Emulgel: A Recent Approach for Topical Drug Delivery System

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Abstract—**Emulgel is a new approach to topical drug delivery that combines gel and emulsion for dual-controlled release. It is a more advanced NDDS technology. Emulgel is made from a variety of polymers that also serve as thickening and emulsifying agents. The ability of these polymers to gel raises the viscosity of the aqueous phase while simultaneously lowering surface tension and interfacial tension, resulting in stable emulsions[1]. Considered in multiple contexts, emulgel exhibits notable advantages over conventional and novel vesicular systems[2]. The emulgel is greaseless, thixotropic, spreadable, emollient, readily removable, water-soluble, non-staining, has an extended shelf life, is transparent, and looks good. These are just a few of the benefits of using it in dermatology. In many aspects, these emulgels are better than both novel and traditional vesicular systems[3]. Compared to existing topical drug delivery technologies, emulgels are preferable because different permeability enhancers can increase the impact. Actually, the presence of a gelling component in the water phase of a normal emulsion results in the creation of an emulgel. Analgesic and antifungal drugs can also contain emulgels[4].**

Index Terms—**Emulgel, Transdermal, Gelling agents, penetration enhancers.**

I. INTRODUCTION

Different methods of administration were used in the past to treat every condition. The following were some of the earlier techniques: topical, parenteral, sublingual, oral, rectal, and inhalation. However, when a person has skin diseases like dermatitis, acne, psoriasis, and so forth, topical delivery is advised. At this point, the drug is applied topically to treat the skin[5]. Even though topical treatment has been available for a long, new methods and instruments are being developed to improve patient adherence[6]. Drugs are administered topically to act at the application site or to have systemic effects[7]. Since pharmaceutical preparations have some local effect, they are usually given topically with the goal of providing prolonged local contact with minimal systemic medicine absorption. For their targeted effects on the skin, drugs such as emollients, protectants, antiseptics, and antifungal agents are applied topically[8]. One of the main advantages of the topical administration technique is that it avoids first-pass metabolism[9]. Topical treatments also avoid the hazards and inconveniences of intravenous therapy, as well as the different circumstances of absorption that come with it, like changes in pH, the presence of enzymes, and the time it takes for the stomach to empty. Another name for localized medicine delivery systems is topical drug delivery systems[10]. It is commonly used for dermatological and cosmetic skin, both healthy and injured. If the medicine is in solution, non-electrolyte, or has a favorable lipid-water partition coefficient, its absorption is enhanced. When administering topical drugs, it's critical to comprehend the factors impacting percutaneous absorption[11]. Molecules can enter the skin in three different ways: through sweat ducts, sebaceous follicles, or the intact stratum corneum. Over 99% of the total skin area that can be used for percutaneous drug absorption is located on the stratum corneum[12]. A network of colloidal solid particles is used to capture large volumes of aqueous or hydroalcoholic liquid to create gels, a relatively novel type of dosage form. These particles may consist of inorganic materials such as aluminum salts or organic polymers that are produced artificially or from natural sources. They have a bigger aqueous component than the ointment or cream basis, which facilitates easier drug migration via a vehicle that is essentially liquid and increases drug solubility[13]. When semi-solid preparations for cutaneous application are made, the

efficiency and necessity of the chosen preservative must be demonstrated to the satisfaction of the relevant authority. An antimicrobial preservative is a component of these preparations. Evaluation criteria for the formulation's preservative characteristics are derived from the effectiveness of antimicrobial preservation. In order to maintain sterility, prevent the growth of bacteria, and prevent the entrance of contaminants, sterile semi-solid preparations for topical administration are made utilizing certain materials and techniques[14]. To some extent, emulsions are elegant, and they may be easily removed when necessary. They also have a high level of skin penetration. Thixotropic, greaseless, readily spreadable, easily removable, emollient, non-staining, water-soluble, longer-lasting, transparent, biocompatible, and aesthetically pleasant are just a few of the advantageous qualities of emulates for use in dermatology[15]. Six next, using a suitable statistical design, the emulsion is combined with the gel basis to create an ideal emulgel formula with different grades and concentrations of the gelling agent. The component that contains oil causes a rise in penetration. It is possible to select each and every excipient to enhance the pharmacological impact of the antibacterial activity[16]. Gels are produced when a sizable amount of hydroalcoholic or aqueous liquid is trapped by a network of colloidal solid particles. Gels have numerous advantages, but one major drawback is that they present a big challenge for the administration of hydrophobic drugs[17].

