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MICROEMULSION FORMULATION AND SCALEUP STUDIES FOR TOPICAL APPLICATION

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ABSTRACT

A microemulsion is thermodynamically stable of two immiscible liquids consisting of the microdomain of one or both liquids stabilized surfactant molecules. The microemulsion is a novel drug delivery system that increases the bioavailability in a biological system. Various screening/optimization studies were carried out to determine several factors that can improve the penetration and deposition of microemulsions in the skin layers. The microemulsion is a mixture of liquid oil, surfactant, and water in an aqueous phase that may contain water-soluble surfactants and co-surfactants which stabilize the system. The oil phase accommodates the lipid-soluble drugs and excipients which are dissolved before the preparation of microemulsion. Microemulsions serve as a delivery system to deliver drugs that allow improved transportation across the subcutaneous (SC) layer of the epidermal skin. This paper has reviewed to investigate current improvements experienced in the field of microemulsions as an important vehicle to transport drugs topically. Further, the scale-up study has to be incorporated in which pharmaceutical product development occurs until it reaches to market. Pilot plant studies of topical microemulsion will be enhanced the quality of the final product and enhance the shelf life of the microemulsion by improving critical material parameters and critical process parameters.

KEYWORD: Microemulsions; Topical drug delivery; Bioavailability; Pilot Scale-up;

Optimization.

1. INTRODUCTION

A microemulsion is a liquid combination of oil, water, and excipients that is frequently mixed with a cosurfactant, which is another excipient. There may be salt or other components in the liquid media, whereas the "oil" is a complicated combination of hydrocarbons and olefins. Microemulsions, unlike conventional emulsions, are formed by mixing the component elements without the high shear conditions that typical emulsions need. Direct (oil distributed in water, o/w) and reversed (water dispersed in oil, w/o) are the two types.[1-3] Microemulsions, at two extremes, may differ in their microstructure from very tiny drops of water dispersed in oil (w/o microemulsion) to tiny oil drops dispersed in water (o/w microemulsion). From one extreme to another of the microstructure: spherical to cylindrical, cylindrical to tubular and the oil-water phase is interconnected andseparated with a very thin layer of surfactant molecules, in the middle, and this is what is called a discontinues microemulsion.[4] Microemulsion systems, in contrast to macroemulsions, theoretically have an indefinite shelflife under normal conditions. Furthermore, the size of the droplets in such microemulsions is constant, ranging from 100 to 1000 A0 (10-100 nm), and the oil/water interfacial tension is very low. Because the droplet size is much less than 25% of the visible region, microemulsions are transparent.[5-6]

The following are three different microemulsion systems that can be utilized for drugs are oil in water, water inoil, and bi-continuous microemulsions. A proper label of surfactants and/or co-surfactants stabilizes the interface in all three forms of microemulsions.[7]

1.1 Advantages of Microemulsion

The advantages of microemulsions are

- Microemulsions are thermodynamically stable systems that self-emulsify due to their stability.
- The technique used has no bearing on the property of microemulsions.
- Because of their small size, microemulsions can be sterilized using filtration.
- Both lipophilic and hydrophilic drugs can be carried in the same microemulsion.
- Microemulsions are simple to make and do not demand a lot of energy during the process.[8]

1.2 Disadvantages of Microemulsion

The disadvantages of microemulsions are

- Surfactant and co-surfactant concentrations must be high.
- High-melting compounds have a limited solubilizing ability for pharmaceutical uses.
- The surfactant must be nontoxic.

