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Role of Nano-emulsion as topical drug delivery system: A Review

(Nano-emulsion as topical drug delivery)

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Abstract: Topical drug delivery offers a fresh alternative to injection and oral delivery, which are the traditional drug distribution routes. In addition to being easy to use and non-invasive, the skin acts as a reservoir to hold medication for a few days. Nanocarriers offer fresh possibilities for the management of skin conditions. Potential nanocarrier faces a significant barrier to tissue infiltration from the skin's barrier function. Nevertheless, in cases of injury or inflammation, such as skin cancer, the barrier is somewhat compromised. It is possible that nanoparticle will facilitate skin penetration. Although a great deal of research has gone into creating nanoparticle for topical use, not much has been accomplished in terms of bringing them into the clinic to treat skin malignancies. The key ideas surrounding skin cancers and the methods used in modern clinical treatment are present in the prior art. This paper provides a comprehensive overview of the many nanoparticle technologies under investigation for the topical treatment of skin cancers and highlights the obstacles preventing these technologies from moving from the bench to the patient's side. The review also aims to provide information on the pathways that regulate the diffusion of nanoparticle into the skin and the interactions that occur within the tissue**.**

Index Terms **- melanoma, nanocarrier, stratum corneum, nanoparticle, non-invasiveness, topical**

INTRODUCTION

Since the skin avoids many of the issues associated with parenteral, inhalation, and oral routes, it is an effective drug delivery channel [Rastogi and Yadav, 2012] The benefits it provides for skin health have piqued the interest of researchers in recent years. The skin controls several substances' entry and exit from the body, avoiding moisture loss and controlling body temperature, in order to preserve homeostasis, or balance, within the body [Patil et al., 2019]. Skin problems account for almost one-third of all human diseases worldwide, making them the fourth most common cause of illness in humans. Nevertheless, their impact is sometimes underestimated. Atopic dermatitis and other chronic inflammatory skin conditions like psoriasis involve intense itching, thus people must learn to live with a disability. Other factors that contribute to this include the high occurrence of skin illnesses, their prolonged morbidity, and the high cost of cutting-edge medicines [Malik et al., 2016]

Certain healthcare systems may be financially threatened by the high incidence of skin cancer and the associated expenses of treatment. Skin disorders are most commonly caused by atopic dermatitis, which is ranked 15th out of all nonfatal diseases. Acne is a type of inflammatory dermatosis that is more common in women and is somewhat common [Bathe et al., 2015; Bertens et al., 2018]. Psoriasis is estimated to affect 2-4% of people in western nations. Because of this, topical treatments for many different diseases are effective; nevertheless, a full understanding of the skin's barrier function is still necessary. The epidermis, the outermost layer of the skin, the dermis, the intermediate layer containing numerous connective fibers, sensory receptors, and sweat glands, and the hypodermis, the subcutaneous layer, make up the complex barrier known as the skin [Monika et al., 2012]. Drug administration via this route has been well studied due to its larger surface area and convenience of use. The main route that goes to the living layers of this skin is very hydrophobic and restricted [Tan et al., 2012]. Therefore, drugs that penetrate the stratum corneum efficiently should be non-irritating, lipophilic or amphiphilic, and significantly smaller in size. However, a lot of compounds that could be useful for medications and cosmetics don't meet these requirements [Mali et al., 2015].

To overcome these obstacles, attention has been focused not only on the active ingredient but also on the form and content of the delivery system's total composition. These benefits encourage pharmaceutical companies to create topical treatments for skin conditions. The skin's ability to act as a barrier reduces the efficacy of treatments that use simple topical formulations, such as lotions and creams [Ramteke et al., 2012; Jeong et al., 2021]. Six To effectively disperse drugs through the skin's natural barriers, several methods have been investigated thus far. These days, many types of nanometric scale transporters are used in an increasing variety of percutaneous procedures. The therapeutic efficacy, bioavailability, and specificity of drugs may all be enhanced by using nanocarriers as drug carriers, which may help boost patient adherence to therapy [Tanwar et al., 2016]. Moreover, the use of nanoparticles in medicine administration can improve drug retention at the illness site within the skin by allowing for customized release kinetics. It has been demonstrated that nanoparticles can enter the skin through the

transappendageal channel, which passes through the ten sweat glands, hair follicles, and sebaceous and pilosebaceous glands [Bodde et al., 1989] This makes it possible for nanoparticles to pass through the outermost layer of defense, the stratum corneum, and into the skin's superficial layers [Joshi et al., 2014].

