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Revolutionizing Skin Healthcare: Unleashing the Power of Nano- Emulgel as a Topical Lipidic Emulsion-Based Nanocarrier

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Abstract: *The development of pharmacological compounds in drug research has yielded numerous therapeutic options for addressing healthcare concerns. However, a significant proportion of these medications are classified under the Biopharmaceutical Classification System (BCS) as class II or class IV, leading to their exclusion from the development process and restricted use in clinical settings. To address this limitation, a promising nano-technological method utilizing lipoidal manufacturing has emerged. This research paper proposes the utilization of a nanoemulsion-based gel, known as nanoemulgel, as a suitable administration route for BCS class II/IV medications. Nanoemulsions offer unique properties such as increased interfacial surface area and enhanced drug dissolution, while gels provide high viscosity and controlled drug release. However, the delivery of hydrophobic drugs remains a challenge for gels. To overcome this drawback, an emulsion-based technique is employed in nanoemulgel formulations. This approach enables the encapsulation of hydrophobic drugs within the lipid droplets of the nanoemulsion, harnessing the gelling properties of the formulation. The resulting nanoemulgel combines the advantages of both systems, facilitating improved drug solubility, bioavailability, and targeted delivery. By exploring the potential of nanoemulgel in delivering BCS class II/IV medications, this research aims to address the limitations associated with these compounds and provide a novel solution for their effective administration. The findings highlight the unique and creative application of nanolipoidal formulations, showcasing their scientific merit in overcoming drug delivery challenges and opening new avenues for therapeutic interventions.*

Keywords: Health care, topical route, BCS class II/IV, bioavailability, nanotechnology, nanoemulgel, emulsifiers, thickeners, hydro alcoholic

I. INTRODUCTION

Since the dawn in pharmaceutical culture in geographic area (2600 B.C.) by the employment of water, and plant for the treatment of disorder, pharmacists are able to develop the age of recent dosing systems [1]. Researches during this field have introduced many routes of administration to deliver the developed trendy dose forms. The dose forms ar largely passionate about the chemical science characteristics of the active compound. Recent trend of synthesis drug development or throughout high turnout screening leads towards development of lipotropic active pharmaceutical agents [2]. Recent applied math reports on poor binary compound solubility of recent chemical entities (NCE) (70%)[3] has crossed the initial report of around four-hundredth NCE with poor solubility [4–9]. lipotropic characteristics of the recently developed drug molecules manifest the issues like poor oral bioavailability, erratic absorption, intra- and inter-subject pharmacokinetic variations and lack of dose proportion [10]. to beat those problems to target solubility sweetening, formulation approach may be a continuous developing method. totally different ways like physical modification, chemical modification and formulation development (Figure 1) will be accustomed improve the solubility of poorly soluble medicine. There are various formulation approaches to enhance the solubility of poorly binary compound soluble medicine like particle size reduction to deliver through nanocarrier system, crystal engineering, amorphous formulation [11–15], many lipide formulations approaches [16], etc. Newer lipide formulation techniques, viz: incorporation of lipotropic part in inert lipide vehicle [17,18], formation of microemulsion or nanoemulsions [19],

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self-emulsifying formulations, liposomes, solid lipide nanoparticles or lipide nanocarriers [20– 22] have become more and more fashionable to beat these issues of lipotropic properties of compounds. Consequently, many route of administration are explored to deliver those formulations supported its distinct blessings and downsides heading in the right direction web site, severity of illness, patients" age and condition, on the market dose kind and eventually for the compliance of the users. Oral route is that the most most popular route anchored in patient compliance, however, oral administration is additional vulnerable to end in internal organ initial pass metabolism, leading towards demand of upper dose [23,24]. Further, stomachic irritation is that the major limitations for the presence of surfactants within the lipide based mostly formulations [25], at the same time the distribution of drug throughout the body will cause ineluctable facet effects. Hence, to remain removed from such unacceptable problems, the non-invasive, non-paining, non-irritating topical delivery offormulation is Associate in Nursing alternate manner related to many blessings like delivery of drug to specific web site of action with reduced general toxicity, turning away of initial pass metabolism and stomachic irritation, increasing unleash rate of drug from formulation to enhance transcutaneous absorption and someday topical application associated with increase bioavailability with sustained unleash profile [26,27]. Besides its blessings delineated , ancient transdermic formulations, viz: ointments, creams, lotions ar in unison with several disadvantages like sticky nature, lack of spreadibility, stability issue, etc., ultimately resulting in patient incompliance. Modernization of transdermic delivery by the formulation unconcealed clear gel and emulgel with bigger patient compliance and improved effectuality. Thus, these formulations ar gaining interest each in cosmetics industries, similarly as in pharmaceutical industries. In spite of scores of blessings of gel and emulgel formulations, delivery of hydrophobic drug still remains a giant hurdle to cross over. Moreover, skin penetration through horny layer is additionally an excellent concern to the researchers for the general activity of the transdermic delivery. Literatures counsel that nanosized topical formulations will enhance permeableness of the active moiety by disrupting the lipide bilayer as evident from the distinct void and empty areas within the nanoemulsion treated skin samples [28] and extent retention of the drug at the positioning of action [29,30]. Nanoemulsion bears a lot of hope being isotropous, clear (or translucent) heterogeneous mixture composed of 2 media (oil and aqueous), one section is distributed in Associate in Nursingother and stable by an surface film of wetter molecules [31]. Studies instructed that nanoemulsions have a better drug solubilization capability than easy micellar solutions, and their natural philosophy stability offers blessings over unstable dispersions, like emulsions and suspensions, as a result of they will be factory-made with very little energy input (heat or mixing) and have a extended shelf-life [18]. despite scores of blessings of nanoemulsion, topical application is proscribed thanks to its low consistency and spreadibility [32]. Researchers have resolved the issues related to nanoemulsion for transdermic delivery through a straightforward conversion of nanoemulsion to nanoemulgel. Nanoemulgels ar nanoemulsion, either of oil-in-water (o/w) or water-in-oil (w/o) kind that additional convert to nanoemulgel by victimization gelling agent [33]. Nanoemulgel possesses gel characteristic with improved nanoemulsion properties for transdermic application. alternative blessings of nanoemulgel embrace its low skin irritation, increase permeableness, and high drug-loading capability for topical delivery in comparison with the opposite carriers like microemulsions, liposomes or solid lipide nanoparticles [34–36]. This mixture delivery system will be utilised to include drug compounds to focus on on bioavailability improvement, increase stability highland and reducing their facet effects [37]. Nanoemulsion ensures adequate nativeization and dispersion of the drug by adequate transcutaneous absorption among the skin to boost its local effectuality and/or through the skin to the circulation to shine its general result and even will cross the rigid blood-brain-barrier to supply intercalary blessings in central nervous system activity [38]. Hanging on the researcher"s interest, patient acceptance and attention-grabbing analysis outcomes within the field of pharmaceutical formulation development, study on nanoemulgel focuses on development of immense variety of delivery system viz: transdermic, dental, vaginal, ocular, nose to brain nanoemulgel for treatment of varied native similarly as general ailments [39–45]. There ar a really few review articles on the market within the literature chiefly that specialize in formulation summary and penetration aspects of emulgel [46], characterization of the nanoemulgel [47], current market merchandise on nanoemulgels and its blessings [48] and delivery of antifungal agents through nanoemulgel delivery [27]. gift article is an in depth review covering elements screening for nanoemulgel formulation combined with its formulation summary and pharmacokinetic and pharmacodynamic parameters of the printed analysis works on nanoemulgel with totally different pharmaceutical merchandise. Therefore, the aim of this study is to convey an outline on the choice criteria of the fundamental part for nanoemulgel and its

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positive/negative role in experimental results on pharmacology, pharmacodynamics, and safety of the drug. Connecting section of the article can reveal the elements and choice criteria for the accomplishment of targeted objective.

II. MATERIALS REQUIRED FOR NANOEMULGEL FABRICATION

Fabrication of nanoemulgel for the purpose of drug delivery through topical route requires a variety of materials suitable and compatible with the skin along with consideration of some important factors such as the amount of drug to be loaded, amount of water to be used and route of permeation of the drug through the skin. A gel-based nanoemulsion formulation for topical use consists of some special materials other than lipids and surfactants such as gelling agent, penetration enhancers, preservative and anti-oxidants. These penetration enhancers actually compromise the skin barriers and help the drug to enter systemic routes finally achieving the desired therapeutic concentration.

Aqueous Phase For the formulation of nanoemulgel,

most commonly distilled water or ultra-purified water is used as the aqueous phase and this phase is responsible for the conversion of emulsion form into the emulgel in the presence of a gelling agent [48].

Oils and Lipids

In nanoemulsion formulation, selection of oils and lipids is the most crucial parameter and responsible for the selection of the other components such as surfactants and cosurfactants. Pharmaceutically approved long-chain triglycerides (LCTs), medium-chain triglycerides (MCTs) and shortchain triglycerides are mainly used for nanoemulsion formulation [49, 50]. As most of the recently approved active pharmaceutical ingredients have solubility and permeability limitation, MCTs are more attractive than LCTs for the emulsification purpose because of their more solubilizing capacity as compared to LCTs [51, 52]. Usually short-chain triglycerides like triacetin, tributyrin, tricaprin etc. are preferred over LCTs considering their better solubility for many drugs such as Paclitaxel [53, 54]. At the time of selection of oil and/or other lipid components, it needs to be sure that the oil phase is pure and free of objectionable components such as peroxides, free radicals, and various unsaponifiable matters like sterols and polymers. Many of these undesired components can be formed during storage and can be responsible for the deterioration of the oil phase and finally leads to the unstable formulation. The number of hydrocarbon chains is one among the many criteria behind the selection of lipids for nanoemulsion formation and the reason is attributed to the nature and quality of emulsification. As far as the nature of emulsification is concerned, lipids with low carbon chain length are found to be better as compared to the lipids with higher carbon chain length [55]. On the basis of availability and other relevant properties here we can see and compare varieties of oils and lipids useful for the nanoemulgel formulation.