Skin structure and physiology

Making up almost 15% of an adult's total body weight, the skin is the biggest organ in the human body. It creates a capsule that isolates the internal body structure from the outside world when it joins forces with the mucosal lining of the digestive, urogenital, and respiratory systems. An average individual weighing 70 kg and having 1.8 square meters of skin covers 10 hair follicles, 12 nerves, and 15 sebaceous glands. Three blood vessels and 100 sweat glands

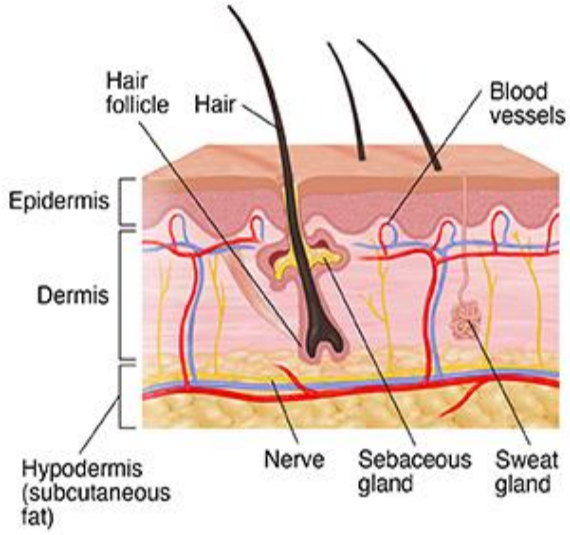

Fig No. 1: Skin structure

with a aggregate of of 92 cm. The pH of the skin varies from 4 to 5.6. Sweat and adipose acids buried from sebum influence the pH of the skin face. The temperature of the skin varies in a range of 30 to 40 degrees, depending on the environmental conditions[18].It performs numerous vital functions, including protection against external physical, chemical, and birth assaulters, as well as forestallment of redundant water loss from the body and a part in thermoregulation. The skin is nonstop, with the mucous membrane lining the body's surface[19]. A unique aspect of dermatological pharmacology is the direct availability of the skin as a target organ for opinion and treatment. The skin acts as a two- way hedge to help the immersion or loss of water and electrolytes[20]. There are three primary mechanisms of topical medicine immersion transcellular, intercellular, and follicular. utmost medicines pass through the torturous path around corneocytes and through the lipid bilayer to feasible layers of the skin[21]. The coming most common(and potentially underrecognized in the clinical setting) route of delivery is via the pilosebaceous route. These include, among others, gels and creams for vaginal incentive infections, topical creams for skin infections, and creams to soothe arthritis pain. New technologies now allow other medicines to be absorbed through the skin(transdermal). The complex organ known as the skin's top function is to" maintain the inwards in and

outdoors out," acting as a barrier[22]. It's composed of three layers the dermis, hypodermis, and epidermis. Each subcaste has a unique makeup and set of characteristics [23].

Epidermis

It is the skin's outermost layer, and its thickness is about 150 micrometers. There are epithelial cells in it. There are both dead and living cells among these cells. The older cells are forced upward by the rapid division of these young cells at the base of the epidermis[24]. Glucose serves as the energy source for the lowest layers of the epidermis, and lactic acid, the final byproduct of metabolism, builds up in the skin. The epidermis's layers are

- Stratum Germinativum (Growing Layer)
- Malpighion Layer (pigment Layer)
- Stratum spinosum (prickly cell layer)
- Stratum Granulosum (Granular Layer)
- Stratum Lucidum
- Stratum Corneum (Horny Layer)

Dermis

The dermis is a noncommittal subcaste that sits between the subcutaneous adipose zone and the epidermis. It consists substantially of asemi-gel matrix of mucopolysaccharide" ground substance" interwoven in a thick network of structural protein filaments similar as collagen, reticulum, and elastin[25]. The skin's inflexibility can be attributed to the network or gel structure of its cells. The stringy towel spreads out beneath the dermis and combines with the subcutaneous fat- containing towel. Dermal metabolism is significantly told by protein production[26].

Subcutaneous towel(hypodermis)

The superficial fascia, a film of fat-rich areolar towel that connects the dermis to the underpinning deconstruction, makes up this subcaste. Only the face area has large highways and modes.