2. TOPICAL DRUG DELIVERY SYSTEM

Topical drug administration is a localized drug delivery technique that uses ocular, intestinal, uterine, and cutaneous channels to deliver medications to any area of the body. The most common route for topical medicine is through the skin. The skin, which is among the most readily available tissues on the body for systemic application, is used for delivery. Topical drugs are used to accomplish surface, local, and systemic effects on the skin. Because of its medicinal properties, including moisturizing, calming, and protective effects, the base can be used alone in specific situations. Some topical formulations, on the other hand, contain therapeutically active compounds that are dispersed or absorbed in the substrate. A wide range of topical formulations appropriate for a variety of medication delivery and therapeutic applications are possible unique combinations of bioactive constituents and foundations. Physical qualities (suspension), intended use (liniments), or composition (hydrophilic creams) are all names used to characterize the basis of topical treatments containing medically bioactive molecules.[10] When a medication is applied to the skin, it avoids the liver first-pass metabolism, stomach pH variations, and plasma possibly to fall that occur when it is taken.[11]

The following are some additional benefits of the topical medication administration system:[12]

- Absorption of drugs as enhanced.
- Potential therapeutic responses are increased.
- Drug exposure to non-exposure tissue/sites and little systemic toxicity.

3. PILOT SCALE-UP TECHNIQUES

A pilot plant is a facility in the pharmaceutical business that converts a lab-scale formula into a commercial product by developing a reliable manufacturing technique. A pilot plant is a pre-commercial production system that employs new production technology and/or manufactures tiny amounts of revolutionary tech things, primarily to learn more about the new tech. The data acquired is then used to design full-scale manufacturing systems and

commercial goods, as well as to identify new research aims and provide backing for financial decisions. Other (non-technical) objectives include encouraging public acceptance of new technologies and defying regulatory requirements. Pilot plant studies must include a thorough examination of the formula to determine its ability to withstand batch scale and process modifications; an overview of the variety of relevant processing facilities as well as the availability of raw materials that meet the product specifications; and production and process control must be analyzed, affirmed, and made official during the pilot plant's scale-up efforts.[13,14]

3.1 Objectives of pilot plant

The goals of the pilot plant are as follows:

- Process and equipment evaluation and validation.
- To determine the process's most important characteristics.
- Production and process control guidelines.
- To supply a master manufacturing recipe as well as manufacturing method guidelines.
- To avoid scaling-up issues.

3.2 Significance of Pilot Plant

- Formula standardization.
- A review of the various processing devices that are relevant.
- Production rate optimization and control.
- Information on equipment infrastructure and physical space requirements during scale-up batches.
- Identifying important aspects to sustain product quality.
- Proper documents and reports to back up GMP.[15]

4. SEMISOLID DOSAGE FORM

Semisolid topical dosage forms include creams, gels, ointments, and pastes. They are made up of one or more active chemicals that have been dissolved or distributed uniformly in an effectively utilized, as well as any necessary inactive ingredients such moisturizing ingredients, viscosity-increasing agents, antimicrobial agents, inhibitors, or capping agents. The choice of a base for semisolid dosage forms is influenced by several factors. The medicinal impact required, the nature of the active component so at the auction site, the shelf life of the finished product, and the context in which the product is intended to be administered are all factors to consider.[16] They usually consist of two phases (oil and water),

one of which is continuous (external) and another scattered (interior) (internal). When the main substance is absorbed in one or even both stages, a three-phase system is produced. Semisolids have a three-dimensional structure that is sufficient to give an undisturbed system solid-like features, but is swiftly broken down and realigned when a force is applied.[17,18] In many situations, a compromise is required to achieve the appropriate level of stability. For example, drugs that hydrolyze quickly are more stable in bases that are hydrophobic than in bases that contain water, although being more efficacious in the latter. The foundation should not irritate or irritate the face, and it should not impede wound healing. It should be utilized because it is clean, fragrant, physiologically and chemically stable, and compatible both with the face and the medicinal component(s) to be assimilated. When strain is applied, the consistency will be such that it distributes and softens fast.

4.1. Ideal properties of semisolid dosage forms

Physical Properties are the texture is silky smooth, and the appearance is elegant. Dehydrating-free non-aggressive, it's non-sticky and won't stain your clothes. It is not hygroscopic. Physiological Properties are Non-infuriating Do not interfere with the function of the membranes or theskin. Skin secretion is miscible with it. The sensitization index is low. Application Properties are Easy to use, effective medication release, and have high aqueous washability.[19]

4.2 Storage properties[20]

According to ICH criteria, it is stable under a variety of real-world storage circumstances.