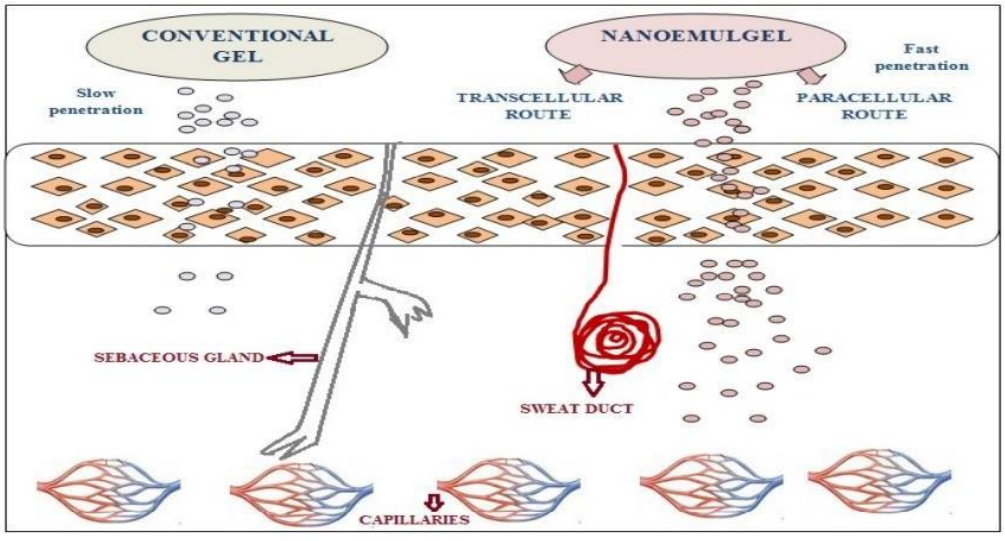

Fig. (1). Graphical representation of nanoemulgel path of action showing penetration of nanoemulgel through both Paracellular and Transcellular route.

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Vegetable Oils

Plants are the source of these oils that are found in the form of fatty acid glycerides. Many plant derivative oils are approved for the topical delivery of drugs such as soybean oil, olive oil, peanut oil, coconut oil, almond oil and castor oil through various drug delivery systems [55, 56, 57]. Many of these oils like sesame oil and soybean oil are also used for the preparation of nanoemulgel [58, 59]. These oils are fixed in nature and comparatively less preferred in many nanolipoidal formulations due to the low solubility of drugs. In topical nanoemulsion formulation, in which these vegetable oils are used, it has been observed that these oils enhance the penetration of drug to the skin by lowering the resistance to permeation [60, 61]. Among all the above discussed vegetable oils, soybean oil is most preferred either alone or in combination with MCTs and short-chain triglycerides for the preparation of topical nanoemulsion [62]. In many topical nanoemulsion formulations approaches, it has been observed that soybean oil possesses better permeability as compared to other oils such as Tributyrin and Myglyol [63]. Soybean oil contains some special kinds of phospholipids known as lecithin, which actually function as a surface-active agent and show a higher affinity towards epidermal tissues [64-65]. Very recently, Siang Yin Lee et al. developed a gel-based nanolipoidal delivery system of Phenytoin including nano and microemulsion with the help of soybean oil and coconut kernel oil. In this work, they successfully demonstrated the fact that nanoemulgel (93.12%) shows much better release as compared to cream-gel (56.42%) and macroemulgel (51.51%) [66]. In a similar work, Wu H et al. developed a topical nanoemulsion for a hydrophilic drug Inulin by using olive oil leading to a significant enhancement of about 5-15 fold [67].

Fatty Acids and Alcohols

Many fatty acids are widely distributed in plant oils. Fatty acids are mainly carboxylic acids along with a long aliphatic chain which are either saturated or unsaturated in nature. Fatty alcohols (or long-chain alcohols) are usually of high-molecular-weight, straight-chain primary alcohols, that range from as few as 4-6 carbons to as many as 22–26 carbons, derived from natural fats and oils. For topical drug delivery, US FDA has approved many oils belonging to the category of fatty acids and alcohols such as Oleic acid, Undecylenic acid, Cetyl alcohol Stearyl alcohol and Oleyl alcohol etc [68]. Similar to other oils, these can also be classified as medium-chain fatty acids (MCFA) and long-chain fatty acids (LCFA) and their chain length depends on the number of carbons present. Generally, MCFAs (C6-C12) are found in liquid or semisolid form whereas LCFAs (C13-C24) are solid in nature. These fatty acids and alcohols as a fabricating agent in the nanoemulsion based gel system not only enhance the permeation but also act as a penetration enhancer [69]. Fatty acids actually enhance the permeation by disorganizing the lipid structure of the subcutaneous [69]. A nanoemulgel containing a non-steroidal anti-inflammatory drug Piroxicam belonging to BCS class II drugs has been developed with oleic acid as an oil phase. The optimized nanoemulgel contains 10% Oleic acid as oil, 35% Tween 80 and Ethanol as a surfactant and a co-surfactant mixture, 55% water, 0.5% drug and 0.5% w/w Carbopol. The fabricated nanoemulgel shows enhanced permeation without using any chemical permeation enhancer [70].

Fatty Acid Ester and Glycerol

These categories of lipids are the most commonly used oil phase for the preparation of nanoemulsion and microemulsions. In case of topical preparation also, these oils are most preferred because of their comparatively better solubility in recently approved APIs. These oils exhibit some of the properties of the surfactants. This category of lipids can be re-categorized as monoglycerides, diglycerides and the oils of this category. Caprylic acid derivatives in the topical nanolipoidal formulations are found to increase the permeability across the subcutaneous layer of skin and finally enhance the permeability of the formulations [71]. Ethyl oleate, Isopropyl myristate, Isopropyl palmitate etc. are the fatty acid esters that are preferably used in the topical nanoemulsions and microemulsion [72]. These oils are also found to increase the partition coefficient of the drug across the skin layers and hence work as a permeability accelerator. Recently an antifungal drug Allyl Amine has been developed as nanoemulgel with the help of Labrafac (propylene glycol caprylate), Cremophore RH40 and Ethanol as an oil, surfactant and a co-surfactant, respectively. Ex vivo skin permeation test of nanoemulgel (NG) formulation showed skin permeability of approximately 20% of the drug, while the marketed cream (MC) showed a permeability of 18% only. The amount of drug retained in the skin by the NG formulation was found to be approximately 31% while for the MC it was found to be only 20%. The NG formulation was found to treat the infected rat skin within 12 days of treatment while the MC took about 16 days for

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complete removal of the infection [73]. In a similar work, a nanoemulgel has been prepared of a disease-modifying anti-rheumatic drug Leflunomide (LFD) with the help of capryol 90 as an oil phase. Other than Capryol 90, Cremophore EL and Transcutol HP are also used as surfactants and Pluronic F127 as a gelling agent. The final formulation shows a better permeability profile. Ex vivo permeation through rat abdominal skin revealed significant improvement in flux, apparent permeability coefficient, steady-state diffusion coefficient and drug deposition in skin due to nanoemulsification of LFD [74]. In another work, Parasuram Rajam Radhika et al. formulated a nanoemulsion based emulgel of a lipophilic drug Flurbiprofen. A combination of Triacetin and Linseed oil was used as an oil phase and Tween 80 as a surfactant. The overall formulation showed increased permeability and better antiinflammatory action [75]. As far as the fatty acid esters are concerned, in a very recent experimental work, an antiparkinson"s drug Selegiline hydrochloride was fabricated into nanoemulgel with the help of Isopropyl myristate as an oil phase and Span 85, Tween 80, PEG 400 were used as surfactants. In the final formulation, Viscup160® was used as a gelling agent. The fabricated formulation showed an enhancement ratio of 3.69 times greater than conventional gel. NEGS4 (optimized formulation) showed 6.56 and 5.53 times increase in bioavailability in comparison to tablet and conventional gel, respectively, along with sustained effect [76].

Surfactants and Co-surfactants

In the fabrication of nanoemulgel, the role of surfactants is to stabilize the final formulation as well as to help in the solubility of the drug used. For the said purpose, the surfactants can be of different chemical nature such as cationic, anionic and non-ionic. Because of their role of emulsification, these surfactants are known as emulsifiers. Sorbitan fatty acid esters and polyoxyethylene sorbitan fatty acid esters are non-ionic surfactants and are preferably used in the preparation of nanoemulgel. In this category. Tween 20, Tween 80 and span 80 are commonly used for the said purpose. Other preferable nonionic emulsifiers include various castor oil derivatives such as Cremophore EL and Cremophore RH, Labrasol, Labrafac, Poloxamar 124 and 188 etc. Selection of emulsifiers in nanoemulsion preparation is a serious issue and is associated with some toxicity factors. The increased amount of surfactants can lead to irritation of skin and hence causing uneasiness. Non-ionic surfactants are mostly preferred because of their comparatively lower toxicity than ionic surfactants [77]. Co-surfactants are mainly used for the purpose of decreasing the concentration of surfactants as well as for better thermodynamic stability of the final formulation. Preferred co-surfactants for the nanoemulgel formulation include Transcutol HP, PEGs, glycerine, PGs, and ethyl alcohol.

Permeation Enhancers

The use of permeation or penetration enhancer is one of the better ways to improve the rate of transport through the skin and related layers [78]. Permeation enhancers are one of the main components of the topical drug delivery system and are preferably used in topical nanoemulsion or nanoemulgel. These permeation enhancers mainly function by interacting with skin constituents and induce a temporary and reversible increase in skin permeability. It also provides an added driving force for the transport of drug into the skin [79]. Permeation enhancer used for the nanoemulgel includes isopropyl myristate, linoleic acid, oleic acid, lecithin etc.

Gelling Agents

The gelling agent is one of the major components of nanoemulgel and it gives texture to the formulation. These are actually cross-linking agents. Carbopole, Poloxamer, Tragacanth, HPMC etc. are some of the gelling agents used in nanoemulgel preparation.

Preservatives

These are the chemical agents used to protect the formulation by the microbial attack and hence increase the shelf life of a formulation. Phenoxyethanol, Benzalkonium chloride, Benzoic acid, Methyl paraben and Propyl paraben are generally used preservatives in the formulation of nanoemulsion [80].

Antioxidants These are the chemical agents used in the formulation to protect the various components from oxidation. Butylated hydroxyl toluene, Ascorbyl palmitate, and Butylated hydroxyl anisole are most preferred antioxidants in topical nanolipoidal preparation [81].

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III. MANUFACTURING OF NANOEMULGEL

Manufacturing of nanoemulgel is actually a multistep process where a developed nanoemulsion is mixed with a suitable gel base. Therefore, here we will first discuss the development and manufacturing of nanoemulsion and then preparation and incorporation of gel base.

Preparation of Nanoemulsion

As nanoemulsion is a non-equilibrium system of structured liquid, the process of fabrication involves a high amount of surfactants and external energy or both. Nanoemulsion formulation can be possible by both high energy and low energy methods depending on the nature and concentration of components [81].

High Energy Methods

As droplet size of nanoemulsion typically ranges from 5- 500nm, the achievement of this size involves high mechanical energy. The input of high energy for fabrication can be achieved by various methods such as high- pressure homogenizers, ultrasound generator, microfluidizer and high shear stirring method [82, 83]. The most significant advantage of a high energy mediated nanoemulsion formulation is the use of low concentration of emulsifiers [84]. From the toxicity point of view, it is a major advantage. On the other hand, the involvement of such high mechanical energy can diminish the significance of the method at industrial scale [85].