The skin engages with the environment, shields the body's surface from harm, and prevents the internal organs from being in direct contact with the outside world. A fatty subcutaneous layer sits on top of the layers of dermis and epidermis respectively [Jhawat et al., 2013]. The four stratified squamous epithelial layers that make up the epidermis are the stratum germinativum, stratum spinosum, stratum granulosum, and stratum corneum. These strata are composed of various keratinocyte subtypes that lack blood channels. Epidermal cells proliferate, differentiate, and move from lower layers to the uppermost layer [Malvey et al., 2019].

The fully mature keratinocyte cells that comprise the stratum corneum layer shed following epidermal turnover. The epidermis also contains Merkel cells, Langerhans cells, melanocytes, and keratinocytes. The dermis' complex structure is divided into two layers.(Rawat et al., 2016; Jasti et al., 2021). In an effort to provide the greatest potential therapeutic outcome, several medication delivery strategies are tested. Their choice is influenced by a number of factors, including the patient's health, the kind and severity of the ailment, and the ease of administration [Kadam et al., 2014]. As drug delivery is the focus of this review, we have explained the purpose of the dermal/transdermal mode of administration. There are presently ten dermal and over twenty transdermal products available in the US, according to the USFDA [Dev et al., 2015] However, most of them are typical dose forms like dermal or transdermal patches.

Apart from these patches, certain regions have been designated for the measurement of sprays and gels. These concoctions are meant to ease regional pain brought on by a variety of illnesses [Patel et al., 2021]. However, the transappendageal route only covers 0.1% of the skin's surface. Thirteen Consequently, it has no appreciable impact on large molecules' and nanoparticles' ability to penetrate the deeper skin layers where the majority of the disease is located. These cutting-edge nanovehicle technologies have the potential to accurately deliver potent drugs to the intended site [Annakula et al., 2010]. The skin reservoirs consisting of designed nano-systems effectively control the delivery of therapeutic drugs to the wounded area of the skin site with a limited effect.

Moreover, site-specific dermal targeting was made possible by nanoparticle, and their narrow size distribution would enhance medication retention [Reddy et al.., 2014]. Encasing therapeutically active compounds in Nanocarriers—which are increasingly being used for topical and skin-targeting delivery—could be a novel way to deliver bioactive chemicals to the skin [Date et al., 2005].These delivery methods allow for release across a longer time frame, which may lead to better absorption, longer acting times, and a reduction in side effects. The primary goal of this study is to assess the various state-of-the-art nanocarrier-based delivery techniques that are employed to enhance therapeutic moiety absorption through the skin and their potential for treating skin-related diseases. Patents pertaining to topical delivery are provided, as well as a summary of topical products that have been marketed [Ali et al., 2015; Akombaetwa et al., 2023]

An overview of nanoemulsion in drug delivery

An emulsion is referred to as a nanoemulsion if its size is less than a few tens or few hundred nanometers [Gopi et al., 2016]. As the system works to achieve a state of low Gibbs free energy, surfactants serve as a barrier to emulsion coalescence and reduce surface tension at the interface between the two immiscible phases [Khan et al., 2006] Because they can dissolve hydrophobic medications easily, lessen severe side effects, and quickly transition into the next generation of smart nanomaterials, nanoemulsions offer significant promise as effective nano-medicines [Yoshida et al., 1999] This article covers emulsion nanomedicine, the production and stability of various emulsion systems, the various types of surfactants, and factors to consider when introducing bioinspired nanoemulsions for drug delivery.

