for molecules to penetrate the skin(20).

It's important to note that many substances, particularly smaller molecules, primarily penetrate the skin through the intercellular micro route, which involves traveling between the cells of the stratum corneum. Consequently, various enhancement techniques have been developed to disrupt or bypass the elegant molecular architecture of the stratum corneum to facilitate the delivery of drugs or other active substances through the skin. These techniques aim to enhance the permeation and absorption of substances, enabling more effective and controlled topical drug delivery (21).

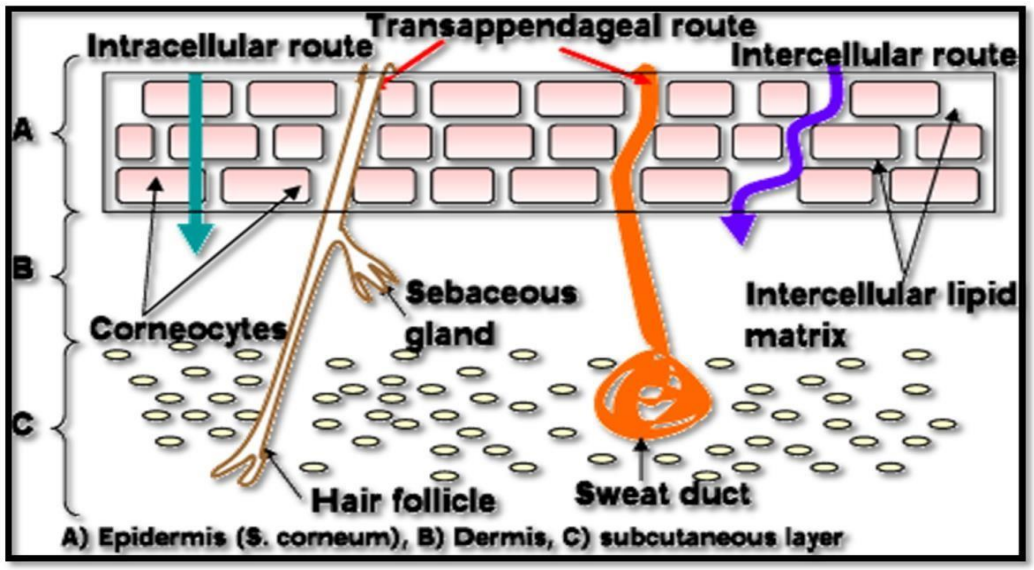

Fig-2: Simplified representation of skin showing routes of penetration

1.3 Emulgel

An emulgel is a unique dosage form created by combining a gel and an emulsion. Emulgels offer significant advantages over both novel vesicular systems and conventional drug delivery systems, making them a compelling choice for various applications(22).

Here are some of the key advantages of emulgels(23):

1.Thixotropic: Emulgels exhibit thixotropy, meaning they become less viscous when subjected to shear forces, allowing for easy spreading during application.

2.Greaseless: They are non-greasy, which enhances patient comfort and compliance.

3.Easily Spreadable: Emulgels can be applied smoothly and evenly, promoting better drug distribution.

4.Easily Removable: They can be easily washed or wiped off after use.

5.Emollient: Emulgels have a soothing and moisturizing effect on the skin.

6.Non-Staining: They do not leave unsightly stains on clothing or skin.

7.Water-Soluble: Emulgels are water-soluble, simplifying application and removal.

8.Longer Shelf Life: They offer extended stability and a longer shelf life compared to some other formulations.

9.Bio-Friendly: Emulgels are generally well-tolerated by the skin and considered bio- friendly.

10.Transparent & Pleasing Appearance: Emulgels have an aesthetically pleasing transparent appearance.

Emulgels overcome this limitation by employing an emulsion-based approach. This allows even hydrophobic therapeutic agents to be successfully incorporated and delivered within the gel matrix(25). This combination of properties and flexibility makes emulgels an attractive option for both cosmetic and pharmaceutical applications.