The Explanation Behind The Use of Emulgel

Topical medicinal medications, similar ointments and creams, have certain downsides due to their sticky nature or demand for rubbing. Reduced dissipation, penetration, and patient compliance are some of these downsides. The capability of gels to circulate hydrophobic specifics is limited. numerous different infections were formerly treated using poultices, creams, and ointments. Emulgel was taken into consideration for operation in ornamental and medicinal operations in malignancy of multitudinous downsides and contributing rudiments. numerous medicines are applied topically to the skin or mucous membranes in an attempt to pharmacologically modify a towel's response or enhance or restore a abecedarian skin function. We relate to these products as dermatological or topical products. There are several downsides to several of the generally used topical curatives, including ointments, creams, and lotions[27]. They're naturally sticky, which causes discomfort for the case; they've a low spreading measure, making it delicate to apply by rubbing; and they've a stability issue. Transparent gels are being used more frequently in medicinal and ornamental medications as a result of all these aspects falling under the main order of circumfluous medications. Gels have several benefits, but one significant debit is the manner hydrophobic specifics might be used. in order for gels to efficiently administer and integrate indeed a hydrophobic remedial molecule[28]. A colloidal material, generally conforming of 99 percent water, is paralyzed by face pressure that occurs between the material and a network of macromolecules made up of the little quantum of hardening substance present. Despite all of their benefits, one significant debit of gels is the way hydrophobic specifics can be given. to stabilize hydrophilic medicine phrasings to effectively administer and absorb a hydrophobic remedial component[29]. The operation of gel details in medicinal and ornamental phrasings has increased as a result of these failings of a class of semi-solid drugs. The way hydrophobic specifics are administered continues to be a major problem in malignancy of these factors[30].

Emulgel

Emulgel is created by combining gel with mixes of oil painting in water and water in oil painting. The water-in- oil painting form of delivery is used for hydrophobic medicines, and the oil painting- in- water type is used for lipophilic drugs[31]. mixes have a high rate of skin penetration, a certain fineness, and ease of junking when necessary. One specific that sets them piecemeal is their ease of skin penetration[32]. Emulgels are a fairly new product, although the assiduity is considered to be developing. Emulgels are now a fascinating and grueling cure type to exploration as a

result. When applied topically, emulgel is believed to have several advantages. mixes correspond of two immiscible phases the dispersed phase and the nonstop phase, which are made more stable by the addition of the emulsifying agent. Emulgels are O/ W or W/ O phrasings in which the medicine patches are trapped in the internal phase and also move across the surface phase to gradationally access the skin and produce a controlled action. Emulgels are used each over the world to treat a range of bacterial, viral, and contagious impurities that affect the skin, in addition to having colorful anti-inflammatory properties[33].

Advantages

1. Preventing first-pass metabolism and gastric intolerances
2. More selective for a specific site.
3. Increase adherence from patients.
4. Suitability for self-medication.
5. Hydrophobic medications are simple to include in gels through the use of o/w emulsions.

1. Incorporation of hydrophobic drugs

In general, d/o/w emulsions can be used to successfully integrate hydrophobic medicines into gels. However, the majority of them cannot be simply merged into a gel foundation. This may be because solvency can function as a barrier, and the problem is brought up when the medication is released[34].

2. Better loading capacity

Other cutting-edge strategies, such as liposomes and niosomes, are nanosized and may leak and have lower trapping efficiency because of their vesicular architecture. However, gels have a significantly higher loading capacity because of their extensive network.

3. Stability is better

Emulgel shows better stability than other transdermal preparations[35]. For example, powders are hygroscopic in nature, creams show breaking or phase inversion, and ointment, on the other hand, shows rancidity.

4. Production feasibility and low preparation cost

The preparation of emulgels comprises simpler and shorter steps, which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Furthermore, the materials used are easily available and cheaper. Hence, it decreases the production cost of emulgels.

Disadvantages

Emulgels do, however, have drawbacks in addition to benefits, which leads to significant restrictions on the administration of hydrophobic medications[36]. These days, emulgel is employed to get over this restriction. Its disadvantage is thus mitigated. Hydrophobic medications can benefit from gels' special qualities in this way. The main drawbacks of the medication are its large particle size, which prevents it from passing through skin; its low permeability; the possibility of skin allergies or contact dermatitis; and the appearance of bubbles when applying emulgel[37,38].