Types of emulsion

In their most basic form, emulsions are made up of two phases: a hydrophilic phase that is spread throughout the hydrophobic phase. When small oil droplets are dispersed through water, these emulsions are called oil-in-water (O/W) emulsions; when water droplets are scattered through oil, they are called water-in-oil (W/O) emulsions. Emulsions that are simple systems that can become more complex by encasing one emulsion within another, or double emulsions, are water-in-oil-in-water (W/O/W) and oil-in-water-in-oil (O/W/O) emulsions. Creating a double emulsion typically requires two steps: first, an internal emulsion needs to form, and then the first emulsion needs to be encircled by a second emulsion. In order to create a second emulsion, it is necessary to maintain the integrity of the first one. Additionally, in order to stabilize each oil-water interface, double emulsions require both lipophilic and hydrophilic surfactants, and there is an increased risk of coalescence and degradation due to diffusion between the phases. These days, more research is being done on uniform double emulsions created with microfluidic devices for applications in food science, as microreactors, or as templates for the manufacture of particles [Mataumoto et al., 1989]. Nano-emulsions are emulsions with droplet sizes ranging from 10 to 100 nm. Generally speaking, nanoemulsions consist of surfactant, water, and oil.

The selection of a surfactant is crucial for the development and stabilization of nanoemulsions. Nanoemulsions are thermodynamically unstable yet kinetically stable. Stated differently, nanoemulsions phase separate in sufficient time. Nanoemulsions have been produced for a wide range of applications in food, cosmetics, and pharmaceuticals. For all of these purposes, these materials need to be secure and biocompatible. As a result, choosing the appropriate oil and surfactants is essential. The most biocompatible oils and surfactants are those that are vegetable or pharmaceutical grade. Proteins and lipids have also been widely used as surfactants in the stabilization of nano-emulsions.

The solid lipid undergoes a gel to crystal phase transition upon freezing, after which it spontaneously breaks up into solid lipid particles. Monodisperse nanoemulsions containing lipid particles smaller than 100 nm were reported after the particles had thawed. The low surfactant concentration (<2%) and large drug loading (50%) of this process demonstrate a new direction in scalable emulsification technology [Sarathchandra et al., 2013].

Components of a Nanoemulsion

An o/w or w/o nanoemulsion is created when an oil phase and a water phase interact. A very thin layer of surfactant, occasionally enhanced by co-surfactant, enervates the microscopic dispersed phase. A summary of the strategies to be applied while selecting oil Several intrinsic properties of the integrating oil have been comprehended in the connecting section [Vandamme et al., 2002].

Selection of oil

One of the most important components of the nano-emulgel is the lipid, or oil, component. Numerous studies are required to determine an appropriate oil phase depending on the stability, permeability, and viscosity of the generated nanoemulsion. The therapeutic benefits of some natural oils can occasionally affect the selection of oil phase as well [Alexander et al., 2013]. It has been shown that vegetable oils (with long-chain fatty acids) have poor emulsification properties, which, depending on the oil's source, result in unstable nano-emulsions. Nevertheless, it was found that when the oil's hydrophobic qualities reduced, the emulsification properties got better.

Conversely, increased hydrophobicity affects the lipophilic drugs' solubility. Selecting the appropriate oil is therefore an important step in formulating a recipe [Warisnoicharoen et al., 2000]. Tea tree oil applied topically as a formulation ingredient may be beneficial for the treatment of bacterial and fungal infections. Another natural oil that is widely recognized for its broad antibacterial properties is tea tree oil. It has been discovered that tea tree oil and itraconazole, an azole antifungal medication, combine to form a stable, thermo-sensitive gel that can be used to treat vaginal candidiasis. When developing the nanoemulgel, an organic solvent was added to boost the drug loading of the tea tree oil. This improvement in itraconazole skin penetration was made possible by the presence of nano-sized droplets of terpinen-4-ol, the primary constituent of tea tree oil [Sapra et al., 2013]. Despite these benefits, the allergic properties of tea tree oil limit its use as a formulation ingredient.