1.3.1 Advantages of Emulgel

Emulgels, which combine the characteristics of gels and emulsions, offer several significant advantages, making them a preferred choice for various applications(26):

a. Effective Delivery of Lipophilic Drugs: Emulgels excel at delivering lipophilic drugs by incorporating them within the gel-based drug-oil-in-water emulsion. This overcomes solubility challenges that hinder drug release into the systemic circulation. Emulgels improve the stability and drug release profile of lipophilic drugs, combining the benefits of both emulsion and gel in a single formulation(13).

b.Exceptional Stability and Longer Shelf Life: Emulgels are among the most stable topical formulations and demonstrate longer shelf life. Unlike hygroscopic issues in topical powders and phase inversion problems in creams, Emulgels do not face such stability challenges, making them superior to traditional topical preparations(27).

c. Higher Loading Capacity: Emulgels offer a greater loading capacity compared to alternative topical preparations. The loading capacity of emulgels is also higher than nanoparticle-based preparations like niosomes and liposomes due to their low entrapment efficacy(28).

d. Cost Efficiency: Emulgels are cost-efficient as the production process is relatively straightforward, requiring minimal steps and no specialized equipment. Most ingredients are readily available and cost-effective, reducing the overall production costs(29).

e. Controlled Release: Emulgels facilitate controlled release of active ingredients, thereby improving the half-life of the drug(30).

f. Reduced Risk of Drug Degradation: The production of Emulgels does not require intense sonication, reducing the risk of drug degradation and leakage(30).

g. Enhanced Patient Compliance: Emulgels are preferred by patients due to their ease of application, non-greasiness, and overall pleasant characteristics, contributing to higher patient compliance(31).

h. Bypassing First Pass Metabolism: Emulgels can bypass first-pass metabolism, potentially reducing gastrointestinal adverse reactions that may occur with oral administration(31).

i. Targeted Action and Easy Termination: Emulgels enable targeted drug delivery, making it easier to terminate therapy when needed.

These advantages highlight the versatility and effectiveness of emulgel as a dosage form for various pharmaceutical and cosmetic applications, addressing key challenges and enhancing patient experience and treatment outcomes(31).

1.3.1 Challenges and Considerations in Emulgel Formulations

While emulgels offer numerous advantages, they also come with specific challenges and considerations:

a. Limited Absorption for High Molecular Weight and Large Particle Size Drugs: Emulgels may have limitations when it comes to drugs with high molecular weight and larger particle sizes. These substances may struggle to effectively penetrate the skin through the emulgel formulation.

b. Formation of Small Bubbles: Emulgels can sometimes develop small bubbles within the formulation. These bubbles can reduce the penetrability of the drug and affect the overall efficacy of the emulgel.

c. Skin Irritation: Skin irritation is a common concern, particularly with certain active ingredients or in individuals with sensitive skin. Emulgels, like other topical formulations, may lead to skin irritation in some cases. It's crucial to carefully select and formulate ingredients to minimize this risk(32).

To address these challenges and considerations, it is essential for formulators to carefully assess the characteristics of the drug and the intended application. They should also conduct appropriate testing and consider patient-specific factors to optimize the formulation for safety and effectiveness. Additionally, addressing any issues related to bubbles in the emulgel and selecting appropriate emulsifiers and excipients can help enhance the performance of the formulation(32).

1.3.2 Classification of Emulgel

The choice of emulgel type depends on the specific requirements of the formulation, including the desired transparency, stability, and permeability, as well as the nature of the active ingredients to be delivered. Each category has its own advantages and considerations, making it important for formulators to select the most suitable emulgel type for the intended application(26). Emulgels can be classified into three major categories based on particle size, each with distinct characteristics and advantages:

a) Macroemulgel: Particle Size greater than 400 nanometers (nm). Macroemulgels are the most commonly used emulgels. They are characterized by a larger particle size, making them opaque and homogenous. However, under a microscope, the droplets of the emulsion can be easily detected due to their large size. Macroemulgels are thermodynamically unstable, which means that over time, the emulsion may separate or change in appearance(33).