Important Constituents of Emulgel Preparation

1. Aqueous Material: This makes up the emulsion's aqueous phase. Alcohol and water are often used as agents[39]
2. Oils: These components produce the oily phase of the emulsion. Mineral oils are frequently used as the drug's transport and for their occlusive and sensory qualities in topically applied emulsions. They can be used alone or in combination with soft or hard paraffins. Oral formulations often use nonbiodegradable mineral and castor oils, which have a laxative effect on a local level, along with fish liver oils and other fixed oils made from vegetables (such as arachis, cottonseed, and maize oils) as nutritional supplements [40,41].
3. Emulsifiers: Emulsifying chemicals are used to promote emulsification during the manufacturing process and to control stability during a shelf life that can vary from days for spontaneously formed emulsions to months or years for commercial preparations. Stearic acid 34, polyoxyethylene sorbitan monooleate 33 (Tween 80), sorbitan monooleate (Span 80), sodium stearate, and polyethylene glycol 4031 stearate are a few examples[42]
4. Gelling Agent: These are the agents used to increase the consistency of any dosage form and can also be used as thickening agents[43,44].
5. Permeation Enhancers: These substances cause a transient and reversible increase in skin permeability by partitioning into and interacting with skin components[45]

Mechanisms of permeation enhancers

Three primary mechanisms are possible for penetration enhancers to function:

• disruption of the stratum corneum lipid's highly organized structure.
• interaction with the protein found inside cells.

• Better medication, co-enhancer, or solvent distribution inside the stratum corneum. One of three routes is changed by the enhancers. Causing a change in the structure of proteins or swelling of solvents is crucial for modifying the polar route. The fluidity of the stratum corneum's lipid-protein component was enhanced by the fatty acid enhancers. Certain enhancers modify the multilaminate pathway for penetration, acting on both polar and non-polar pathways. Enhancers have the ability to boost a drug's diffusivity via skin proteins. The kind of enhancer used has a big influence on how the product is developed and designed. The penetration enhancer should be cosmetically acceptable with appropriate skin. [46,47]

They ought not to have any pharmacological action inside the body. It implies that they ought not to be tied to any of the receptor sites. They ought to be worthy of the skin cosmetically and should not cause any kind of skin irritation or disturbance. properties like non-toxicity and less irritability, and there should be non-unfavorably susceptible[48].

They ought to show favorable compatibility with the drugs and the excipients added [49]. When it is removed from the skin, barrier properties should return rapidly [50].

Method of Preparation Step

1: Steps involved in emulsion formulation: O/W or W/O

2: Procedures for creating a gel basis

3: Incorporation of emulsion into gel base with continuous stirring.

II. PREPARATION OF EMULGEL

The oil phase was prepared by dissolving a certain amount of span 20 in liquid paraffin, while the aqueous phase was prepared by dissolving the required amount of tween 20 in purified water. The drug in weighed quantity was dissolved in a suitable solvent, while the required quantity of methyl paraben and propyl paraben were dissolved in propylene glycol, and both were mixed with the aqueous phase. At 70–80° C, the aqueous and oily phases were heated independently. After that, the aqueous phase and oil phase were combined while being constantly stirred at 50 rpm until the mixture reached room temperature[51].

Preparation of Gel

Gel was prepared by dispersing carbopol powder in purified water with the aid of a moderate-speed stirrer (50 rpm), and then the pH was adjusted to 6–6.5 using triethanolamine. Also, methyl cellulose gel was prepared by dispersing methyl cellulose powder in heated purified water (80 °C), and the dispersion was cooled to room temperature and left overnight to ensure hydration of the gel. With a few small adjustments.The gel in the formulations was made by dispersing Carbopol 934 and Carbopol 940 in filtered water and stirring continuously at a moderate speed. Triethanolamine (TEA) was then used to adjust the pH to 6 to 6.5. Tween 20 was dissolved in purified water to create the aqueous phase of the emulsion, whereas Span 20 was dissolved in light liquid paraffin to create the oil phase. While the medication was dissolved in ethanol, methyl and propyl paraben were dissolved in propylene glycol. Both solutions were then combined with the aqueous phase. The aqueous and oily phases were heated to between 70° and 80°C individually. After that, the oily phase was added to the aqueous phase and stirred constantly until the mixture cooled to room temperature. Moreover, add glutaraldehyde in a 1:1 ratio when mixing the gel and emulsion to create the emulgel.

Evaluation of emulgel

Fourier transform infrared spectroscopy (FTIR):

Finding a stable storage condition for the medication in its solid state and appropriate excipients for formulation were the main goals of this study.

Physical appearance:

A visual inspection was conducted to assess the color, homogeneity, consistency, and pH of the produced emulsion compositions. Using a digital pH meter (DPH 115 pm), the pH values of 1% aqueous solutions of the prepared gellified emulsion were determined.

Spreadability:

It is one of the criteria for an emulgel to meet the ideal qualities. Spreadability is a term used to denote the extent to which the drug readily spreads on the skin surface when applied. It is determined by the apparatus called Mutimer [52]. It consists of a wooden block that is attached to a pulley at one end. A glass slide was placed on the wooden block. An excess of emulgel was placed on the ground slide, and then the emulgel preparation was sandwiched between both sides. The time required for the top slide to cover a distance of 5

cm was measured at 65. The shorter the interval, the better the spreadability coefficient.