Surfactant

The nanoemulsion system, which decreases the interfacial tension and adjusts the dispersion entropy between two immiscible liquids to stabilize their thermodynamically unstable combination, requires surfactants as a crucial component. stability, security, and heavy drug use. High emulsification capabilities and loading capacity are prerequisites for surfactants employed in the production of nano-emulsion [Silva et al., 2015]. Fast absorption of an efficient surfactant into the interface between the two immiscible phases is necessary to prevent the nano-droplets from coalescing and to dramatically lower interfacial tension in the nanoemulsion formulation.

Factors influence the selection of surfactants

The first and most important feature is the associated toxicity of the surfactant used. Selecting the appropriate surfactant is essential since too much of one can irritate the GI tract and skin when applied topically and orally, respectively [Manson et al., 2006]. It was therefore advised that the formulation use the least amount of surfactant feasible. Another factor for selection is the HLB value of the surfactant. Based on their HLB values, the currently available surfactants are divided into two categories: w/o emulsifying agent HLB 3-8 and o/w emulsifying agent HLB 8-16. Therefore, the HLB value of the chosen surfactant needs to be more than 10 in order to create an o/w nanoemulsion [Pore et al., 1992]

Co-surfactant

Co-surfactant aids in the emulsification of oil in the aqueous phase with surfactant in the nanoemulsion system. Co-surfactant provides the necessary fluidity, lowers the interfacial tension, and speeds up the emulsification process in this system by combining with surfactant and penetrating into the surfactant layer. Co-surfactant is added to the interfacial film to give it flexibility because surfactant typically cannot form a fluid interfacial film or a temporary negative interfacial tension on its own. Co-surfactants can aid in the solubilization of the oil by altering the curvature of the oil-water interface [Wang et al., 2015].

The selection of a co-surfactant is essential because the way lipophilic medications or therapeutic agents are released influences how they partition between the aqueous and oil phases due to the interaction between the co-surfactant and surfactant. The mass ratio of the surfactant and co-surfactant was found to have a substantial effect on the phase diagram properties, notably the position and size of the nanoemulsion zone. It was shown that the surfactant is unable to effectively reduce the interfacial tension when the co-surfactant is either absent (1:0) or present at lower concentrations. With regard to propylene glycol/carbitol and 20, this is true. On the other hand, a broader nanoemulsion zone and less interfacial tension are produced when the ratio of surfactant to cosurfactant is 1:1. The nanoemulsion area shrank first when the surfactant amount was decreased (3:1), and then the surfactant quantity increased (2:1). [Hua et al., 2004].

Furthermore, an inverse relationship has been observed between the co-surfactant concentration and the nanoemulsion area on the phase diagram. Researcher stated that the cosurfactant concentration ratio increased, the nanoemulsion area in the phase diagram of the mixture of Tween 80 (surfactant) and carbital (cosurfactant) decreased. Similarly, it was mentioned that an increase in the co-surfactant concentration in comparison to the surfactant (1:2) could result in a decrease in the nanoemulsion area compared to a 1:1 ratio. A report states that two non-ionic surfactants with different HLB values were able to generate an emulsion more stable than a mixture of surfactant and cosurfactant with similar HLB values. It has been observed as a result that selecting the optimal ingredients for a nanoemulsion is a challenging area of research [Syed et al., 2014]. The connecting section of the article will discuss the different parts of the formulation process utilized in the lab to make nanoemulsions and how different hydrogels are employed to change the physical state of the nanoemulsions.

Function

Nanoemulsion are drug carriers used in the delivery of pharmaceuticals. The main objective of using nanoemulsion is to increase the drug bioavailability of the transdermal pharmaceutical delivery method [Rai et al., 2018]. Using a phase diagram, we can select the constituents of a nanoemulsion by considering the ratios of the oil phase, surfactant/co-surfactant, and water phase. The application of nanoemulsion directly into skin organs is used to administer topical medications. The most useful medicinal application to date has been created to permeate the entire thickness of the skin and produce systemic effects. For nanoemulsions, there are several delivery options, such as topical, transdermal, ocular, perioral, percutaneous, and parenteral drug administration.