b) Nanoemulgel: Particle Size: Less than 100 nanometers (nm). Nanoemulgels are formulated by incorporating a nanoemulsion into the gel. They aim to develop a thermodynamically stable dispersion that is transparent and homogenous in nature. The droplets in nanoemulgels are very small, typically less than 100nm in size, resulting in better permeability. Nanoemulgels are designed to be more stable than macroemulgels, making them a preferable choice for certain applications(4).

c) Microemulgel: Particle Size between 100nm and 400nm. Microemulgels fall in between macroemulgels and nanoemulgels in terms of particle size. They offer a compromise between the transparency and permeability of nanoemulgels and the simplicity and stability of macroemulgels. Microemulgels are relatively stable and can be a versatile option for various formulations(34).

1.3.3 Components of Emulgel:

Emulgels are formulated by carefully selecting and combining these key components to create a stable, effective, and versatile drug delivery system capable of accommodating a wide range of drug types and therapeutic applications. Emulgels, which are versatile formulations used for delivering both lipophilic and hydrophilic drugs, incorporate emulsions into a gel matrix. Emulgels are formulated by carefully selecting and combining these key components to create a stable, effective, and versatile drug delivery system capable of accommodating a wide range of drug types and therapeutic applications. The choice of emulsion type (oil-in-water or water-in-oil) depends on the nature of the drug to be delivered.

Emulgels are composed of essential components, including(35):

a) Aqueous Material:

Commonly Used: Water and alcohol are the most frequently used aqueous materials, forming the aqueous phase of the emulsion(36).

b) Oils:

Commonly Used Oils: Mineral oils, such as liquid paraffin, are the preferred choice for the oily phase of the emulsion

in emulgels. Mineral oil can be used alone or in combination with other oils, such as hard and soft paraffin. Castor oil, known for its laxative properties, can also be used. Some other oils selected for their medicinal properties include jojoba oil, archais oil, cottonseed oil, maize oil, and fish liver oil(36).

c) Emulsifiers:

Role: Emulsifiers are crucial for maintaining the stability of the emulsion. They are surfactants used for the process of emulsification. Emulsifiers for Oil-in-Water Emulsion: Nonionic surfactants with an HLB (Hydrophilic-Lipophilic Balance) higher than 8, such as Spans and Tweens, are used for the formation of oil-in-water emulsions.

Emulsifiers for Water-in-Oil Emulsion: For water-in-oil emulsions, where mineral oils like liquid paraffin have an HLB lower than 8, they are used. Common Emulsifiers: Examples of commonly used emulsifiers include PEG 40 stearate, Span 80, Tween 80, stearic acid, and sodium stearate(36).

d) Gelling Agent:

Role: Gelling agents provide gel-like properties to the formulation, enhancing its consistency. Relationship with Drug Release: Studies have shown that the concentration of the gelling agent is inversely proportional to the extent of drug release. Common Gelling Agents: Carbopol, HPMC 2910, HPMC K4M, and others are commonly used gelling agents for emulgels(36).

e) Permeation Enhancer:

Role: Permeation enhancers are responsible for improving the skin's penetration of the drug. They achieve this by implementing various mechanisms to enhance skin permeability. These mechanisms may include disrupting the stratum corneum or altering skin proteins. Common Permeation Enhancers: Examples of commonly used permeation enhancers are oleic acid, clove oil, lecithin, eucalyptus oil, menthol, and more(36).