Low Energy Methods

Low energy methods of nanoemulsion fabrications have more or less similar preference as high energy methods and include various methods such as spontaneous emulsification, phase inversion methods, emulsion inversion points etc. However in comparison to high energy methods of nanoemulsion preparation. Higher amount of surfactants is used, which provides smaller globules of low and uniform polydispersity index (PDI) [86]. These low-energy methods make use of the phase transitions that take place during the emulsification process as a result of a change in the spontaneous curvature of the surfactant [87]. With the help of the details of fabrication method , it will be easy to understand the nature of nanoemulsion, which can be briefly described as:

High Energy Methods

High-pressure

Homogenization In this technique, a high-pressure homogenizer (microfluidizer) or piston homogenizer is used to reduce the globule size up to nanoscale range. In the microfluidizer technique, during the emulsification process, a very high pressure of about 500-20,000 psi is applied along with the impact, attrition, turbulence and hydraulic shear. Several types of forces such as hydraulic forces, shear forces and cavitations forces act together to convert macro emulsion into the coarse emulsion and then the product is subjected to the same process to obtain the droplets of desired size and polydispersity index (PDI) [88]. The number of cycles of the homogenization is an important factor for the desirable emulsification. In this process, low concentration of surfactant is used with negligible chances of contamination. In piston kind of homogenization process the homogenizers work on colloid mill principle. In this process of nanosized droplets formation, the coarse emulsion is applied to a gap of less than 10µm dimension. Here in the piston, a continuous rotating rotor and a fixed stator work on the coarse emulsion and after many cycles of rotation with high shear, the coarse emulsion changes to the desired size of droplets [89].

Ultrasound Generation

In this method, the coarse emulsion is converted into desired nanosized emulsion droplets with the help of a sonicator probe. The sonicator probe creates high sonication sound waves of more than 20 KHz. The high intensity of sound waves breaks the coarse emulsion into fine droplets of nanosize (5-500nm). Various kinds of probes with various dimensions are available for the size reduction up to desirable limits. Along with the kinds of the probe, the input power and time for sonication decide the size of the droplet [90].

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Low Energy Methods

Nanoemulsion formation by low energy methods is a spontaneous phenomenon where emulsification takes place by changing the curvature or interfaces of the components, mainly surfactants used in the formulation. This change in the interface or curvature can be seen as a function of the temperature and physicochemical properties of the material used in the formulation. When the curvature of surfactant changes by keeping the components constant and changing the temperature, the applied method is known as phase inversion temperature (PIT). On the other hand, when there is a change in interface is obtained by keeping the temperature constant and changing the type and concentration of components, the method is known as phase inversion composition (PIC) or emulsion inversion point (EIP) [91, 92]. In the category of low energy methods, spontaneous emulsification (SE) method is one of the widely accepted and feasible methods on both small and large scale. Here in this method, the desired size of droplets is achieved by mixing two liquid phases. Types of low energy methods can be briefly described as

Phase Inversion

Methods Phase inversion methods are used for the formation of kinetically stable nanoemulsion, based on factors such as temperature, chemical environment of the component including pH, ionic strength as well as various physicochemical properties of the components used. On the basis of two different factors, this method can be categorized as PIT and PIC. In emulsion formation process, the conversion of oil in water (o/w) emulsion to water in oil (w/o) or vice versa takes place and it is just based on the function of inversion of the phases by involving the above-mentioned factors. In phase inversion temperature (PIT) method, the change in geometry of the interface of the surfactant (mainly non-ionic in nature) is achieved by changing the temperature of the formulation and the composition is kept constant. With a gradual increase in temperature, the coarse emulsion gets heated up and causes the surfactant to get solubilized in oil phase resulting in the transformation of o/w emulsion to w/o emulsion. At this stage, the surfactant curvature remains negative [93]. When an intermediate temperature is achieved which is also known as HLB temperature, the non-ionic surfactant shows a similar affinity for aqueous and oily phase, where the ternary system has exceptionally low interfacial tension and spontaneously, the curvature typically reaches to zero value [93]. Ternary system, at this stage, typically consists of a Dphase bicontinuous microemulsion or a mixture of a D-phase bicontinuous microemulsion with lamellar liquid crystalline phases. It can also be noticed that nano-sized emulsion droplets and desired polydispersity index can bbe obtained by fast cooling of the single-phase or multiphase bicontinuous microemulsions maintained at either PIT or a temperature above PIT (transitional-phase inversion) [93]. As the high temperature is an important part of the process, this can be a threat to the thermosensitive drug for the formulation [94]. As far as the phase inversion composition (PIC) method is concerned, here the temperature is kept constant and change in the composition is allowed for the inversion process. Most preferably pseudo ternary phase diagram method is used for the formulation of nanoemulsion using phase inversion composition method. The major disadvantage of this method over higher energy required methods is that the surfactant is used in higher amount in it [95].

Spontaneous Emulsification Method

It is one of the most feasible methods of nanoemulsion preparation on lab and industrial scale and involves two liquid phases, one aqueous phase and another is an organic phase. The aqueous phase consists of a hydrophilic surfactant of various categories such as Tween, Span etc. and the organic or oil phase consists of components such as Capriole 90 or any similar material such as Acetone, Ethyl methyl ketone etc. in which drug is pre-solubilised [96]. In this process, the spontaneous formation of nanoemulsion is achieved when the organic phase is added slowly to the aqueous phase and followed by evaporation of the organic phase. The process can be aided by mild stirring with the help of a magnetic stirrer which creates small convection currents helpful in the distribution of oil droplets in the bulk solvent.

Preparation of Gelling Agent

In fabrication of a nanoemulgel, the purpose of using a gelling agent is to change the physical form from liquid to semi-solid which has many advantages in terms of patient compliances. Various categories of the gel base for the purpose of gelling can be prepared by adding the polymer in purified water and stirred continuously with a glass rod or any other suitable mechanical device until desired texture achieved and then pH should be adjusted [98]. In various experimental

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works, the preparation of the gelling agent is carried out by adding the polymer in purified water by a cold method. In cold method, the components are added in purified water at 20˚C followed by the addition of gelling polymer and cooling the water up to 4˚C [97, 98].

Incorporation of Gelling Agent

After the preparation of nanoemulsion as well as the gelling agent, both are mixed and a nanoemulgel is prepared. Here a liquefied form of water in oil (w/o) or oil in water (o/w) nanoemulsion is converted into a thick and semisolid nanoemulgel with the help of various polymeric gelling agents. This gel form can change again into a solution form after applying a mechanical force such as rubbing. This property of the material is known as thixotropy where gel to sol and sol to gel transformation occurs on the application of shear stress and reversal of the same respectively without a change in volume [58]. Innumerable polymers have been used as gelling agents such as Carbomer 940, Carbopol 943, Chitosan, Carbopol 934, Carbopol 940, Poloxamer 407, Methyl cellulose etc. for the preparation of nanoemulgel of desired characteristics for various applications [99-104].

IV. IN VITRO CHARACTERIZATION TECHNIQUES OF NANOEMULGEL

Nanoemulgel is a topical preparation containing nanosized emulsified droplets along with a gelling agent suitable for application on the skin. This semisolid dosage form requires a vast category of analytical techniques for characterization of various physicochemical properties which can resemble stability and desired functionality of the dosage form. Various characterizations significant for promoting stability and other physicochemical properties of a nanoemulgel include zeta potential, droplet size, polydispersity index (PDI), pH, viscosity and related rheological analysis, swelling index, spreadability etc. Other than these characterizations, in vitro release studies and permeability studies are important for the analysis of dosage form. For better understanding, methods and techniques for analyzing significant properties of a nanoemulgel can be briefly described as below

Zeta Potential

As nanoemulgel is basically a composition of nanosized emulsion droplets along with a gelling agent, the formulation can exhibit an electrical charge due to the involvement of various types of surface-active agents. The nature and characteristics of electrical charge on the surface of emulsified droplets are very crucial for the stability of entire dosage form [105]. Zeta potential is the measurement of electrical charges at the shear plane. The shear plane is the distance from the globule surface where the various counter ions are attached to the globules in the electrical field [106]. The surface charge depends on the nature of the emulsifiers incorporated in it; the surface is negatively charged if an anionic surfactant is used and is positively charged if a cationic surfactant is used [107]. Zeta potential can be measured with the help of various instruments which include, ZC-2000 (Zeecom-2000, Microtec Co. Ltd, Chiba, Japan), Malvern Nanosizer/Zetasizer® nano-ZS ZEN 3600 (Malvern Instruments, USA) etc [86, 108].

Droplet Size Measurement and Polydispersity Index (PDI)

Droplet size measurement and polydispersity index are the most important characterizations of nanoemulgel preparation. In any nanolipoidal formulation, size of droplets/particles can be directly related to the stability, drug release as well as in vivo performance of dosage form and hence, resembles a significant property for the analysis [109]. In nanoemulgel, the size of droplets can range from 5 to 500nm. Generally, dynamic light scattering (DLS) method is used for the determination of droplet size. In dynamic light scattering technique, the measurement of transitional diffusion co-efficient is carried out by observing the interaction between the laser beam and dispersion [110]. Master sizer 2000 laser diffractometer (Malvern Instrument, UK) and similar instruments following dynamic light scattering techniques can also be used for the purpose. The mean droplet size can also be determined by Stokes-Einstein equation with a condition that the dispersion should be very diluted and there should not be any interaction between the droplets [111]. Polydispersity index or particle size distribution reflects thesize distribution of droplet diameter and it can be measured by analyzing the intensity of scattered light as a function of angle between the incident and scattered beam which follows the light scattering theory [112].

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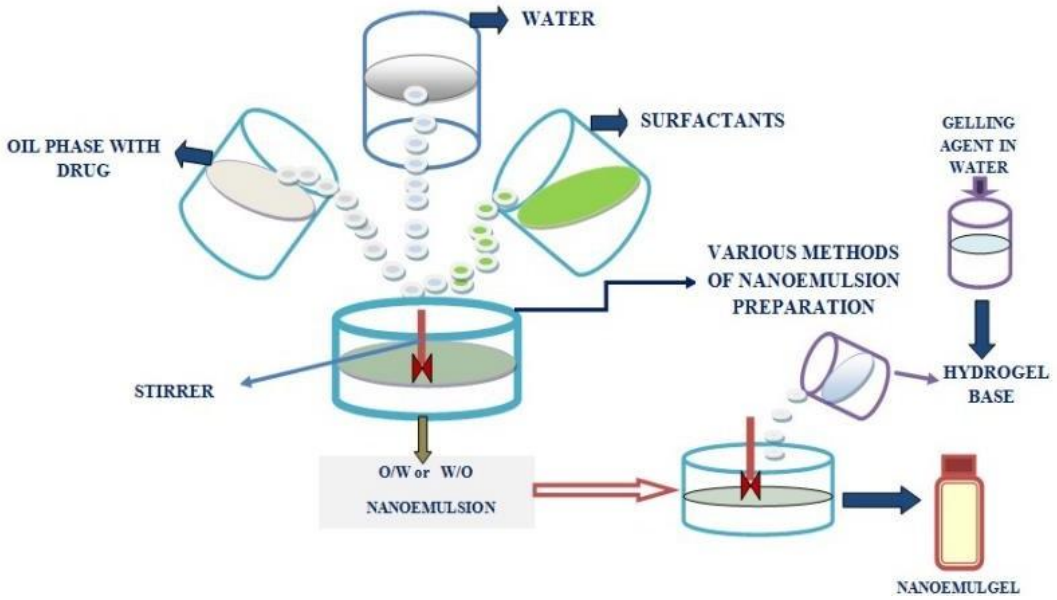

Fig. (2). Schematic diagram of nanoemulgel preparation.