Nanoemulsions have an opalescent, transparent appearance. Preparing nanoemulsions requires a range of techniques. Nanoemulsions have an opalescent, transparent appearance. Surfactant, viscosity, lipophilicity, drug content, pH, concentration of each component, and formulation technique are some of the factors that affect nanoemulsions [Reza et al., 1938; Eqbal et al., 2021]. It is impractical to test every variable at every level. Formulation design offers an excellent approach to experimental design that saves both money and time. The nanoemulsion is one of the most efficient dispersed nanosystems with droplet sizes as small as sub-microns. In general, clear or semi-transparent systems with high stability are known as nanoemulsion [Eqbal et al., 2021]. They exhibit a high level of stability. Its submicron droplet size and high surfactant content make it an efficient transdermal delivery vehicle. Research shows that nanoemulsion is a far more effective drug delivery technology than other transdermal medication administration systems. The kind and type of co-surfactant and surfactant used increases the efficiency of the nanoemulsion [Salim et al., 2016; Choudhary et al., 2017]. Thus, this study focuses on the nanoemulsion potential as a topical and transdermal delivery strategy.

Formation and characteristics of nanoemulsions

It is necessary to have a solid understanding of the science underlying the nanoemulsion's production in order to control the droplet size. The process of making nanoemulsions usually involves two steps. First, a macro-emulsion is made, which is subsequently converted into a nanoemulsion [Nor Bainun et al., 2015] This section provides an overview of how preparation techniques have affected nanoemulsion qualities over the years, highlights advancements in the field, and describes the methods used for nanoemulsion preparation over the years [Kumar et al., 2021]. High energy methods and low energy methods are the two primary categories of nanoemulsion preparation techniques. Particle size, viscosity, turbidity, conductivity, interfacial tension test, surface properties, and thermodynamic stability are only a few of the numerous attributes of nanoemulsions. A number of techniques are used to apply some of these qualities; they are discussed below [Gupta et al., 2016]. The stability of the emulsion system is significantly impacted by the surface charge of the nanoemulsion droplets.

A small electrode is used to measure a nanoemulsion surface charge. Zeta potential is significant because it is associated with both the short- and long-term stability of emulsions. While low zeta potential emulsions tend to flocculate or coagulate, which could result in poor emulsion performance stability in terms of the body, high zeta potential emulsions (positive or negative) are electrically stabilized [De Oca-Avalos et al., 2017]. When there are more repulsive forces than attractive forces in an emulsion with a high zeta potential, the system is more stable. Zeta potential is a technique for figuring out surface charge properties and extending the physical stability of Zeta PALS, which is the apparatus used to assess nanoemulsion surface charges. The measurements were performed using diluted nanoemulsion formulations 16, and the data were computed using the oil droplets' electrophoretic mobility [Jiang et al., 2013] At least ±20 mV is preferred.

Drug release mechanisms from nanoemulsions

It is true that a w/o NE does not move through the skin in the same way as a hydrophilic or hydrophobic medicament. Studying the transdermal transport of a hydrophilic chemical given via NE systems is crucial since skin penetration requires increased lipophilicity [Sari et al., 2015]. It was proposed that unless water from the NE efficiently penetrates transdermally, a hydrophilic medication would not be accessible for percutaneous transfer from NEs. As a result, adequate water mobility within the NE vehicle and substantial water percutaneous transfer across the epidermal barrier are necessary. Furthermore, in this case, droplet size and the PS of the active chemical are more significant than o/w [Liu et al., 2014]. The methods for creating various kinds of nanoemulsions are covered in this part, along with the differences between conventional and nanoemulsions. The importance of steric hindrance, surface charge, and emulsifier properties such as ionization, molecular weight, and hydrophobic aliphatic chain is also emphasized [Miastkowska et al., 2020] There are differences between nanoemulsion and standard emulsion in terms of weight, droplet size, and preparation method.

These clear differences mean that conventional emulsions are less likely to be in stable form. This is due to the larger emulsion globule size. There is a significant gravitational pull on these globules and less repulsive force between the droplets. [Abbasi et al., 2020]. This makes it possible to see the sedimentation and ripening of Ostwald.