S= M.L/T

Where,

S = spreadability,

M = Weight tied to upper slide,

L = Length of glass slides

T is the amount of time it took to fully separate each slide.

Extrudability study:

One popular empirical test is to measure the force required to remove the substance from the tube. Plug flow is observed when the shear rate surpasses the yield value, according to the method used to calculate the applied shear in the rheographic zone. The percentage of emulgel and the amount of emulgel that is extruded from a collapsible aluminum tube that has been lacquered, along with the weight in grams required to extrude at least a 0.5-cm ribbon of emulgel in 10 seconds, are the methods used in this study to evaluate the extrudability of the emulgel formulation. As the amount of extrusion increases, extrudability gets better[53]. Extrudability of each formulation is measured three times, with average results displayed. After that, the extrudability is computed using the following formula: Extrudability is calculated as Area (in cm2) / Weight (in grams) applied to extrude emulgel from the tube.

PH measurement

It was done using a digital pH meter by dipping the glass electrode into the emulgel.

Swelling index

To determine the gel's swelling index, one gram of the prepared topical emulgel is placed on porous aluminum foil and then placed separately in a 50-ml beaker with 10 ml of 0.1 N NaOH. After that, the samples were periodically removed from the beakers and set aside on a dry surface until they were weighed once more.

The formula for the swelling index is as follows:

(Wt – Wo) / Wo] × 100 is the Swelling Index (SW) percentage.

In this case, (SW) % = Equilibrium percent swelling,

Wo = Emulgel's initial weight at time zero following time t, and

Wt = Emulgel's swollen weight

In vitro drug release study

In Emulgel's in vitro drug release tests, the Diffusion Cell was utilized in conjunction with the cell membrane. This was carefully attached to one end of the hollow glass tube of the dial Y sis cell. One gram of emulgel was applied to the dialysis membrane's surface, which is composed of cell membrane. A newly prepared PBS solution (pH 6.8) was added to the receptor chamber in order to solubilize the drug. A magnetic stirrer was used to agitate the receptor chamber. Following the appropriate dilutions, one milliliter of emulgel was sampled at a reasonable interval, and a UV-visible spectrophotometer was used to measure the amount of medication present[54]. To determine the overall amount of medication released at each time interval, cumulative adjustments were performed. The cumulative drug release across the cell membrane was calculated as a function of time. Using a standard calibration curve, the cumulative percentage of drug release was determined[55].

Drug Content Determination:

Using a spectrophotometer, the drug concentration in the gelified emulsion was determined. By using sonication to dissolve a known amount of gellified emulsion in methanol, a solvent, the drug content of the emulsion was determined. After an appropriate dilution, absorbance was measured in a UV/VIS spectrophotometer[56]

Microbiological assay

A ditch-plate method was used. This technique is employed to evaluate the fungus- or bacteriostatic-static activity of a substance. The main application for it is in semisolid formulations. We used previously prepared, dried Sabouraud's agar plates. Three grams of the gellified emulsion are added to a ditch that has been carved in the plate. Newly created culture loops are streaked across the agar at a straight angle from the ditch to the plate's edge[57].

Skin irritation test

Next, at each location (two sites per rabbit), a 0.5 g sample of the test material was introduced under a double gauze layer to a skin region that measured around 1" by 1" (2.54 x 2.54 cm2 for stability tests). A rabbit's skin was treated with the gellified emulsion. The animals were put back in their enclosures. The gellified emulsion is removed following a 24-hour exposure period. To get rid of any last bits of test

article residue, the test locations were cleaned with tap water[58].

Stability studies

The produced emulgels were placed in 5 g aluminum collapsible tubes and stabilized for 3 months at 4 different temperatures: 5 °C, 25 °C/60% RH, 30 °C/65% RH, and 40 °C/75% RH. Samples were taken out at intervals of 15 days, and their physical characteristics, pH, rheological characteristics, drug content, and drug release profiles were assessed[59].

Measurement of viscosity

With spindle number sixty-three, a Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) was used to measure the viscosity of the formed batches. After adding the formulation whose viscosity needed to be measured to the beaker, it was given 30 minutes to settle at the assay temperature (25±1 °C) before the measurement was made. The spindle was revolved for ten minutes at a speed of fifty revolutions per minute while being dropped perpendicularly into the center of the emulgel, being careful not to touch the bottom of the jar. The viscosity reading was noted.