According to the Stock"s law, the mean droplet size can be obtained from an equation: ! = g 18 D! ρ! ɳ Where: V = rising velocity of the droplet (m/s) g = gravitational constant (9.81m/s2) D = droplet diameter (m) ρd = density difference between heavy phase and ligh phase(kg/m3) ɳ = dynamic viscosity

Rheological Characterizations

It has been discussed that a nanoemulgel contains oil, surfactants and a gelling agent as fabricating components. A minute change in the physicochemical properties of formulation components can greatly affect the rheological properties of a dosage form such as viscosity and flowability. The change in viscosity can further affect the stability factors as well as drug release and other biological functions. Taking these factors into consideration, it is very essential to understand the rheological properties of nanoemulgel. Viscosity measurement can be carried out with different kinds of viscometers [113].

Mucoadhesive Property

Usually , nanoemulgel preparations are delivered through mucosal layer such as nasal mucosa. In this kind of delivery system, it is important to analyze the mucoadhesive strength. The mucoadhesive strength can be defined as the force required for detaching the dosage form from the nasal mucosal tissue. Here for this test, a modified method can be used [114]. In this method, nasal tissue of sheep can be used. One can obtain the tissue from a local slaughterhouse. The fresh tissue should be used just after separation. In the experimental procedure, a precalibrated force-displacement transducer is required. Here, the exposed mucosal part of the sheep nasal mucosa is fixed to the upper probe with the help of a cyanoacrylate adhesive, then the probe needs to be attached to the transducer for obtaining the electronic data indicating the force [115]. The bioadhesive force (expressed as detachment stress) can be determined by using the equation as: Detachment stress (!"#$!"!)= !" ! Here, m is the weight added to the balance for detachment of the gel from the tissue, g is the acceleration due to gravity i.e. 980 cm/s2 and A is the surface area of tissue. 4.5. Spreadability Testing Desirable spreadability is one of the important criteria for the selection of a topical delivery system. In nanoemulgel dosage form, spreadability can be determined by some special apparatus made up of a wooden block [116] or glass [117] having a pulley on the opposite end. With the help of this apparatus, spreadability is measured which comes under „Slip" and „Drag" method [118].

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V. APPLICATION OF NANOEMULGEL

Among all the recently developed drug delivery systems, nanoemulgel has emerged as one of the affluent and promising novel delivery systems for topical preparations having numerous pharmacological activities. Following various pharmacological categories, the impact of nanoemulgel drug delivery can be defined as follows

Anti-inflammatory Application

Inflammation is a local manifestation of the body"s physical reactions in which the part of the body produces redness and swelling with pain [119]. There can be various reasons associated with inflammation. There are many drugs both from synthetic and natural sources which can be used as an anti-inflammatory agent. The delivery of these drugs as nanoemulgel is expected to provide better pharmacodynamic action over other delivery systems. Recently a typical nanoemulgel preparation of lornoxicam, a nonsteroidal antiinflammatory drug (NSAID) was developed [120]. The optimized lornoxicam formulation was effectively prepared with the help of a spontaneous self-emulsification method. The nanoemulgel was composed of Labrafac, Tween 80, Transcutol P with Pluronic F68 and Carbopol 934 as an oil, a surfactant, a cosurfactant and a gelling agent, respectively. The comparative study of the prepared nanoemulgel with conventional gel reveals that the nanoemulgel shows a significant increase in permeability coefficient and enhancement ratio over the conventional gel. The in vivo study also reveals a better anti-inflammatory effect of nanoemulgel as compared to the conventional marketed gel [121]. In another experimental work, a nanoemulgel dosage form was developed using oil of Swietenia macrophylla(SM) having various phytopharmacological properties [122], like antioxidant, antimicrobial activity, anti-inflammatory activity, anti-HIV activity, antiulcer activity, antifungal activity, antimalarial and antidiarrheal activity. In this present experimental work, the anti-inflammatory action of Swietenia macrophylla oil is the matter of interest. Here, the nanoemulgel is prepared by developing a nanoemulsion of SM oil followed by the incorporation of the same in a hydrogel. Here, the nanoemulsion of SM oil was prepared by using both phase inversion technique as well as the self-emulsifying method by using sucrose monoester fatty acid as a surfactant and glycerol as a co-surfactant. As a gelling agent, different grades of Carbopol (934 and 940) were used. The optimised nanoemulgel formulation was stable with an emulsified droplet size of 114nm with a zeta potential of -43.1mv. The anti-inflammatory test was carried out by using carrageen, an induced rat paw oedema method and it was found that the inhibition of inflammation by using SM oil nanoemulgel was higher in comparison to the simple oil solution [123]. In a similar proof of concept study, a nanoemulgel containing anti-inflammatory drugs Aceclofenac and Capsaicin was developed. In this present study, the researcher demonstrates a different approach to compare the advantage of nanoemulgel dosage form. Here, the nanoemulgel was prepared and its various pharmacokinetic and pharmacodynamic studies were carried out in comparison with the nanoemulsion, nanomicelle, marketed formulation Aceproxyvon and also the free drug Aceclofenac and Capsaicin. In the first step of the experiment, nanoemulsion and nanomicelle, the two different nanolipoidal formulations were separately prepared. The nanoemulsion was prepared with olive oil and miglyol in a ratio of 1:1 and Polysorbate 80 and Transcutol in a ratio of 1:1 as a mixture of oils and mixture of surfactants, respectively. On the other hand, nanomicelle was prepared by the solvent evaporation method using vitamin E TGPS and acetone. Finally, the nanoemulgel was prepared by adding both the dosage forms i.e. nanoemulsion and nanomicelle and a gelling agent Carbopolon by continuous stirring. The final concentration of the drug(s) was optimised. The optimized nanoemulgel was used for in vitro release study, skin permeation study and other in vivo studies. As a result, it has been found that the combination of nanoemulgel and nanomicelle i.e. nanoemulgel is better than the individual drug delivery as the combined system utilises the maximum possible paths for the absorption of the active pharmaceutical ingredients [124].

Anti-psoriatic Application

Psoriasis is a chronic and T lymphocyte-mediated autoimmune inflammatory disease. It is characterized by abnormal patches on the skin due to epidermal hyperproliferation as well as angiogenesis [125]. It also affects joints and tendons with itching to the body. Patches generally seem red in colour. There are many antipsoriatic agents used topically but their clinical benefits are limited due to low bioavailability. Nanoemulgel delivery system for the antipsoriatic drugs bears much hope for their successful clinical effects. Recently, a nanoemulgel drug delivery system was developed using Betamethasone dipropionate (BD) as an antipsoriatic agent. In this development procedure, the nanoemulsion

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was prepared by using eucalyptus oil and babchi oil. Tween 20 and ethanol were used as a surfactant and a co-surfactant, respectively. The phase titration method was used for the fabrication of nanoemulsion. Further, nanoemulsion was converted into nanoemulgel with the help of Carbopol 934. Pharmacokinetic studies reveal that the formulated nanoemulgel provides enhanced permeation of the drug and reduces the dosing frequency. The nanoemulgel formulation also provides sustained drug release for the desired period of time. Anti-inflammatory effect of the optimized formulation evaluated by using the carrageenan-induced paw edema method was observed to be improved as compared to marketed gel formulation [126]. In a different proof of concept study, Swati Pund et al. formulated an antipsoriatic nanoemulgel of Leflunomide (LFD). LFD is one of the most recently approved, effective and valuable drugs for psoriatic arthritis [127]. Since there are many drugs showing unproductive clinical benefits for rheumatic arthritis and melanoma due to various side effects and low permeability through the transcutaneous membrane, LFD nanoemulgel bears much hope for the same clinical condition. In this study , the nanoemulgel of LFD was prepared by developing nanoemulsion of the drug by selfemulsifying method using Capryole 90, Cremophore EL and Transcutol HP as an oil, surfactant and a co–surfactant respectively. The process was followed by the conversion of nanoemulsion into nanoemulgel using pluronic F127. The finally optimised, stable nanoemulgel of LFD showed significant enhancement in the permeability of the drug through rat abdominal skin. Cell line study using human HaCaT, melanoma A375 and SK-MEL-2 cell lines showed a significantly enhanced therapeutic response. The enhanced permeability and other pharmacokinetic parameters enable the nanoemulgel to reduce the dose of the drug and hence the dose-related toxicity [76].

Antifungal Application

Fungal infections are one of the primary reasons for skin diseases. Out of many fungal infections, onychomycosis is a severe one and accounts for half of the nail diseases [128]. Ketoconazole is a BCS class II antifungal agent of imidazole class. Ketoconazole is taken orally for the treatment of chronic mucocutaneous fungal infection of nail and skin having a poor cure rate. Nanoemulgel can be a better choice for the delivery of Ketoconazole as compared to oral delivery. With this motive and proposal, Asiya Mahtab et al. developed a nanoemulgel of ketoconazole. In the procedure of nanoemulgel development, the first nanoemulsion of ketoconazole was prepared by high-pressure homogenization method followed by the construction of the pseudoternary phase diagram. Then the prepared nanoemulsion was converted into a nanoemulgel with the help of a gelling agent, Carbopol Ultrez 21. The ex-vivo translingual permeation studies showed the optimized nanoemulsion, nanoemulgel and drug suspension of KCZ through goat hooves to be 62.49 ± 2.98%, 77.54 ± 2.88% and 38.54 ± 2.54%, respectively, in 24 h. The antifungal effect of nanoemulgel on Trichophyton rubrum and Candida albicans showed a significant zone of inhibition in comparison to the drug solution. Results of skin and histopathological studies on rat skin indicated safe topical use and further showed enhanced permeation of the developed nanoemulgel [129]. In another recent experimental work, Maha E. Elmataeeshy et al. developed a nanoemulgel containing Terbinafine Hcl (TB). TB is a synthetic Allyl amine derivative, a poorly water-soluble antifungal drug and is very useful in the treatment of various fungal infections causing fingernail and toenail infection. The nanoemulgel of Terbinafine Hcl consists of nanosized emulsion droplets prepared by low energy method with the help of pseudo ternary phase diagram method. In the preparation of nanoemulsion, Peceol was selected as oil phase and Tween 80 and propanol was selected as a surfactant and a co-surfactant, respectively. After the successful development of nanoemulsion, the same is converted into the nanoemulgel using a gelling agent Carbopol 940. A comparative in vitro study of permeation and an in vivo study of anti- fungal activity of marketed product Lamisil emulgel and the optimized nanoemulgel were carried out. As a result of the studies, it was found that nanoemulgel formulation shows remarkably improved permeability and also shows a superior antifungal activity as compared to the marketed product [130].