- Semisolids should be maintained at temperatures below 25°C unless otherwise specified; they should not be allowed to freeze, and they should be kept in a tightly sealed container or, if the preparation contains water or other volatile substances, in an airtight container. Preferably, the containersare collapsible metal tubes from which the preparation can be easily extruded. Store in a sterile, airtight, tamper-proof container if the preparation is sterile.

4.3 Different types of semisolid

4.3.1Ointments: are semi-solid, homogenous preparations that are administered externally to the face or nasal mucosa. Emollients or active substances are applied to the skin for protective, therapeutic, or preventive purposes, as well as when a measure of opacity is needed.

4.3.2 Hydrophobic ointment: The majority of hydrophilic (lipid-soluble) ointments are dehydrated, which means they only absorb a small amount of water. The substrates for their formulation are water-insoluble hydrocarbons such as hard, soft, and petrolatum, cooking oil, animal proteins, beeswax, artificial glycerides, and polyalkyl siloxanes.

4.3.3 Water-emulsifying ointments: They can absorb large amounts of water. To make them hydrophilic, they usually begin with a hydrophobic fatty base and then add a waterinsoluble substance such as wool fat, sheep solvents, stearic acid esters, glycerides, or unsaturated fats. They can also be manufactured without emulsions, allowing for higher volumes of aqueous phase to be included. When producing watery liquids or solutions, these ointments come in handy.

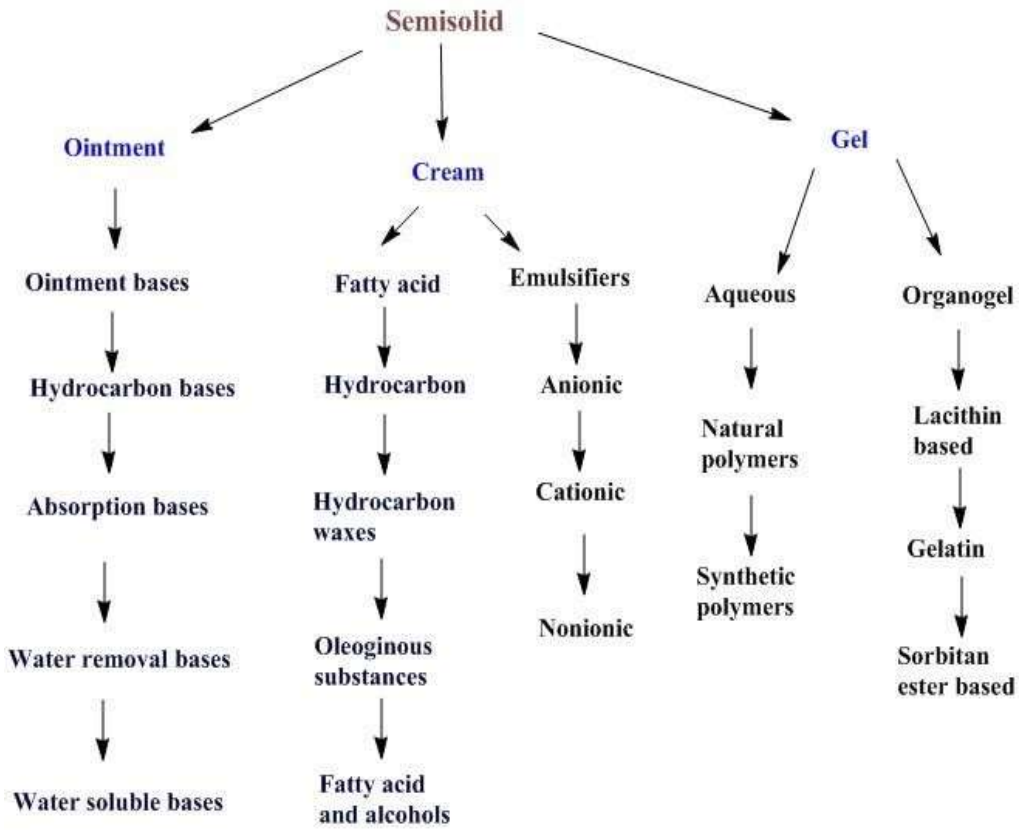
4.3.4 Water miscible ointment bases are hydrophilic. Polyethylene glycols (polyethylene glycols) are extensively employed as bases (macrogols) in both liquid and solid form.[17] Bases are water-miscible. Polyethylene glycols, both liquid and solid, are commonly used as bases (macrogols).[17]