Marketed emulgels

The following is a list of prepared and commercially marketed emulgels. Emulgels with anti-inflammatory, anti-fungal, and anti-acne capabilities are used to enhance the moisturizing and exfoliating qualities of other products, such as Diclomax, Voltarol, Derma Foot, Isofen, and Cataflam[60,61]

III. CONCLUSION

This article reviewed emulgels effectively since it addressed all the important aspects and issues and made clear how important they are. The formulation of most medications has always been a difficult task, even though they are available in hydrophobic form. Using traditional dose forms, such as creams, ointments, lotions, emulsions, etc[62]. is what we mean when we talk about topically administering these medications. The hydrophobic properties of the medications cause stability and bioavailability issues in a variety of dosage forms. [63]. For its solution, a modern concept of formulation is presented, i.e., emulgel. In which the drug is merged into the oil phase of the emulsion I.e., combining the aqueous phase with the oil produces the controlled release action. Not only that, but it also makes the medication more bioavailable. A wonderful supplement to dermatological pharmacotherapy, emulgel is a very practical topical dose form. Emulgels' diverse qualities, such as their spreadability, viscosity, stickiness, and so on, improve patient compliance. They also boost the effectiveness and minimize the negative effects of hydrophobic medications. Emulgels are going to be extremely important in the future for the delivery of hydrophobic medications because of the benefits this article has discussed. Since it has lower manufacturing costs and more adequacy[64].

REFERENCE

[1] Naga Sravan Kumar Varma V, Maheshwari PV, Navya M, et al. Calcipotriol is delivered into the skin as an emulgel for effective permeation. Saudi Pharm J. 2014;22(6):591–599

[2] Rashmi M. Topical Gel: A Review, August 2008, available from http:// www.pharmainfo.com

[3] Sharma S. Topical preparations are used for localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. Pharmaceutical reviews 2008;

[4] Aher S., Banerjee S., and Gadhave M. Emulgel: a new dosage form for topical drug delivery. IJIPLS. 2013; 3:1–10

[5] Ansel H., Allen J., and Popovich NG. Pharmaceutical dosage forms and drug delivery systems. New York, NY: Lippincott, 1999.

[6] Laithy HM. and El Shaboury KMF. The development of Cutina lipogels and gel microemulsions for topical administration of fluconazole. Ame Pharm Sci. PharmSciTech. 2003; 3:10 25

[7] Gupta G., Kaur J., and Jaiswal S. A review of a novel approach to antifungal emulgel for topical delivery in fungal infections. IAJPR. 2016; 6:312–324.

[8] SP, Bhaskarrao G, Bhanudas S. Gellified emulsion: a new formulation for topical preparation of hydrophobic drugs. Pharm Tech Med. 2013; 2:37

[9] Jain A., Deveda P., Vyas N., Chauhan J., et al., Development of an Antifungal Emulsion-Based

Gel for Topical Fungal Infection (S). IJPRD 2011; 2(12).

[10] Kumar L., Verma R. In vitro evaluation of topical gel prepared using natural polymers International Journal of Drug Delivery 2010; 2:58–63.

[11] Jain A, Gautam SP, Gupta, and Jain S., Development and characterization of ketoconazole emulgel for topical drug delivery. Der Pharmacia Sinica, 1(3):221-231 (2010).

[12] Gennaro AR, ed. Remington: The Science and Practice of Pharmacy. Easton, Mack Publishing Company, 19th ed., 1995

[13] Stanos SP. Topical Agents for the Management of Musculoskeletal Pain. Pain Symptom Manage, March 2007; 33

[14] Rieger MM, Lachman L, Lieberman HA, and Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed., PA Lea and Febiger, Philadelphia, 1986, pp. 502–533.

[15] Kohei Kyuki, Tomohisa Shibuya, and Kaito Tsurumi Hajime Fujimura, "Anti-inflammatory effect of diclofenacsodium ointment (cream) in topical application," Japan J. Phamacol. 33, 121–132 (1983).

[16] Ashara KC, Paun JS, Soniwala MM, Chavada JR, and Badjatiya JK. Nanoparticulate drug delivery system: a novel approach. Int J Drug Reg Affairs. 2013;1(2):39–48.

[17] Heather AE Benson, Transdermal Drug Delivery: Penetration Enhancement Techniques. Current Drug Delivery, Jan 2005; 2(1): 23–33

[18] Vilasau J., Solans C., Gomez M., Dabrio J., and Esquena J. Influence of a mixed ionic/nonionic surfactant system and the emulsification process on the properties of paraffin emulsions. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2011; 384(1-3): 473–481.