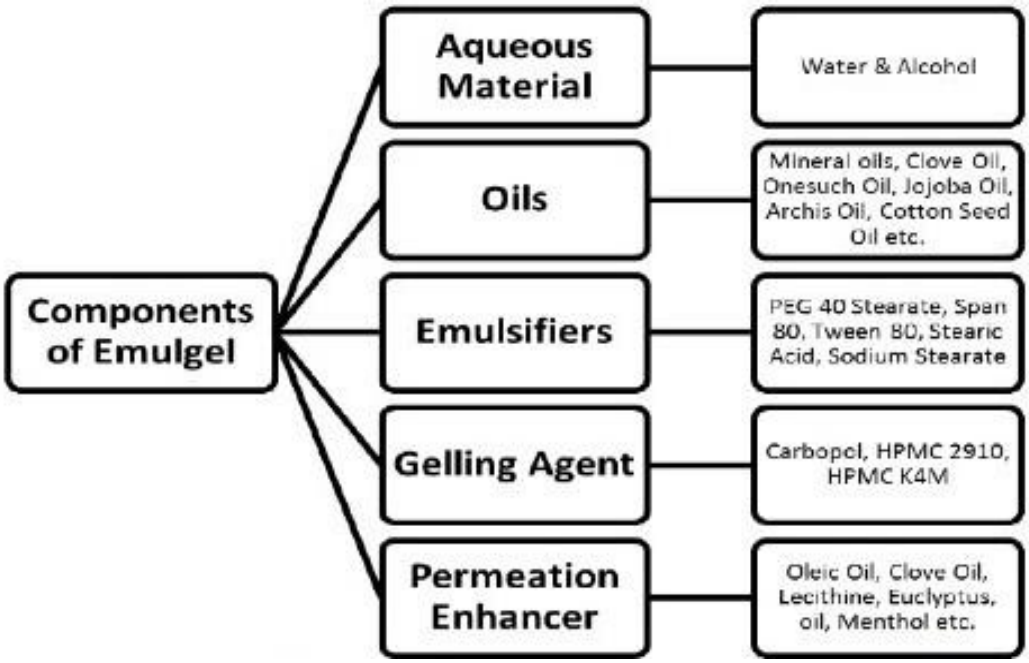

Fig-4: Components of Emulgel along with frequently implemented compounds

1.3.4 Method of Preparation of Emulgel

Emulgels, as the name suggests, consist of two major components: an emulsion and a gel. These components are prepared separately and then combined to create the emulgel formulation. The process typically involves the following steps(12):

1. Preparation of Emulsion: The emulsion is created by mixing the aqueous and oily phases together to form a homogeneous biphasic dosage form. Depending on the nature of the drug and the desired characteristics of the emulsion, either an oil-in-water or water-in- oil emulsion may be prepared(11).

2. Preparation of Gel: A gel is prepared separately by adding a gelling agent to an aqueous or oily medium. The choice of gelling agent and medium depends on the formulation requirements and the drug to be delivered(37).

3. Incorporation of Emulsion into Gel: The gel and the emulsion are gently mixed to combine them and develop the emulgel formulation. This step ensures the even distribution of the emulsion within the gel matrix. An alternative method for the development of emulgels involves the following three major steps(38):

- Dispersion of Polymer in Water: The polymer is dispersed by stirring in water, typically at 900 rpm for about 20 minutes. This step aims to create a stable aqueous dispersion of the polymer.
- Neutralization of the Polymeric Aqueous Dispersion: Sodium hydroxide solution is used to neutralize the polymeric aqueous dispersion. This neutralization process results in a clear and stable gel formation.
- Emulsification of the Oil Phase: After neutralization, the polymer undergoes complete hydration to form a gel. The oil phase is emulsified, and the two components are then combined to create the emulgel formulation.

The specific method chosen for emulgel preparation may vary depending on the desired characteristics of the formulation and the nature of the drug being delivered. Careful attention to the preparation process is essential to ensure the stability and effectiveness of the emulgel as a drug delivery system (35).

Fig-5: Emulgel preparation method

2. REVIEW OF LITERATURE

1) Montero Matamala A. et al. (2022)

Acute postoperative pain is a normal and expected part of the patient's postsurgical trajectory, and its intensity, severity, and duration vary with surgery-related and patient factors. In a subset of patients, postoperative pain does not resolve as the tissue heals but instead transitions to chronic postoperative pain, a challenging condition to treat and one associated with decreased quality of life, sleep and mood disorders, and neuropathy. Promptly and adequately treating acute postoperative pain can reduce the risk that it will transition into chronic postoperative pain. Numerous agents are available that may help treat postoperative pain, including nonsteroidal anti-inflammatory drugs, opioids, antidepressants, anticonvulsants, and others. In this connection, it is also important to consider patient factors, such as mental health status and comorbidities, as well as the type and duration of surgery(42).