4.3.5 Creams: They are opaque emulsion systems that are semi-solid and homogeneous. The consistency and rheological properties of emulsions are influenced by the type of emulsion, either water-in-oil (w/o) or oil-in-water (o/w), as well as the structure of the particulates in the internal phase. Creams are intended to be applied to the face or mucous for therapeutic, therapeutic, or preventative applications, especially where an inotropic action is not needed.

4.3.6 Gels: They are semisolid preparations that consist of a liquid phase within a muti polymer network with physiochemical cross-linking using appropriate gelling agents. They are usually homogeneous and clear.

4.3.7 Hydrophobic gel: Liquid paraffin with polyethylene, fatty oils gelled with colloidal silica, or aluminum or zinc soaps are examples of (oleogel) bases.

4.3.8 Hydrophilic gel: These bases such as water, glycerol, or propylene glycol are typically utilized, which are subsequently gelled with suitable agents such as tragacanth, starches, cellulose derivatives.



4.3.9 Pastes: These are semi-solid, homogenous formulations containing high levels of resistant particulate ingredients dispersed on a suitable basis (typically not less than 20 percent). Pastes are generally lower greasy, more absorbent, and stiffer in consistency than ointments due to a large number of powdered components present. Some pastes are madeup of a single phase, such as hydrated pectin, whereas others are made up of a thick, durable material that does not move at temperature. The pastes should adhere nicely to the face. They frequently provide an outer cover that keeps water from evaporating.

4.9.10 Poultices: Poultices, sometimes known as a cataplasm, is an ancient kind of topical treatment. It's a mushy mass of vegetable ingredients or clay that's normally warmed up 5before use. Kaolin poultice BP ismade by combining dry, heavy kaolin and boric acid with glycerin and heating them together. The fragrantchemicals are stirred in when they have cooled. While the skin is still warm, the substance is placed on treatment and administered to it (Figure 1).

5. NOVEL ADVANCES IN SEMISOLID DOSAGE FORMS

Microemulsion gel: To overcome the limitations of cutaneous distribution caused by low water solubility, topical microemulsion devices for the antiacne medication nadifloxacin

(NDFX) were invented and developed. When compared to traditional topical medicines, a microemulsion technology for targeted delivery has a lot of promise. The goal of NDFX is to increase and maximize therapeutic efficacy by enhancing both its solubility and transdermal penetrating. Most drugs, including triptolide aceclofenac and diclofenac diethylamine, can be prepared using the traditional microemulsion method, which involves dissolving the medication in oils and then micro emulsifying it.[21] Because NDFX is more soluble in agents than in oils, in this study, a different technique was adopted to dissolve weakly water-soluble drugs into o/w microemulsions, which required first dissolving the drug in a hydrocarbon chain.[22]