Stability Considerations

Nanoemulsion systems have a huge surface area and small droplet size, stability is one of the most critical characteristics. Because of the stability that nano-emulsions small droplet sizes offer against creaming or sedimentation brought on by Brownian motion, the diffusion rate is higher than the sedimentation rate brought on by gravity [Sun et al., 2014; Alam et al., 2015]. Ostwald ripening, or molecular diffusion, is the primary cause of nanoemulsion instability due to the polydispersity of the emulsion and the distinct solubility of large and small droplets. The Lifshitz-Slezov and Wagner theories predict a linear relationship between the cube of the radius, r3, and time, t. The slop in these theories is the Ostwald ripening rate. In order to predict the droplet dynamics and diameter, the LSW theory makes the assumption that the dispersed phase droplets are spherical and that the distance between them is greater than the molecular diffusion of the dispersed phase in the continuous phase [Kong et al., 2011].

This theory states that the Ostwald ripening rate in O/W emulsions is directly proportional to the oil's solubility in the aqueous phase. Although it has been demonstrated that the amount of micelles in the continuous phase, which stop oil molecules from migrating into it, increases as surfactant concentration rises, Ostwald ripening rate actually falls with surfactant concentration. The Ostwald ripening process is inhibited when the surfactant concentration is raised below the critical micelle concentration (CMC), since tiny droplets with low interfacial tension and a monodisperse dispersion develop [Ali et al., 2014]. Polymeric surfactants have been introduced to o/w nanoemulsions to adjust the interfacial tension, increase Gibbs dilatational elasticity, and strongly adsorbed at the O/W interface, hence reducing Ostwald ripening. The dispersed phase of nanoemulsions can be stabilized against Ostwald ripening by the addition of an insoluble surfactant.It was discovered that adding a second surfactant with the same alkyl chain length and a higher degree of ethoxylation than the primary surfactant decreased the Ostwald ripening rate for an ethoxylated nonionic surfactant system [Delmas et al., 2011; Makidon et al., 2010]

Ostwald ripens according to the Arhenius law of temperature reversal, therefore keeping the nanoemulsions at the optimal temperature can slow down the ripening process. To lessen the consequences of an Ostwald ripening, a second ingredient

that is insoluble in the continuous phase, like squalane, can be added to the dispersed phase [Rahn-Chique et al., 2012]. When it comes to inhibiting Ostwald ripening, high-pressure homogenization-prepared nanoemulsions have demonstrated superior stability compared to those generated using the PIT approach. Additionally, research indicates that W/O emulsions have a slower Ostwald ripening than O/W emulsions with the same hydrocarbon. Ostwald ripening of nanoemulsions can be inhibited by a variety of factors, including the physical characteristics of the constituent parts, the mutual solubility of the phases, the kind and concentration of the surfactant utilized, the production process, and the storage environment [Ding et al., 2023].

Current Challenges with Topical Drug Delivery Using Nanoemulsions

Formulation Challenges

The stratum corneum (SC), the uppermost layer of skin and the rate-limiting stage for epidermal drug transport, is the most challenging barrier to overcome for dermal penetration. The choice of components for the topical delivery method also considers critical physicochemical parameters of the medication, including log, pKa, solubility, and molecular mass [Yukuyama et al., 2017]. When choosing a topical carrier, medications like ACE that are acidic and unstable need to be taken into account carefully. Because of its acidic group, the excipients should not only hide the medication's propensity to irritate skin but also foster an environment that maximizes topical diffusion while maintaining chemical integrity [Ganta et al., 2014].

Regulatory Aspects to Take into Account

While regulatory definitions for nanoemulsions are typically lacking, scholars and international regulatory agencies have defined nanomaterials in a number of ways that apply to nanomaterials in general. "Food that has been cultivated, produced, processed, or packaged using nanotechnology techniques or tools, or to which manufactured nanomaterials have been added," is the widely accepted definition of nanofoods, according to Joseph and Morrison (2006) [Wani et al., 2018]. Conversely, the European Commission (2011) defines a nanomaterial as "any natural, incidental, or synthetic material" that accounts for the physical state, size, and dispersion of material particles.