Cardiovascular Application

As nanoemulgel can deliver the drug to the systemic circulation, drugs of various pharmacological categories can be delivered through the topical route. With this novel approach, some cardiovascular agents need to be developed showing better pharmacokinetic effect in comparison to the available conventional dosage form. Telmisartan, an angiotensin type II receptor blocker was developed as nanoemulgel and the pharmacokinetic profile was characterized

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in comparison to the conventional gel formulation. Telmisartan nanoemulgel was prepared with the help of phase diagram method. Formulation of nanoemulgel consists of Labrafil M 2125 CS as oil, Acrysol as a surfactant and Carbitol as a co-surfactant. For the conversion of nanoemulsion into nanoemulgel, Carbopol was used as a gelling agent. In vitro and in vivo studies of the optimised nanoemulgel of Telmisartan were carried out and it was found that the nanoemulgel shows improved permeability in comparison to the conventional gel formulation [130].

In Alopecia

Alopecia is a disease which is characterized by partial or complete loss of body hairs. Further alopecia can be of two types, alopecia areata and androgenic alopecia . Minoxidil is a well-established and approved drug for the treatment of the alopecia [131]. In spite of being the drug of choice, the clinical effect of Minoxidil is disappointing in many conventional delivery systems at pharmacokinetic platform [132]. Nanoemulgel can be a suitable way of delivery for Minoxidil to achieve desirable therapeutic effects [133]. Approach for nanoemulgel formulation of various categories of drugs is summarized in the below given Table 1

VI. PATENTS RELATED TO EMULGEL PREPARATION

Literature related to patents on nanoemulgel formulation are either scant or nonexistent to date. However, nanoemulgel as an emerging potential delivery system for so many therapeutically active agents is attracting researchers and industrial formulation scientists. In recent years, a number of patent publications have been subjected to both natural and synthetic APIs (active pharmaceutical ingredients). A herbal preparation containing neem oil is developed as nanoemulgel. This formulation is claimed to have spermicidal activity. Nanoemulsion part of a formulation is composed of neem oil, sodium lauryl sulphate and water. The nanoemulsion is prepared by high-pressure homogenizer. Size of emulsion droplets was found to be 250-600nm. Finally, the nanoemulgel was prepared by adding Carbopol polycarbophil as a gelling agent [134]. Diclofenac is a well known NSAID (non-steroidal anti- inflammatory drug). Novartis AG has submitted a European patent application for emulsion based gel of Diclofenac diethylamine [135]. Details of some patent application are given below in Table 2.

VII. CURRENT AND FUTURE PROSPECTIVE OF NANOEMULGEL

According to various studies discussed in this current review, it can be interpreted that in the process of developing various novel drug delivery systems, nanoemulgel has emerged as one of the best choices for drug delivery through topical routes. Nanoemulgel has been developed with an aim to enhance the pharmacodynamics and pharmacokinetics of countless poorly bio-available drugs with better patient convenience. Currently, innumerable lipophilic drugs of various therapeutic categories are being developed as nanoemulgel, showing better therapeutic profile. In the health care system, the nanoemulgel is used for many acute and chronic diseases such as fungal diseases, inflammation, cardiovascular problems, psoriasis, alopecia etc. With all these advantages of drug delivery, the future prospects of nanoemulgel seem to be lucrative and it can be expected that nanoemulgel as a delivery system will be a hope for various categories of drugs which have been eliminated from development pipeline due to different reasons such as low bioavailability, clinical in-efficacy etc.

Table 1. List of drugs formulated as nanoemulgel. Here: O: oil, S: surfactant. Co. S: Co-surfactant, GE: gelling agent.

Sl. No.	Drug Incorporated	Composition of Nanoemulgel	Application	Comparative PK/PD Effect	Ref.
1.	Itraconazole	O: EugenolS: Labrasol Co.S:TranscutolP, Lecithin GE: Carbolpol	Antifungal.	Enhanced permeation. 7.28 mg release in 24 hr. 3.diffusion control.	[136].
2.	Quercetin	O: Cinnamon oilS: Tween 80 Co.S: Carbitol GE: Poloxamer.	Antimicrobial and Anti- Inflammatory.	1. 92.4% release in 6 hr Where Quercetin loaded gel shows <3% release in the same time.	[137].

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3.	Curcumin	O: Emu oil S: Cremophor RH40 Co.S:Labrafil M2125CS GE: Carbopol.	Anti-inflammatory	Improvement in anti-inflammatoryactivity with nanoemulgel as com-pared to the pure drug.	[138].
4.	Cyclosporine	O: Oleic acidS: Tween 80 Co.S: Transcutol P GE: Guar gum.	Immunosuppressive agent.	Improved permeation as comparedto nanoemulsion and marketed formulation.	[139].
5.	Glibenclamide	O:Labrafac Triacetin (1:1) S:Tween 80 Co.S:Diethylene glycol monoethyl Ether GE: Carbopol 934.	Anti-hyperglycemic.	3.92 fold increase in relative bioa-vailability compared to an oral drug suspension.	[140]
6.	Carvedilol	O:Oleic acid: IPM(3:1)S: Tween 20 Co.S: Carbitol G.E: Carbopol-934.	Antihypertensive.	plasma conc. was increased 6.41fold compared to the marketed formulation and enhanced bioavailability.	[141].
7.	Meloxicam	O: Almond oil and peppermint oil(1:2) S: Tween 80 Co.S: Ethanol GE: carbopol 940.	Anti-inflammatory.	higher *in vitro* release rate enhanced bioavailability.	[142].
8.	Mangosteen Extract	O: vergin coconut oilS: Tween 80 Co.S: Span 80 GE: xanthan gum.	Antifungal, antibacterial, antioxidant, antiviral and antitumoral.	Enhanced Nanoemulgel penetration of skin (95%) of its total mangostin content compared to the skin penetration result of the nanoemulsion formulation.	[143].
9.	Ferulic Acid	O: Isosteryl isostearateS: Labrasol Co.S:Plurol isostearique GE: Carbopol 940.	Antioxidant activity.	Enhanced permeation of nanoemulgel (96.95%) compared to gel (61%).	[144].
10.	Fluconazole	O: Capmul MCMS: Tween 80 Co.S: Transcutol P GE: Carbopol 934.	Antifungal.	3.71 folds higher permeation compared to commercial eye dropwith increased antifungal activity.	[145].

Table 2. List of emulgel patent products where an emulsion with a gelling agent is used.

Sl. No.	Patent Name	Product	Inventors	Publication Date	Ref.
1	WO2006082596A2	Neem oil contraceptive	Kamalinder Kaur Singh, Pratima Arun Tatke, Shruti Dhuru.	2006-08-10	[146].
2.	EP 2 055 298 A1	Diclofenac gel Voltaren Emulgel	NOVARTIS AG	2009-05-06	[147].
3	US20120093882A1	Voveran	Sunilendu Bhushan Roy,Shafiq Sheikh, Jay Kothari, Jitendra Patel	2012-04-19	[148].
4	WO2008051186A2	Nanoemulsion containing Composition having anti-in-flammatory activity	James R Baker NANOBIO CORPORATION	2008-05-02	[149].

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VIII. CONCLUSION

The development of nanoemulgel as a topical lipidic emulsion-based nanocarrier represents a significant advancement in drug delivery for skin healthcare applications. This innovative approach has shown promising results in addressing the challenges associated with BCS class II/IV medications, which are often excluded from development processes due to their classification. By incorporating nanoemulsions into gels, the benefits of both systems can be harnessed, including enhanced drug dissolution, improved bioavailability, and controlled release.

The research discussed in this review article underscores the potential of nanoemulgel in overcoming the limitations of hydrophobic drug delivery, a common drawback of conventional gels. Through the emulsion-based technique, hydrophobic drugs can be efficiently encapsulated within the lipid droplets of the nanoemulsion, allowing them to benefit from the unique features of the gel matrix.

While the application of nanoemulgel has demonstrated significant advantages in drug delivery, further research is warranted to explore its full potential. Future studies should focus on optimizing formulation parameters, such as the choice of lipids, surfactants, and emulsifying agents, to enhance stability, drug loading, and release characteristics. Additionally, investigating the influence of nanoemulgel on skin penetration, cellular uptake, and pharmacokinetics will provide valuable insights into its mechanism of action and efficacy.

Furthermore, the potential of nanoemulgel extends beyond BCS class II/IV medications. It can be explored for the delivery of a wide range of therapeutic agents, including hydrophilic drugs, peptides, and bioactive compounds. The versatility and flexibility of nanoemulgel make it a promising candidate for personalized medicine, targeting specific skin and individual patient needs. In conclusion, the utilization of nanoemulgel as a topical lipidic emulsion- based nanocarrier holds immense potential for revolutionizing skin healthcare. This research paves the way for future advancements in drug delivery systems, offering improved treatment options, enhanced efficacy, and better patient outcomes. With continued exploration and innovation, nanoemulgel-based formulations are poised to make a significant impact in the field of dermatology and skincare.

REFERENCES

[1]. Posey L. Michael, Pharmacy: An Introduction to the Profession, 2nd edition | American Pharmacists Association, (n.d.).

[2]. V. Weissig, C. Lizano, V.P. Torchilin, Selective DNA release from DQAsome/DNA complexes at mitochondria-like membranes., Drug Deliv. 7 (2000) 1–5. doi:10.1080/107175400266722.

[3]. A Beig, J. Miller, D. Lindley, R. Carr, Head - To - Head Comparison of Different Solubility - Enabling Formulations of Etoposide and Their Consequent Solubility – Permeability Interplay, J. (2015).

[4]. A.A. Gade Abhishek V, K.S. Salunkhe, S.R. Chaudhari , Gadge P.B, Dighe G.S, Review on: Self Micro-Emulsifying Drug Delivery System, Am. J. PharmTech Res. (2015) 50–66.

[5]. H. Pham-The, T. Garrigues, M. Bermejo, Provisional classification and in silico study of biopharmaceutical system based on Caco-2 cell permeability and dose number, Molecular. (2013).

[6]. P. Kesharwani, S. Banerjee, S. Padhye, F.H. Sarkar, A.K. Iyer, Parenterally administrable nano-micelles of 3, 4-difluorobenzylidene curcumin for treating pancreatic cancers, Colloids Surfaces B Biointerfaces. (2015)

[7]. A. Jain, K. Jain, P. Kesharwani, N.K. Jain, Low density lipoproteins mediated nanoplatforms for cancer targeting, J. Nanoparticle Res. 15 (2013) 1888.