5.1 Submicron emulsion vehicle system containing solid lipid nanoparticles

In standard creams, the average droplet size ranges from 10 to 100 micrometers. Drug-loaded oil droplets have been observed to have poor penetration into deep epidermal layers in such formulations. Microparticles ranging in size from 3 to 10 m have been discovered to selectively infiltrate follicular ducts, while particles bigger than 10 m remain on the skin surface and those smaller than 3 m are dispersed randomly throughout hair follicles and the stratum corneum. Researchers created the submicron emulsion vehicle system (SMS)to improve medication permeability by taking these limits into account. A SMEVS's submicron lipid particles enter the stratum corneum's layers, enhancing fluidity and disrupting barrier continuity. By establishing a drug depot in theskin, significant hydration of the skin, aided by gap creation, allows submicron emulsion particles to penetrate. As a result, the medicine is delivered slowly, continuously, and ina controlled manner throughout the body. A SMEVS can be made by homogenizing medium-chain triglyceride emulsion with a high-pressure homogenizer. Furthermore, the addition of lecithin, a good dispersion agent, leads to a significant particle size reduction, usually between 100 and 300 nm. This method is particularly beneficial for delivering hydrophobic drugs that are mixed into the organic phase of sub-micron emulsions to improve stratum corneum penetration. According to studies[23], SMEVSs can administer diazepam and other steroidal and nonsteroidal anti-inflammatory drugs transdermally. When utilizing active ingredients that are irritating at high levels or when applying a drug to the epidermis for an extended period, sustained release is critical. The release characteristics of glyceryl behenate SLNs loaded with vitamin A were examined. Over 24 hours, the release kinetics were evaluated using Franz diffusion cells. Within the first 6 hours following retinol, SLN showed controlled release. Overtime (12–24 hours), the release rate increased and sometimes even surpassed that of equivalent nanoemulsions. Pure SLN

dispersions have a very low viscosity. SLN can be safely incorporated into topical dosage forms such as hydrogels or creams, unlike membranous vesicles. In the Franz diffusion cell, these preparations showed a regulated release over 12-18 hours. A 24-hour rise in release rate was discovered, similar to SLN dispersions. There was a strong link between polymorphic transitions and higher drug release.[24]

6. QUALITY BY DESIGN FOR SCALE UP

According to the International Council for Harmonization (ICH) Q8 (R2) document, quality by design (QbD) is "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management." A QbD strategy includesthe following elements: (i) identification of critical quality attributes (CQAs), (ii) risk analysis, (iii) design of experiments (DoE), and (iv) identification of essential process parameters (CPPs). CQAs are measurable quality characteristics that have a significant impact on the final product's quality. Risk studies, such as a failure mode, effect, and criticality analysis (FMECA), are used once CQAs have been identified to strategically rank likely failure modes and cut down the list of process parameters to be used in a substantial impact on quality of service. The DoE then is developed to analyze the correlations between the control factors and the CQAs in a more efficient manner. DoE allows for sophisticated investigations in which many parameters are changed at the same time, lowering the number of required experimental runs and increasing efficiency.[25] CPPs, or process factors that have a high impact on CQAs, are found using statistical regression procedures (logistic regression, regression analysis, etc.) and other such modeling tools for each DoE run.

QbD approaches may be used to create high-quality nanoformulations while reducing risk, effort, and expenditures. QbD has already been utilized to generate a variety of submicron compositions in recent years, including lipid nanoparticles, emulsions, particulates, micelles, and suspensions.[26] Recent examples include doxorubicin and curcumin-encapsulated liposomes[27], itraconazole-containing topical microemulsion hydrogels, furosemide nanosuspensions[28], aceclofenac-loaded nanostructured lipid carriers[29], rosuvastatin ca solid lipid nanoparticles, quercetin-salicylic acid nano mixed micelles[30], and rosuvastatin In this study, microemulsions are used as a model to demonstrate the use and application of QbD approaches to nanoformulation creation. Microemulsions are optically transparent emulsions with sizes between 20 and 100 nanometers.[31] Emulsion inverting is a phenomenon that

occurs when microemulsionsspontaneously emulsify due to their thermodynamic stability. The emulsion goes.