2) Mayoral Rojals V. et al. (2022) Postoperative pain is prevalent and often undertreated. There is a risk that untreated or sub- optimally treated postoperative pain may transition into chronic postoperative pain, which can be challenging to treat. Clinical guidelines recommend the use of multimodal analgesia, including nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and, in some cases, opioids. NSAIDs are a broad class of drugs with different attributes such

as cyclo-oxygenase (COX)-1 or COX-2 selectivity, onset of action, and analgesic potency. NSAIDs are associated with gastrointestinal and cardiovascular side effects and should be administered at the lowest effective dose for the shortest effective duration but can be effective in postoperative pain. The role of opioids in postoperative analgesia is longstanding but has recently come under scrutiny. Opioids are often used in multimodal analgesic combinations in such a way as to minimize the total consumption of opioids without sacrificing analgesic benefit. Special clinical considerations are required for surgical patients already on opioid regimens or with opioid use disorder(43).

3) Okolišan D. et al. (2022)

This study proposes a simple and effective method to obtain ultra-thin membranes based on κ-carrageenan. Two types of membranes were obtained, one based on κ-carrageenan and the second type based on κ-carrageenan, hydroxyethyl cellulose and the plasticizer (glycerol). Three non-steroidal anti-inflammatory drugs (Dexketoprofen trometamol, Meloxicam, Diclofenac sodium) and a glucocorticoid (Dexamethasone) were introduced, looking for the best option for incorporation. The obtained membranes were characterized by FTIR, TG/DTG and UV-VIS methods and the data collected following these methods indicated success in terms of the incorporation of the active substance, as well as the high thermal stability in the temperature range 37-100 °C of both the matrices of membrane types, as well as the membranes with the drug incorporated(44).

4) Zhang X. et al. (2022)

Biowaiver based on the biopharmaceutics classification system (BCS) has been widely used in the global market for the approval of new generic drug products to avoid unnecessary in vivo bioequivalence (BE) studies. However, it is reported that three out of four formulations of dexketoprofen trometamol (DEX) tablets (BCS class I drug) failed the first BE study(45).

5) Zobdeh F. et al. (2022)

This systematic review summarizes the impact of pharmacogenetics on the effect and safety of non-steroidal anti-inflammatory drugs (NSAIDs) and antidepressants when used for pain treatment. A systematic literature search was performed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines regarding the human in vivo efficacy and safety of NSAIDs and antidepressants in pain treatment that take pharmacogenetic parameters into consideration. Studies were collected from PubMed, Scopus, and Web of Science up to the cutoff date 18 October 2021(46).

6) Joanna K. et al. (2022)

The findings of the review confirmed that dexketoprofen is a very good pain reliever that is more potent than paracetamol. Dexketoprofen has a similar effect to lidocaine and dexmedetomidine. Dexketoprofen at the dose of 25 mg combined with tramadol at the dose of 75 mg therapy is effective in relieving acute and postoperative pain. The combination of metoclopramide and dexketoprofen gave better results than monotherapies in patients with migraine(47).

7) Cureus. et al. (2022)

Acute postoperative pain is a normal and expected part of the patient's postsurgical trajectory, and its intensity, severity, and duration vary with surgery-related and patient factors. In a subset of patients, postoperative pain does not resolve as the tissue heals but instead transitions to chronic postoperative pain, a challenging condition to treat and one associated with decreased quality of life, sleep and mood disorders, and neuropathy. Promptly and adequately treating acute postoperative pain can reduce the risk that it will transition into chronic postoperative pain(48).

8) Mejía-Abril G and Zubiaur P. (2021)

FA-S and DO have been consultants or investigators in clinical trials sponsored by the following pharmaceutical companies: Abbott, Alter, Chemo, Cinfa, FAES, Farmalíder, Ferrer, GlaxoSmithKline, Galenicum, Gilead, Italfarmaco, Janssen-Cilag, Kern, Normon, Novartis, Servier, Silver-pharma, Teva, and Zambon. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest(49).