[8]. P. Kesharwani, L. Xie, S. Banerjee, G. Mao, S. Padhye, F.H. Sarkar, et al., Hyaluronic acid-conjugated polyamidoamine dendrimers for targeted delivery of 3,4- difluorobenzylidene curcumin to CD44 overexpressing pancreatic cancer cells., Colloids Surf. B. Biointerfaces. 136 (2015) 413–423.

[9]. B. Gorain, H. Choudhury, E. Biswas, A. Barik, P. Jaisankar, T.K. Pal, A novel approach for nanoemulsion components screening and nanoemulsion assay of olmesartan medoxomil through a developed and validated HPLC method, RSC Adv. 3 (2013). doi:10.1039/c3ra41452c.

[10]. B. Gorain, H. Choudhury, A. Kundu, L. Sarkar, S. Karmakar, P. Jaisankar, et al., Nanoemulsion strategy for olmesartan medoxomil improves oral absorption and extended antihypertensive activity in hypertensive rats, Colloids Surfaces B Biointerfaces. 115 (2014) 286– 294.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, June 2023

[11]. A. Kaushal, P. Gupta, A. Bansal, Amorphous drug delivery systems: molecular aspects, design, and performance, Crit. Rev. (2004).

[12]. A. K. Kawakami, M. Pikal, Calorimetric investigation of the structural relaxation of amorphous materials: Evaluating validity of the methodologies, J. Pharm. Sci. (2005).

[13]. R. Ghanghoria, P. Kesharwani, H.B. Agashe, N.K. Jain, Transdermal delivery of cyclodextrin-solubilized curcumin, Drug Deliv. Transl. Res. 3 (2013) 272–285. doi:10.1007/s13346-012-0114-y.

[14]. A. Kishore Uttam Kothule, Prashant Kesharwani, Suresh Kumar Gidwani, Paraag Gide, Development and Characterization of Chitosan Nanoparticles and Improvement of Oral Bioavailability of Poorly Water Soluble Acyclovir, Res. J. Pharm. Technol. 3 (2010) 1241–1245.

[15]. A. Gorain, M. Tekade, P. Kesharwani, A.K. Iyer, K. Kalia, R.K. Tekade, The use of nanoscaffolds and dendrimers in tissue engineering, Drug Discov. Today. (2017).

[16]. A Pouton, Lipid formulations for oral administration of drugs: non-emulsifying, selfemulsifying and "self-microemulsifying"drug delivery systems, Eur. J. Pharm. Sci. (2000).

[17]. V. Bali, M. Ali, J. Ali, Nanocarrier for the enhanced bioavailability of a cardiovascular agent: In vitro, pharmacodynamic, pharmacokinetic and stability assessment, Int. J. Pharm. 403 (2011

[18]. A. S. Shafiq-un-Nabi, F. Shakeel, S. Talegaonkar, J. Ali, S. Baboota, A. Ahuja, et al., Formulation development and optimization using nanoemulsion technique: a technical note., AAPS PharmSciTech.

[19]. A H. Choudhury, B. Gorain, B. Chatterjee, U.K. Mandal, P. Sengupta, R.K. Tekade, Pharmacokinetic and Pharmacodynamic Features of Nanoemulsion Following Oral, Intravenous, Topical and Nasal Route., Curr. Pharm. Des. (2016

[20]. A R. Parveen, S. Baboota, J. Ali, A. Ahuja, S.S. Vasudev, S. Ahmad, Oil based nanocarrier for improved oral delivery of silymarin: In vitro and in vivo studies, Int. J. Pharm. 413 (2011) 245–253.

[21]. S. Mansuri, P. Kesharwani, R.K. Tekade, N.K. Jain, Lyophilized mucoadhesivedendrimer enclosed matrix tablet for extended oral delivery of albendazole., Eur. J. Pharm. Biopharm. Off. J. Arbeitsgemeinschaft Für Pharm. Verfahrenstechnik e.V. 102 (2016) 202–13.

[22]. A Shukla, V. Mishra, P. Kesharwani, Bilosomes in the context of oral immunization: development, challenges and opportunities, Drug Discov. Today. 21 (2016) 888–899.

[23]. K. Shafaat, B. Kumar, S.K. Das, R. Ul Hasan, S.K. Prajapati, Novel nanoemulsion as vehicles for transdermal delivery of Clozapine: In vitro and in vivo studies, Int. J. Pharm. Pharm. Sci. 5 (2013) 126–134.

[24]. J. Zhou, M. Zhou, F.F. Yang, C.Y. Liu, R. Le Pan, Q. Chang, et al., Involvement of the inhibition of intestinal glucuronidation in enhancing the oral bioavailability of resveratrol by Labrasol containing nanoemulsions, Mol. Pharm. 12 (2015) 1084–1095.

[25]. S. Kotta, A.W. Khan, S.H. Ansari, R.K. Sharma, J. Ali, Anti HIV nanoemulsion formulation: Optimization and in vitro-in vivo evaluation, Int. J. Pharm. 462 (2014) 129–134.

[26]. M. Iqbal, S. Md, J. Sahni, S. Baboota, Nanostructured lipid carriers system: recent advances in drug delivery, J. Drug. (2012).

[27]. J. Kaur, J. Kaur, S. Jaiswal, G. Gupta, RECENT ADVANCES IN TOPICAL DRUG DELIVERY SYSTEM, Pharm. Res. (2016).

[28]. F. Shakeel, S. Baboota, A. Ahuja, J. Ali, S. Shafiq, T. Kommuru, et al., Skin permeation mechanism and bioavailability enhancement of celecoxib from transdermally applied nanoemulsion, J. Nanobiotechnology. 6

[29]. A X. Huang, X. Peng, Y. Wang, Y. Wang, D.M. Shin, M.A. El-Sayed, et al., A reexamination of active and passive tumor targeting by using rod-shaped gold nanocrystals and covalently conjugated peptide ligands, ACS Nano. 4 (2010) 5887– 5896.

[30]. L.A. Delouise, Applications of Nanotechnology in Dermatology, J. Invest. Dermatol. 132 (2012) 964–975.

[31]. A F. Gao, Z. Zhang, H. Bu, Y. Huang, Z. Gao, J. Shen, et al., Nanoemulsion improves the oral absorption of candesartan cilexetil in rats: Performance and mechanism, J. Control. Release. 149 (2011) 168–174.

[32]. S. Khurana, P.M.S. Bedi, N.K. Jain, Preparation and evaluation of solid lipid nanoparticles based nanogel for dermal delivery of meloxicam, Chem. Phys. Lipids. 175–176 (2013) 65–72.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, June 2023

[33]. A S. Pund, S. Pawar, S. Gangurde, D. Divate, Transcutaneous delivery of leflunomide nanoemulgel: Mechanistic investigation into physicomechanical characteristics, in vitro anti-psoriatic and anti-melanoma activity, Int. J. Pharm. 487 (2015) 148–156.

[34]. O. Sonneville-Aubrun, J. Simonnet, F. L"alloret, Nanoemulsions: a new vehicle for skincare products, Adv. Colloid. (2004).

[35]. A T. Tadros, P. Izquierdo, J. Esquena, C. Solans, Formation and stability of nanoemulsions, Adv. Colloid Interface Sci. 108 (2004) 303– 318.

[36]. A Solans, P. Izquierdo, J. Nolla, N. Azemar, M.J. Garcia-Celma, Nano-emulsions, Curr. Opin. Colloid Interface Sci. 10 (2005) 102–110.

[37]. A T. Formariz, V. Sarmento, A. Silva-Junior, Doxorubicin biocompatible O/W microemulsion stabilized by mixed surfactant containing soya phosphatidylcholine, Colloids Surfaces B.

[38]. A B. Gorain, H. Choudhury, R.K. Tekade, S. Karan, P. Jaisankar, T.K. Pal, Comparative biodistribution and safety profiling of olmesartan medoxomil oil-in-water oral nanoemulsion, Regul. Toxicol. Pharmacol. 82 (2016) 20–31.

[39]. C. Aparna, P. Srinivas, K.S.K.R. Patnaik, ENHANCED TRANSDERMAL PERMEABILITY OF TELMISARTAN BY A NOVEL NANOEMULSION GEL, Int. J. Pharm. Pharm. Sci. 7 (2015) 335–342.

[40]. A R.K. Harwansh, P.K. Mukherjee, S. Bahadur, R. Biswas, Enhanced permeability of ferulic acid loaded nanoemulsion based gel through skin against UVA mediated oxidative stress, Life Sci. 141 (2015) 202–211.

[41]. Hussain, A. Samad, S.K. Singh, M.N. Ahsan, M.W. Haque, A. Faruk, et al., Nanoemulsion gel-based topical delivery of an antifungal drug: in vitro activity and in vivo evaluation, Drug Deliv. 23 (2016) 642–65

[42]. A M.A. Mirza, S. Ahmad, M.N. Mallick, N. Manzoor, S. Talegaonkar, Z. Iqbal, Development of a novel synergistic thermosensitive gel for vaginal candidiasis: An in vitro, in vivo evaluation, Colloids Surfaces B Biointerfaces. 103 (2013) 275–282.

[43]. A M. Srivastava, K. Kohli, M. Ali, Formulation development of novel in situ nanoemulgel (NEG) of ketoprofen for the treatment of periodontitis, Drug Deliv. 7544 (2014) 1–13

[44]. S.A. Tayel, M.A. El-Nabarawi, M.I. Tadros, W.H. Abd-Elsalam, Promising ionsensitive in situ ocular nanoemulsion gels of terbinafine hydrochloride: Design, in vitro characterization and in vivo estimation of the ocular irritation and drug pharmacokinetics in the aqueous humor of rabbits, Int. J. Pharm. 443 (2013) 293–305.

[45]. E. Rahmani-Neishaboor, R. Jallili, R. Hartwell, V. Leung, N. Carr, A. Ghahary, Topical application of a film-forming emulgel dressing that controls the release of stratifin and acetylsalicylic acid and improves/prevents hypertrophic scarring., Wound Repair Regen. 21 (n.d.) 55–65.

[46]. Panwar N. Upadhyay, M Bairagi, S Gujar, G Darwhekar Emulgel. A Review. Asian Journal of Pharmacy and Life Science 2011; 1(3): 333-43.

[47]. Bandyopadhyay S, Katare OP, Singh B. Optimized self nanoemulsifying systems of ezetimibe with enhanced bioavailability potential using long chain and medium chain triglycerides. Colloids Surf B Biointerfaces 2012; 100: 50-61

[48]. A Singh Y, Meher JG, Raval K, et al. Nanoemulsion: Concepts, development and applications in drug delivery. J Control Release 2017; 252: 28-49.

[49]. Calder PC. Hot topics in parenteral nutrition. Rationale for using new lipid emulsions in parenteral nutrition and a review of the trials performed in adults. Proc Nutr Soc 2009; 68(3): 252-60.