Through a minor surface tension intermediate phase before inverting during emulsion inversion. Adjusting the system's saline, pH, or temperature, all of which alter the hydrophilic/lipophilic balance, can regulate emulsification.[32] Conversely, the solutiontitrated with a standard[33] can be used to emulsify by modifying the content (for example, by changing the water-to-oil ratio). Many groups have utilized the design of experiments or QbD to develop microemulsions using water titration. Many of the otherstudies are only concerned with microemulsion composition. As previously stated, the QbD method employs a statistical experimental design. Discover CPPs and The rate of water addition and the rate of stirring have been reported to alter microemulsion diameter in several studies.[34] It's critical to understand the impact of process variables on microemulsion parameters like diameter to optimize the chances of success magnitude. As a result, we feel that a thorough understanding both of content and processing conditions is necessary for excellent microemulsion creation. Approaches that look at both composition and process are known as mixed manipulated variable investigations. Using mixed process variable methods, microemulsion electro-coagulation chromatography methods for the identification of diclofenac[35] and almotriptan[36] and its contaminants have been developed. To our knowledge, no documentation exists for the mixed measured process approach for the creation of a microemulsion utilizing water titrationStatistical regression approaches are used to discover CPPs and describe the relationships between CPPs and CQAs. Simulating microemulsions has been done using multiple linear regression (MLR), partial least squares[37], logistic regression[38], and convolutional neural networks (ANN). Artificial neural networks have the benefit of being able to discover nonlinear correlations as well as all conceivable connections. On the other hand, artificial neural networks are unable to properly replicate the influence of each variable on the result.[39] MLR, on the other hand, assigns a numerical value (regression coefficient) to eachinput variable and evaluates the influence of each independent variable on the result. MLR was used to assess the effects of microemulsion mixture and liquid titration variables on day 1 size, polydispersity index (PDI), and 30-day percent diameter growth. Partially least-squares have more input parameters than iterations, and logistic regression contains binary output variables. Thus, logistic regression may be used to predict a binary answer, such as whether a microemulsion formulation meets a CQA requirement. As a consequence, logistic regression was used to model the likelihood of

microemulsion formulations meeting CQA criteria. In the study described, we employed the QbD approach to developing a microemulsion as an exemplar of nanoformulation. The researchers wanted to (1) find stable, resilient microemulsions and (2) understand the mechanisms that affect microemulsion size, PDI, and durability. To order to achieve the aim, they used CQAs which might make detecting stable microemulsions simpler. We then utilized FMECA to identify prospective CPPs as an exemplar of a danger analysis technique. These likely CPPs were used to produce the screening mixture process variable DoE. Using the screening DoE, we were able to find a solution space during which microemulsion size, PDI, and stability were all dependent on microemulsion composition. We augmented the screening DoE with MLR and logistic regression models to even further investigate this design parameter. As a function of microemulsion composition, MLR was used to predict microemulsion diameter, PDI, and 30-day percent diameter change, while logistic regression was used to predict 30- day percent diameter change.

Examine CQAs that show a low level of stress. Extensive quality control enabled the development of more accurate logistic models (thermal cycling and shelf life research). Because we had a better understanding of these processes, we were able to discover stable, durable microemulsions then scale them up a microemulsion composition tenfold. To gather and assess processing data more effectively, a mix of DoE, multiple regression, and regression analysis can be used. This research shows how QbD methods may be used to create a wide range of nanoformulations.

7. Scale-up of Nanoemulsions

In recent years, several research groups all over the world have focused their efforts on developing biocompatible nanoscale systems for the efficient encapsulation, preservation, and transport of delicate active substances.[40]

Several research groups have looked at nanoemulsions related to biological surfactant molecules and vegetable fats as an encapsulating medium for active compounds with applications in food, drug research, and beautification.[41] Nanoemulsions, which are colloidal carriers of two or more liquids, are stabilized by surfactant molecules. These are highly stable and may be produced with lower surfactant ratios, making them valuable in a wide range of industries. Nanoemulsions can be transparent, translucent, or milky based on the scale of the droplets. Nanoemulsions are classified as either water- in-oil (w/o) or oil-in-water (o/w) based on the quantity and chemical composition of the components. To prepare them, high-

energy emulsification techniques or low-energy emulsification methods are utilized. Because of their tiny droplet size (usually 20-500), nanoemulsions are resistant to physical instability, flocculation, and creaming.