9) Mititelu-Tartau L. et al. (2021)

The present study reports on the in vivo biocompatibility investigation and evaluation of the effects of liposomes containing dexketoprofen in somatic sensitivity in rats. Original liposomes entrapping dexketoprofen, with mean size of 680 nm and good stability, were designed. Laboratory analysis indicated no substantial variances between the three treated groups. The treatment with liposomes containing dexketoprofen resulted in a prolongation of the latency time response, statistically significant in the interval between 90 min and 10 h, in the hot plate test(50).

10) Barkat Ali et al. (2020)

The main aim of the topically applied drugs is to provide local drug contact to the skin and minimize general absorption of drugs. Ocimum basilicum (OB) is popular for folk medicines, having official acceptance in many countries. The aim of this study was to formulate and evaluate the efficacy of topical application of OB-based emulgel on wound healing in animal model. The prepared formulations (OB emulgel) were assessed for FTIR analysis, stability studies, physical appearance, rheological behavior, spreadability, patch/sensitivity test and in vitro drug release. The in vivo wound healing effect was evaluated and compared with commercially available Silver Sulfadiazine cream Quench® in wound-induced rabbits by macroscopic and histopathological evidence. The OB extract/drug was compatible with the selected polymer and other excipients and indicated the suitability of the polymers/excipients for preparation of topical emulgel(51).

11) Alper A. et al. (2021)

Dexketoprofen trometamol (DT)-loaded poly-lactic-co-glycolic acid) (PLGA) NPs were produced by double emulsion-solvent evaporation method. The NPs were variously characterized for drug loading and release, particle profile, as well as by thermal analysis, x-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR) and nuclear magnetic resonance analysis (1H-NMR). Furthermore, the NPs were evaluated for cytotoxicity against NIH-3T3 cells by 3-(4,5-dimethylthiazol-2- Yl)-2,5- diphenyltetrazolium bromide (MTT) assay. Results showed that the DT-loaded NPs demonstrated nano structural characteristics and extended drug release. Particle size was in the range of 243 and 295 nm which remained unchanged in drug stability testing in simulated gastrointestinal media. Encapsulation efficiency ranged from 49 – 64 % for all the formulations. Higuchi and Korsmeyer-Peppas were the best-fit release kinetic models for the NPs containing 5 and 10 % DT, respectively. The NPs with 10 % DT presented no significant cytotoxicity at the doses and periods studied(52).

12) Kaya C. et al. (2019)

Intrathecal administration of non-steroidal anti-inflammatory drugs is more efficacious for post-operative pain management. Cyclooxygenase inhibiting non-steroidal anti- inflammatory drugs like (S) (+)-Ketoprofen, may be effective at lower intrathecal doses than parenteral ones. Preclinical safety regarding possible neurotoxicity associated with the intrathecal (S) (+)- Ketoprofen was not evaluated. Here we analyzed the neurotoxicity of intrathecally administered (S) (+)-Ketoprofen in rats(53).

13) Yin LN and Zhang YW (2019)

The influence of chiral excipient D-chitosan (CS) on the stereoselective release of racemic ketoprofen (rac-KET) microspheres has been investigated in comparison to those microspheres containing individual enantiomers in vitro and in vivo. Stereoselectivity was observed in vitro release test, with R-KET release slightly higher than that of S-KET, especially in 3% rac-KET loading microspheres. Stereoselectivity is dependent on the content of chiral excipient and pH of release medium(54).

14) Esparza-Villalpando V. et al. (2018)

Use of dexketoprofen trometamol (DEX) to manage acute postoperative pain. However, controversies surround the impact of the use of this drug in preoperative analgesic protocols. The aim of the present meta-analysis was to evaluate the effectiveness of the preoperative administration of DEX under postoperative pain conditions. Electronic and manual searches were conducted through diverse electronic databases. A systematic review and meta-analysis to evaluate the analgesic efficacy of the preoperative administration of DEX was performed including Randomized Clinical Trials (RCTs) published between 2002 and 2017. Suitable individual studies were evaluated through a quality system, and the

data were extracted and analyzed(55).