[50]. Manuel-y-Keenoy B, Nonneman L, De Bosscher H, et al. Effects of intravenous supplementation with alpha-tocopherol in patients receiving total parenteral nutrition containing medium- and longchain triglycerides. Eur J Clin Nutr 2002; 56(2): 121-8.

[51]. Hippalgaonkar K, Majumdar S, Kansara V. Injectable lipid emulsions-advancements, opportunities and challenges. AAPS PharmSciTech 2010; 11(4): 1526-40.

[52]. A Choudhury H, Gorain B, Karmakar S, et al. Improvement of cellular uptake, in vitro antitumor activity and sustained release profile with increased bioavailability from a nanoemulsion platform. Int J Pharm 2014; 460(1-2): 131-43.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, June 2023

[53]. Derle D, Sagar B, Sagar P. Microemulsion as a vehicle for transdermal permeation of nimesulide. Indian J Pharm Sci 2006; 68(5): 622-5.

[54]. Kasturi R. Pawar & R. Jayachandra Babu. Lipid Materials for Topical and Transdermal Delivery of Nanoemulsions, Critical Reviews™ in Therapeutic Drug Carrier Systems 2014; 31(5): 429– 458.

[55]. Nastiti CMRR, Ponto T, Abd E, Grice JE, Benson HAE, Roberts MS. Topical Nano and Microemulsions for Skin Delivery. Pharmaceutics 2017; 9(4)9040037

[56]. Siang Yin Lee, et al. Lipid-Based Delivery System for Topical Phenytoin. In: Journal of Applied Pharmaceutical Science Vol. November 2016; 6: p. (11)014-020.

[57]. Dhawan B, Aggarwal G, Harikumar S. Enhanced transdermal permeability of piroxicam through novel nanoemulgel formulation. Int J Pharm Investig 2014; 4(2): 65-76.

[58]. Bajerski L, Michels LR, Colomé LM, et al. The use of Brazilian vegetable oils in nanoemulsions: an update on preparation and biological applications. Braz J Pharm Sci 2016; 52(3): 347-63.

[59]. Deapsari , et al. Penetration of Ubiquinone (Q10) Nanoemulsion Using Olive Oil Through Rat Skin. International Journal of Pharmaceutical and Clinical Research 2017; 9(2): 169-72.

[60]. R. SCHOLFIELD. Composition of Soybean Lecithin. Reprinted from the jozmzal of the American Oil Chemists‟. Society 1981; 58(10): 889-92. [28] van Hoogevest P, Wendel A. The use of natural and synthetic phospholipids as pharmaceutical excipients. Eur J Lipid Sci Technol 2014; 116(9): 1088-107.

[61]. Kato A, Ishibashi Y, Miyake Y. Effect of egg yolk lecithin on transdermal delivery of bunazosin hydrochloride. J Pharm Pharmacol 1987; 39(5): 399-400.

[62]. Hoeller S, Sperger A, Valenta C. Lecithin based nanoemulsions: A comparative study of the influence of non-ionic surfactants and the cationic phytosphingosine on physicochemical behaviour and skin permeation. Int J Pharm 2009; 370(1-2): 181-6.

[63]. A Wu H, Ramachandran C, Weiner ND, Roessler BJ. Topical transport of hydrophilic compounds using water-in-oil nanoemulsions. Int J Pharm 2001; 220(1-2): 63-75.

[64]. Barry BW. Lipid-protein-partitioning theory of skin penetration enhancement. J Control Release 1991; 15(3): 237-48.

[65]. Lopes LB, VanDeWall H, Li HT, et al. Topical delivery of lycopene using microemulsions: enhanced skin penetration and tissue antioxidant activity. J Pharm Sci 2010; 99(3): 1346-57.

[66]. S, Keyhanfar F, Amani A. Design and evaluation of oral nanoemulsion drug delivery system of mebudipine. Drug Deliv 2016; 23(6): 2035-43.

[67]. UrmilaSri Syamala. Development & Optimization Of Allyl Amine Antifungal Nanoemulgel Using 23 Factorial Design: For The Treatment Of Tinea Pedis. European Scientific Journal December 2013. SPECIAL/ edition vol.4 ISSN: 1857 – 7881 (Print) e - ISSN 1857- 7431.

[68]. A Pund S, Pawar S, Gangurde S, Divate D. Transcutaneous delivery of leflunomide nanoemulgel: Mechanistic investigation into physicomechanical characteristics, in vitro anti-psoriatic and antimelanoma activity. Int J Pharm 2015; 487(1-2): 148-56. 2016; 9(6): 210-223.

[69]. A Setya Sonal. Appraisal of Transdermal Water-in-Oil Nanoemulgel of Selegiline HCl for the Effective Management of Parkinson‟s Disease: Pharmacodynamic, Pharmacokinetic, and Biochemical Investigations. AAPS PharmSciTech February 2018; 19(2)

[70]. Hauss DJ. Oral lipid-based formulations. Adv Drug Deliv Rev 2007; 59(7): 667-76.

[71]. A Mortazavi S, Aboofazeli R. An Investigation into the Effect of Various Penetration Enhancers on Percutaneous Absorption of Piroxicam. Iran J Pharm Res 2003; 2: 135-40.

[72]. A Inayat Bashir Pathan. C Mallikarjuna Setty. Chemical Penetration Enhancers for Transdermal Drug Delivery Systems. Trop J Pharm Res 2009; 8(2): 173-9.

[73]. Srivastava M, Kohli K, Ali M. Formulation development of novel in situ nanoemulgel (NEG) of ketoprofen for the treatment of periodontitis. Drug Deliv 2016; 23(1): 154-66.

[74]. Ernoviya Ernoviya et al. Optimization and evaluation of topical ketoconazole nanoemulsion. Asian J Pharm Clin Res 2018; 11(5): 143-6.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, June 2023

[75]. Solè I, Maestro A, Gonzalez C, Solans C, Gutiérrez JM. Optimization of nano-emulsion preparation by low-energy methods in an ionic surfactant system. Langmuir 2006; 22(20): 8326-32.

[76]. Mason TG, et al. Extreme Emulsification: Formation and Structure of Nanoemulsions. J Phys Condens Matter 2006; 9(1): 193-9.

[77]. Graves S, Meleson K, Wilking J, Lin MY, Mason TG. Structure of concentrated nanoemulsions. J Chem Phys 2005; 122(13)134703

[78]. Peng Jie, Dong Wu-jun, Li Ling, et al. Effect of high-pressure homogenization preparation on mean globule size and large diameter tail of oil-in-water injectable emulsions journal of food and drug analysis 2015; 23: 828 -835.

[79]. Kotta S, Khan AW, Ansari SH, Sharma RK, Ali J. Formulation of nanoemulsion: a comparison between phase inversion composition method and high-pressure homogenization method. Drug Deliv 2015; 22(4): 455-66.

[80]. Lovelyn C, Attama AA, et al. Current State of Nanoemulsions in Drug Delivery. J Biomater Nanobiotechnol 2011; 2: 626-39.

[81]. Leong TS, Wooster TJ, Kentish SE, Ashokkumar M. Minimising oil droplet size using ultrasonic emulsification. Ultrason Sonochem 2009; 16(6): 721-7.

[82]. A Forgiarini A, et al. Formation of nano-emulsions by low energy emulsification methods at constant temperature. Langmuir 2001; 17: 2076-83.

[83]. Porras M, et al. Properties of water-in-oil (W/O) nano-emulsions prepared by a low-energy emulsification method. Colloids Surf A Physicochem Eng Asp 2008; 324(1-3): 181-8.

[84]. Chime SA, et al. Nanoemulsions - Advances in Formulation. Characterization and Applications in Drug Delivery. Application of Nanotechnology in Drug Delivery 2014; pp. 76-126.

[85]. Jennifer S. Komaiko and David Julian McClements. Formation of Food-Grade Nanoemulsions Using Low-Energy Preparation Methods: A Review of Available Methods. Compr Rev Food Sci Food Saf 2016; 15: 331-52.

[86]. Sengupta P, Chatterjee B. Potential and future scope of nanoemulgel formulation for topical delivery of lipophilic drugs. Int J Pharm 2017; 526(1-2): 353-65.

[87]. A Pund S, Rasve G, Borade G. Ex vivo permeation characteristics of venlafaxine through sheep nasal mucosa. Eur J Pharm Sci 2013; 48(1- 2): 195-201.

[88]. Irving R. Res. 1972; 6: pp. 571-82.

[89]. Howard A. Barnes. Thixotropy-a review. J Non-Newt Fluid Mech 1997; 70(1–2): 1-33.

[90]. Arora R, et al. Nanoemulsion Based Hydrogel for Enhanced Transdermal Delivery of Ketoprofen Adv Pharm 2014; 1-2.

[91]. Khushboo , et al. Formulation and evaluation of topical nano emulgel of adapalene World. J Pharm Sci 2015; 3(4): 1013-24.

[92]. A Kaur A, Saxena Y, Bansal R, et al. Intravaginal Delivery of Polyphenon 60 and Curcumin Nanoemulsion Gel. AAPS PharmSciTech 2017; 18(6): 2188-202.

[93]. A Hosny KM, Banjar ZM. The formulation of a nasal nanoemulsion zaleplon in situ gel for the treatment of insomnia. Expert Opin Drug Deliv 2013; 10(8): 1033-41.

[94]. A Elosaily GH. Formulation and In vitro Evaluation of Nystatin Nanoemulsion-Based Gel for Topical Delivery. J Am Sci 2012; 2012(8): 541-8.

[95]. Lakshmi P, Kumar GA. Nanosuspension technology: A review. Int J Pharm Pharm Sci 2010; 2(4): 35-40.

[96]. Hasenhuettl GL. Synthesis and commercial preparation of food emulsifiers.Food Emulsifiers and Their Applications. 2nd ed. New York: Springer Science Business Media 2008; pp. 11-37.

[97]. A Araújo FA, Kelmann RG, Araújo BV, Finatto RB, Teixeira HF, Koester LS. Development and characterization of parenteral nanoemulsions containing thalidomide. Eur J Pharm Sci 2011; 42(3): 238-45

[98]. HD, et al. Nanoemulsions for Food Applications: Development and Characterization. Food Bioprocess Technol 2012; 5: 854- 67.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, June 2023

[99]. Horne DS. Light scattering studies of colloid stability and gelation.New physicochemical techniques for the characterization of complex food systems. London: Blackie Academic & Professional 1995; pp. 240-67.

[100]. Saifullah M, Ahsan A, Shishir MRI. Production, stability and application of micro- and nanoemulsion in food production and food processing industry.Emulsions: Nanotechnology in the AgriFood Industry. London: Academic press, Elsevier Inc. 2016; Vol. 3: pp. 405- 42.

[101]. Chiesa M, et al. Thermal conductivity and viscosity of water-in-oil nanoemulsions. Colloids Surf A Physicochem Eng Asp 2008; 326(1- 2): 67-72.