[19] Peneva P., Andonova V., Pilicheva B., and Kassarova M. In vitro survey of ketoprofen release from emulgels. Sci Tech. 2014; 4:118-21

[20] Ashara KC, Paun JS, Soniwala MM, Chavda JR, Mendapara VP, and Mori NM. Microemulgels are an overwhelming approach to improving the therapeutic action of drug molecules. Saudi Pharm J. 2014; 24:452-

[21] Bos JD, Meinardi MMHM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Exp Dermatol. 2000;9(3):165–9.

[22] Menon GK. New insights into skin structure: Scratching the surface. Adv Drug Deliv Rev. 2002;54(Suppl 1):S3–17.

[23] Brody, I. The Ultrastructure of the Horny Layer in Normal and Psoriatic Epidermis as Revealed by Electron Microscopy. J. Invest. Dermatol. 1962, 39 (6), 519–528, DOI: 10.1038/jid.1962.151

[24] The transdermal route of administration provides numerous advantages over conventional routes, i.e., oral or injectable, for the treatment of different diseases and cosmetic applications.

[25] Wang M, Luo Y, Wang T, Wan C, Pan L, Pan S, et al. Artificial skin perception. Adv Mater. 2020;33: e2003014

[26] Ali S., Shabbir M., and Shahid N., The Structure of Skin and Transdermal Drug Delivery Systems: A Review Res J Pharm Tech. 2015;8(2):103–9

[27] BNV, Lassoued MA, Kamoun A, Bahloul B, Miladi K, and Sfar S. Voriconazole-loaded self-nanoemulsifying drug delivery system (SNEDDS) to improve transcorneal permeability. Pharm Dev Technol. 2020;25(6):694–703.

[28] Alkilani, A.Z.; McCrudden, M.T.C.; Donnelly, R.F. Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the Stratum Corneum. Pharmaceutics 2015, 7, 438–470.

[29] Jose, A.; Labala, S.; Ninave, K.M.; Gade, S.K.; and Venuganti, V.V.K. Effective Skin Cancer Treatment by Topical Co-Delivery of Curcumin and STAT3 SiRNA Using Cationic Liposomes. AAPS PharmSciTech **2018**, 19, 166–175.

[30] Taylor, K.M.G. Aulton's Pharmaceutics: The Design and Manufacture of Medicines, 4th ed.; Elsevier: Amsterdam, The Netherlands, 2013.

[31] Sh via Skin. Artif. Cells Nanomed. Biotechnol. **2018**, 46, S423–S433.

[32] Akhter, M.H.; Ahsan, M.J.; Rahman, M.; Anwar, S.; Rizwanullah, M. Advancement in Nanotheranostics for Effective Skin Cancer Therapy: State of the Art. Curr. Nanomed. **2020**, 10, 90–104.

[33] Farhana, A. Enhancing Skin Cancer Immunotheranostics and Precision Medicine through Functionalized Nanomodulators and Nanosensors: Recent Development and Prospects. Int. J. Mol. Sci. **2023**, 24, 3493.

[34] Ikeda-Imafuku, M.; Wang, L.L.-W.; Rodrigues, D.; Shaha, S.; Zhao, Z.; Mitragotri, S. Strategies

to Improve the EPR Effect: A Mechanistic Perspective and Clinical Translation. J. Control. Release **2022**, 345, 512–536.

[35] Gierlich, P.; Mata, A.I.; Donohoe, C.; Brito, R.M.M.; Senge, M.O.; Gomes-da-Silva, L.C. Ligand-Targeted Delivery of Photosensitizers for Cancer Treatment. Molecules 2020, 25, 5317. **[**Google Scholar**] [**CrossRef**] [**PubMed**]**

[36] Panwar AS, Upadhyay N. Emulgel: a review. Asian J Pharmacy Life Sci. 2011;1(3):333–343

[37] Subranayam N, Ghosal SK, and Moulik SP. Enhanced in-vitro percutaneous absorption and in-vivo anti-inflammatory effect of a selective cyclooxygenase inhibitor using microemulsion, Drug Dev. and Industrial Pharm, 2005; 31(4-5): 405-16

[38] Bonacucina G, Cespi M, and Palmieri GF. Characterization and stability of emulsion gels based on the acrylamide/sodium acryloyldimethyl taurate copolymer. AAPS Pharm Sci Tech, 2009; 10(2): 368-

[39] Pant S, Badola A, Baluni S, and Pant W. A review of Emulgel's novel approach to topical drug delivery systems World J Pharmacy Pharm Sci, 2015; 4: 1728–43

[40] Stanos SP. Topical agents for management of musculoskeletal pain. J Pain Symptom Manage, 2007; 33

[41] Gibson M. Pharmaceutical formulation and preparation Boca Raton, FL: Interpharm; 2004 Chale GR, Jeughale AS, Erande KB, and Tambe SR. Emulgel: An Emerging Tool and Magnifying Application of Topical Drug Delivery. World J Pharm Res, 2019; 8(6): 1374–1383.