15) Rambe AS. et al. (2017)

The purpose of this study is to see the effect of Dexketoprofen on TNF-α, IL-1, and IL-6 serum levels in Chronic Tension-Type Headache (CTTH) patients and its correlation with pain severity. The study subjects were recruited consecutively from the study population.

Venous blood was taken at baseline to measure serum levels of TNF-α, IL-1, and IL-6 and after ten consecutive days of Dexketoprofen 25 mg once daily. Dexketoprofen decreased pain intensity significantly ($p = 0.001$) but had no effect on TNF-α IL-1 nor IL-6 serum levels. NRS score had a weak and non-significant negative correlation with TNF-α, a weak and non-significant positive correlation with IL-1, and a very weak and non-significant negative correlation with IL-6 serum levels(56).

16) Fornasari D. et al. (2017)

Acute and chronic pain have an important socio-economic impact. To help physicians to choose the appropriate drug, especially for cancer pain, in 1986 WHO developed a three- step analgesic "ladder" for cancer pain relief in adults. Later it has also been used for acute pain and chronic noncancer pain. In step I nonsteroidal anti-inflammatory drugs (NSAIDs) are considered with or without adjuvants, in step II the use of weak opioids for mild- moderate pain, with or without NSAIDs and adjuvant, is suggested, while the step III is reserved to strong opioids for moderate-severe pain with or without non-opioids or adjuvants(57).

17) Gaskell H. et al. (2017)

To assess the efficacy and safety of single dose oral ketoprofen and oral dexketoprofen compared with placebo for acute postoperative pain, using methods that permit comparison with other analgesics evaluated in the same way, and criteria of efficacy recommended by an in-depth study at the individual patient level (58).

18) J Clin Anesth. et al. (2016)

The aim of this study is to compare the effects of intravenous single-dose dexketoprofen trometamol and diclofenac sodium 30 minutes before the end of the surgery on relief of postoperative pain in patients undergoing laparoscopic cholecystectomy(59)

19) Khullar R. et al. (2012)

The objective of the study was to prepare emulgel of mefenamic acid, a NSAID, using Carbapol 940 as a gelling agent. Mentha oil and clove oil were used as penetration enhancers. The emulsion was prepared, and it was incorporated in gel base. The formulations were evaluated for rheological studies, spreading coefficient studies, bioadhesion strength, skin irritation studies, in vitro release, ex vivo release studies, anti- inflammatory activity and analgesic activity. Formulation F2 and F4 showed comparable analgesic and anti-inflammatory activity when they compared with marketed diclofenac sodium gel. So, it can be concluded that topical emulgel of mefenamic acid possess an effective anti-inflammatory and analgesic activity(60).

20) Zippel H and Wagenitz A. (2006)

This study aimed to evaluate the analgesic efficacy and tolerability of dexketoprofen trometamol, a nonsteroidal anti-inflammatory drug, in comparison with that of racemic ketoprofen (both administered by intravenous infusion), in patients with postoperative pain(61).

21) Barbanoj MJ et al. (2001)

Dexketoprofen trometamol is a water-soluble salt of the dextrorotatory enantiomer of the nonsteroidal anti-inflammatory drug (NSAID) ketoprofen. Racemic ketoprofen is used as an analgesic and an anti-inflammatory agent and is one of the most potent in vitro inhibitors of prostaglandin synthesis(62).

Conclusion & Discussion – The relevant drug delivery system encompasses a choice of dosage forms considered for application to the skin, contribution an ideal alternative for addressing skin disorders and contained treatment. Notably, this system presents the distinct advantage of bypassing first-pass metabolism, which can drastically alter remedy

efficacy. Moreover, it mitigates the risks and inconveniences associated with intravenous route therapy. Topical formulations are available in diverse consistencies, including solid, semisolid, and liquid forms, further enhancing their adaptability and efficacy in healthcare and pharmaceutical applications. emulgel containing drug can be most promising and convenient drug delivery system.

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