[102]. Lakshmana PS, et al. Nanoemulgel for Transdermal Delivery of Cyclobenzaprine Hydrochloride: Design, Characterization and In vitro Studies. Nov Appro Drug Des Dev 2017; 1(5): 555-75.

[103].A Jones DS, Woolfson AD, Brown AF, Coulter WA, McClelland C, Irwin CR. Design, characterisation and preliminary clinical evaluation of a novel mucoadhesive topical formulation containing tetracycline for the treatment of periodontal disease. J Control Release 2000; 67(2-3): 357-68.

[104]. Majithiya RJ, et al. Thermoreversible mucoadhesive gel for nasal delivery of sumatriptan. 2006.

[105]. Lalit Kumar et al. In vitro evaluation of topical gel prepared using natural polymer. Int J Drug Deliv 2010; 2: 58-63.

[106]. Gurjot Kaur et al. Topical Nanoemulgel: A Novel Pathway for Investigating Alopecia. J Nanomed Nanotechnol 2017; 8: 472.

[107]. Srdan V. Stankov. Definition of Inflammation, Causes of Inflammation and Possible Anti-inflammatory Strategies. Open Inflamm J 2012; 5: 1-9.

[108].A Dasgupta S, Ghosh SK, Ray S, Kaurav SS, Mazumder B. In vitro & in vivo studies on lornoxicam loaded nanoemulsion gels for topical application. Curr Drug Deliv 2014; 11(1): 132-8.

[109]. Eid , et al. A review on the phytopharmacological effect of Swietenia macrophylla.

[110]. Eid AM, et al. Preparation, Characterization and AntiInflammatory Activity of Swietenia macrophylla Nanoemulgel. J Nanomed Nanotechnol 2014; 5(2): 190.

[111].A Somagoni Jaganmohan. Nanomiemgel - A Novel Drug Delivery System for Topical Application - In vitro and In vivo Evaluation PLoS ONE 2014; 9(12): e115952.

[112]. Rahman BS. Anwar F, Al-Abbasi FA, Kumar V NanotechnologyBased Nano Bullets in Anti-psoriatic Drug Delivery: State of the Art Nanoscience in Dermatology. Elsevier 2016; pp. 157-66.

[113].A Sarfaraz Alam Md, et al. Design and Characterization of Nanostructure Topical Gel of Betamethasone Dipropionate for Psoriasis. J Appl Pharm Sci 2012; 2(10): 148-58. [83] Herrmann ML, Schleyerbach R, Kirschbaum BJ. Leflunomide: an immunomodulatory drug for the treatment of rheumatoid arthritis and other autoimmune diseases. Immunopharmacology 2000; 47(2- 3): 273-89.

[114]. Kaltwasser JP. Leflunomide in psoriatic arthritis. Autoimmun Rev 2007; 6(8): 511-4.

[115]. Elewski BE, Hay RJ. Update on the management of onychomycosis: highlights of the Third Annual International Summit on Cutaneous Antifungal Therapy. Clin Infect Dis 1996; 23(2): 305-13.

[116]. Mahtab A, Anwar M, Mallick N, Naz Z, Jain GK, Ahmad FJ. Transungual Delivery of Ketoconazole Nanoemulgel for the Effective Management of Onychomycosis. AAPS PharmSciTech 2016; 17(6): 1477-90.

[117]. Elmataeeshy ME, et al. Enhanced transdermal permeability of Terbinafine through novel nanoemulgel formulation; Development, in vitro and in vivo characterization. Future Journal of Pharmaceutical Sciences 2018; 4(1): 18-28.

[118].APARNA. Enhanced transdermal permeability of telmisartan by a novel nanoemulsion gel. Int J Pharm Pharm Sci 2015; 7(4): 335- 42.

[119]. Parhi R, Terapalli BR, Teja BB. Formulation and in vivo evaluation of minoxidil topical gel. Turk J Pharm Sci 2014; 11: 153-62. [90] Usmania BA, Kataria MK. Minoxidil emulgel for androgenic alopecia: A literature review including patents. Int J Pharm Drug Anal 2017; 5(3): 49-58.

[120].A Olsen EA, Dunlap FE, Funicella T, et al. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. J Am Acad Dermatol 2002; 47(3): 377-85.

IJARSCT
ISSN (Online) 2581-9429
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International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, June 2023

[121]. Rani D, et al. Formulation Development and In vitro Evaluation of Minoxidil Bearing Glycerosomes. AJBR 2016; 4: 27-37.

[122].A .Sunitha S, et al. Design, Development and Evaluation of Nanoemulsion and Nanogel of Itraconazole for Transdermal Delivery. J Sci Res Pharm 2014; 3(1): 6-11.

[123].A Aithal GC, Nayak UY, Mehta C, et al. Localized In Situ Nanoemulgel Drug Delivery System of Quercetin for Periodontitis: Development and Computational Simulations. Molecules 2018; 23(6): 1363.

[124]. Jeengar MK, Rompicharla SV, Shrivastava S, et al. Manish KumarJeengar et al. Emu oil based nano-emulgel for topical delivery of curcumin. Int J Pharm 2016; 506(1-2): 222-36.

[125]. Mahesh B, et al. Enhanced permeability of cyclosporine from a transdermally applied nanoemulgel. Pharm Sin 2015; 6(2): 69-79.

[126]. Wais M, et al. Formulation development ex-vivo and in vivo evaluation of nanoemulsion for transdermal delivery of Glibenclamide. Int J Pharm Pharm Sci 20135: 747-54.

[127].A Singh BP, et al. Kumar, B., Jain, S.K., Shafaat, K., Development and characterization of a nanoemulsion gel formulation for transdermal delivery of carvedilol. Int J Drug Dev Res 2012; 4(1): 151- 61.

[128].A Drais HK, et al. Formulation Characterization and Evaluation of Meloxicam Nanoemulgel to be Used Topically. Iraqi J Pharm Sci 2017; 26(1) [100] Kamarza Mulia et al. Formulation and characterization of nanoemulgel mangosteen extract in virgin coconut oil for topical formulation. 2018.

[129].A Harwansh RK, Mukherjee PK, Bahadur S, Biswas R. Enhanced permeability of ferulic acid loaded nanoemulsion based gel through skin against UVA mediated oxidative stress. Life Sci 2015; 141: 202-11.

[130]. Pathak MK, Chhabra G, Pathak K. Design and development of a novel pH triggered nanoemulsified in-situ ophthalmic gel of fluconazole: ex-vivo transcorneal permeation, corneal toxicity and irritation testing. Drug Dev Ind Pharm 2013; 39(5): 780-90.

[131]. Singh Kamalinder Kour et al. Herbal contraceptive formulations. WO2006082596A2, 2006.

[132].A NOVARTIS AG. Diclofenac in emulsion-gel form EP 2 055 298 A1, 2009. [105] Roy Sunilendu Bhushan, Sheikh Shafiq, Kothari Jay, Patel Jitendra. Stable Pharmaceutical Composition of Diclofenac US20120093882A1, 2012.

[133]. James R. Nanoemulsion containing Composition having anti- inflammatory activity. WO2008051186A2, 2008.

[134].EMULGEL – A NOVEL SURROGATE APPRAOCH FOR TRANSDERMAL DRUG DELIVERY SYSTEM, Indo Am. J. Pharm. Res.

[135]. Indo Am. J. Pharm Res. 4 (2014). [S. Bhavesh, C.N. Shah, NANOEMULGEL: A COMPREHENSIVE REVIEW ON THE RECENT ADVANCES IN TOPICAL DRUG DELIVERY, Pharma Sci. Monit. 7 (n.d.) 346–355.

[136].A P. Chellapa, A.T. Mohamed, E.I. Keleb, A. Elmahgoubi, A.M. Eid, Y.S. Issa, et al., Nanoemulsion and Nanoemulgel as a Topical Formulation, IOSR J. Pharm. 5 (2015) 2250–3013.

[137]. Ajazuddin, A. Alexander, A. Khichariya, S. Gupta, R.J. Patel, T.K. Giri, et al., Recent expansions in an emergent novel drug delivery technology: Emulgel, J. Control. Release. 171 (2013) 122–132

[138].W. Warisnoicharoen, A.B. Lansley, M.J. Lawrence, Nonionic oil-in-water microemulsions: The effect of oil type on phase behaviour, Int. J. Pharm. 198 (2000) 7–27.

[139].A B. Sapra, P. Thatai, S. Bhandari, J. Sood, M. Jindal, A. Tiwary, A critical appraisal of microemulsions for drug delivery: part I., Ther. Deliv. 4 (2013) 1547–64.

[140].A T.. Vandamme, Microemulsions as ocular drug delivery systems: recent developments and future challenges, Prog. Retin. Eye Res. 21 (2002) 15–34.

[141].A.C. Williams, B.W. Barry, Penetration enhancers, Adv. Drug Deliv. Rev. 64 (2012) 128–137.

[142].R. Arora, G. Aggarwal, S.L. Harikumar, K. Kaur, R. Arora, G. Aggarwal, et al., Nanoemulsion Based Hydrogel for Enhanced Transdermal Delivery of Ketoprofen, Adv. Pharm. 2014 (2014) 1–12

[143].B. Dhawan, G. Aggarwal, S. Harikumar, Enhanced transdermal permeability of piroxicam through novel nanoemulgel formulation, Int J Pharma Investig. 4 (2014

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, June 2023

[144].V. Zanardo, D. Giarrizzo, M.K. Jeengar, P.S. Kumar, D. Thummuri, S. Shrivastava, et al., Re. "Review on emu products for use as complementary and alternative medicine"., Nutrition. 31 (2015) 415

[145].M.K. Jeengar, P. Sravan Kumar, D. Thummuri, S. Shrivastava, L. Guntuku, R. Sistla, et al., Review on emu products for use as complementary and alternative medicine, Nutrition. 31 (2015) 21–27.

[146].M.K. Jeengar, S. Shrivastava, S.C. Mouli Veeravalli, V.G.M. Naidu, R. Sistla, Amelioration of FCA induced arthritis on topical application of curcumin in combination with emu oil, Nutrition. (2015).

[147].F. Mondello, F. De Bernardis, A. Girolamo, A. Cassone, G. Salvatore, K. Martin, et al., In vivo activity of terpinen-4-ol, the main bioactive component of Melaleuca alternifolia Cheel (tea tree) oil against azole-susceptible and -resistant human pathogenic Candida species, BMC Infect. Dis. 6 (2006) 158.

[148].J. Reichling, U. Landvatter, H. Wagner, K.H. Kostka, U.F. Schaefer, In vitro studies on release and human skin permeation of Australian tea tree oil (TTO) from topical formulations, Eur. J. Pharm. Biopharm. 64 (2006) 222–228. \

[149].I.A. Southwell, S. Freeman, D. Rubel, Skin Irritancy of Tea Tree Oil, J. Essent. Oil Res. 9 (1997) 47–52.