Pharmaceuticals and other bioactive compounds are being administered by numerous routes of administration, and nanoemulsions made with biocompatible and nontoxic components are being evaluated for several uses. O/w nanoemulsions, in particular, are effective encapsulation and distribution systems for solubilized active substances. Packaging at the nanotechnology enhances the stability, durability, and pharmacological activities of bioactive substances. Nanoemulsions, on the other hand, are difficult to apply topically due to their low viscosity. Aside from biological devices, the flexibility of the packed nanoemulsions prevents the inclusion of diverse lipophilic bioactive ingredients into functional food gels. Integrating o/w nanoemulsions laden with lipid- soluble pharmacological activities into hydrogels has been offered as a solution to these problems.[42] Crosslinked polymer networks are made up of pass hydrophilic polymers. Because of the occurrence of hydrophilic functional groups connected to the chitosan backbone, they may absorb large amounts of water and physiological.

Hydrophilic gels can be generated synthetically or spontaneously using pectin, alginate, guar gum, as well as other cellulosic derived polymeric.[43] Various lipophilic bioactive compounds have been proposed as delivery methods for nanoemulsion-based hydrogels, including silymarin, cardamom argan oil[44], pentyl gallic acid[45], glycitein[46], and mint oil.[47] Hydrogels with loaded nanoemulsions might be employed in a range of topical functional foods and pharmaceutical compositions The purpose of this study has been to develop and characterize lipophilic chemical carriers using (a) nanoemulsions and (b) nanoemulsion-based biomaterials. This was accomplished by creating a succession of o/w nanoemulsions containing freshwater as the continuous liquid phase, biodegradable oils as the dispersed phase, and living thing ground compounds. The o/w nanoemulsions were made using relatively low or elevated emulsification procedures. Following that, selected nanoemulsions were used to encapsulate vitamin D3 and curcumin. Loaded nanoemulsions were introduced to polymerized and co-polymeric biomaterials based on carbohydrates with various mixtures.[48] The influence of content and emulsifier process on the characteristics of o/w nanoemulsions and nanoemulsion-based hydrogels was investigated structurally.[49]

The ability of the suggested nanoemulsions and nanoemulsion-based biocompatible to release

encapsulated active ingredients were also examined.[50]

Table 1: Patent involved in nanoformulations.

Patent number	Title	Patent year	Type of nanoformulation
JP2017019870A	Method and Composition for Administration f trpv1 agonist	2018	Method andcomposition trpv1agonist
US8691785B2	Compositions andmethod for non-parenteral delivery of oligonucleotides	2019	Composition and method of oligonucleotides
US4146499A	Method for preparing microemulsions	1997	Method for microemulsions
WO1994022928A1	Microemulsion polymerization systems and coatedmaterials made Therefrom	1995	Microemulsions system and coatedmaterial
US6071975A	Method of preparingsilicone oil-in-water microemulsions	2000	Method of silicon oil-in-water microemulsions
EP0291213A2	Organopolysiloxane microemulsion, process for its production andapplication	1988	Microemulsions production and its application
WO2014160079A1	Microemulsion Topical Delivery Platform	2014	Microemulsion topical platform
CN103655217B	Procyanidine micro-emulsion eye cream and preparation method	2013	Procyanidine microemulsions and preparation method
WO2010093523A2	Foamable microemulsion compositions for topical administration	2009	Foamable microemulsions for topical administration

CONCLUSION

Microemulsions are a viable medication delivery technique for addressing drug-related problems and developing improved care therapy solutions. Pharmaceutical microemulsions continue to show considerable promise in medication delivery to the dermis or for topical applications. Only pilot-scale production following best practices for medication conveyance systems has been considered in this paper. Important control formulation parameters and process elated variables for desired quality were included.Biocompatible vehicles enhanced drug permeation and solubilization in the skin layer. Co-surfactants andsurfactants used in manufacturing microemulsion selected to increase the penetration efficiency of the topical and can be used in the treatment of chronic skin infection.

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