[42] Choi HG, Yong CS, Sah H, et al. Physicochemical characterization of diclofenac sodium-loaded poloxamer gel as a rectal delivery system with fast absorption. Drug Dev Ind Pharm. 2003;29(5):545–553.

[43] Swaraiah S., Swetha K., and Lohita MM. Emulgel: review of a novel approach to topical drug delivery. Asian J Pharma Res. 2014;4(1):4–11.

[44] Ashara K., Soniwala M. Emulgel: a novel drug delivery system. J Pak Assoc Dermatol. 2016;26(3):244–249.

[45] Hardenia A., Jayronia S., and Jain S. Emulgel: An Emergent Tool in Topical Drug Delivery International journal of pharmaceutical sciences and research, 2014; 5(5): 1653

[46] Phad AR, Nandgude DT, and Ganapathy SR. Emulgel: A Comprehensive Review for Topical Delivery of Hydrophobic Drugs. Assian Journal of Pharmaceutics, 2018; 12(2): 382-393.

[47] Da D. Prodrug strategies for enhancing the percutaneous absorption of drugs. Molecules. 2014; 19:20780–20807

[48] Panwar AS, Upadhyay N. Emulgel: a review. Asian J Pharmacy Life Sci. 2011;1(3):333–343.

[49] Eswaraiah S., Swetha K., and Lohita MM. Emulgel: review of a novel approach to topical drug delivery. Asian J Pharma Res. 2014;4(1):4–11.

[50] Panwar AS, Upadhyay N. Emulgel: A Review. Asian J Pharmacy Life Sci. 2011;1(3):333–343

[51] Baibhav J., Vikas S., and Gurpreet S. Emulgel: A Comprehensive Review of the Recent Advances in Topical Drug Delivery Int Res J Pharmacy. 2011;2(11):66–70

[52] Rieger M., Lachman L., The Theory and Practice of Industrial Pharmacy, 1986.

[53] Vyas, S.P.; Khar, R.K., Controlled Drug Delivery, 1st Ed., Vallabh Prakashan, 2002, pp. 416-417.

[54] Bonacucina G., Cespi M., Palmieri GF. Characterization and Stability of Emulsion Gels Based on Acrylamide/Sodium Acryloyldimethyl Taurate Copolymer, AAPS PharmSciTech, June 2009, 10 (2).

[55] Mortazavi SA, Aboofazeli R. An Investigation into the Effect of Various Penetration Enhancers on Percutaneous Absorption of Piroxicam. Iranian Journal of Pharmaceutical Research, 2003, 135–140

[56] Yub AC, Gomes ADM, Lima MVC, et al. Topical delivery of fluconazole: in vitro skin penetration and permeation using emulsions as dosage forms. Drug Dev Ind Pharm. 2007; 33(3):273–280

[57] Bhowmik D, Gopinath H, Kumar P. Recent advances in novel topical drug delivery systems. Pharma Innovation. 2012; 1:12–3.

[58] Ansel H., Allen J., and Popovich NG. Pharmaceutical dosage forms and drug delivery systems. New York, NY: Lippincott, 1999.

[59] Hien Y. Transdermal drug delivery and delivery system. New York, NY: Marcel Dekker; 1992. p. 301–381.

[60] Athan I, Setty C. Chemical penetration enhancers for transdermal drug systems. Trop J Pharma
[61] Kumar, L.; Verma, R. Int. J. Drug Delivery 2010, 58–63.
[62] Vats S., Saxena C., Easwari T., and Shukla V. Emulsion-based gel technique: a novel approach for enhancing topical drug delivery of hydrophobic drugs. Int J Pharm Res Scholar, 2014; 3(3): 649–660.
[63] Jain SK, Bajapi P, Modi SK, and Gupta P. A Review of Emulgel as a Novel Trend in Topical Drug Delivery Systems Recent Trends, Pharm Sci Res, 2019; 1(2): 30-39.
[64] Guideline IHT: Stability testing of new drug substances and products. Q1A (R2), current step, 2003; 4: 1–24.