The advantages of new technology to exceed the disadvantages, it is imperative to comprehend the political problems at play. Furthermore, imposing direct regulatory measures like required labeling and creating a public registry of manufacturers and goods may be necessary to fortify the laws governing food nanotechnology. identifies a few topics for discussion between legislators, industry, and the government about the regulations controlling the use of nanotechnology in food [Ozogul et al., 2019] According to size and biodegradability, nanoparticle classified into four classes and linked the longevity of each class in the human body. It is said that the high-risk class of particles is biopersistent, and the low-risk class is biodegradable. According to the authors, it is essential that the human body totally gets rid of or breaks down the nanoparticles [Maali et al., 2013].

REFERENCES

1. Rastogi V, Yadav P (2012) Transdermal drug delivery system: An overview. Asian Journal of Pharmaceutics 6(3).
2. Patil P, Datir S, Saudagar R. A review on topical gels as drug delivery system. Journal of Drug Delivery and Therapeutics, 2019, Vol. 9, no. 3s, pp. 989-994.
3. Malik S, Mital DN, Kaur G (2016), Topical drug delivery systems: a patent review. Expert opinion on therapeutic patents, 2016. 26(2): pp. 213-228.
4. Bertens CJ (2018). Topical drug delivery devices: A review. Experimental eye research, Vol. 168, pp. 149-160.
5. Bathe R, Kapoor R (2015). Transdermal drug delivery system: formulation, development and evaluation-An overview. Drug Deliv, Vol. 6: pp. 7-12.
6. Monika B, (2012). Transdermal drug delivery system with formulation and evaluation aspects: overview. Research Journal of Pharmacy and Technology, Vol. 5, no. 9, pp. 1168-1176.
7. Tan X (2012) Topical drug delivery systems in dermatology: a review of patient adherence issues. Expert opinion on drug delivery Vol. 9, no. 10, pp. 1263-1271.
8. Mali AD (2015). An updated review on transdermal drug delivery systems. Skin, Vol. 8, no. 9, 305-312.
9. Ramteke K, Dhole S, Patil S (2012) Transdermal drug delivery system: a review. Journal of Advanced Scientific Research, 2012, Vol. 3, no. 01, pp. 22-35.
10. Jeong WY (2021). Recent advances in transdermal drug delivery systems: A review. Biomaterials research, Vol. 25, no. 1: pp. 24.
11. Tanwar H, Sachdeva R (2016) Transdermal drug delivery system: A review. International journal of pharmaceutical sciences and research, Vol. 7, no. 6, pp. 2274-2278.
12. Boddé H, Verhoeven J, Van Driel L (1989) The skin compliance of transdermal drug delivery systems. Critical reviews in therapeutic drug carrier systems, Vol. 6, no. 1, pp. 87-115.
13. Joshi M, Butola B, Saha K (2014), Advances in topical drug delivery system: Micro to nano-fibrous structures. Journal of Nanoscience and Nanotechnology, Vol. 14, no. 1, pp. 853-867.
14. Jhawat VC (2013) Transdermal drug delivery systems: approaches and advancements in drug absorption through skin. Int J Pharm Sci Rev Res, Vol. 20, no. 1, pp. 47-56.
15. Malvey S, Rao JV, Arumugam KM (2019) Transdermal drug delivery system: A mini review. Pharma Innov, Vol. 8, pp. 181-197.
16. Rawat A, Bhatt GK, Kothiyal P (2016) Review on transdermal drug delivery system. Indo Am J Pharm Sci, Vol. 3, pp. 423-428.
17. Jasti BR, Abraham W, Ghosh TK (2021) Transdermal and Topical drug delivery systems, in Theory and practice of contemporary pharmaceutics. CRC Press. Vol 3, no.4, pp. 423-454.
18. Kadam AS, Ratnaparkhi MP, Chaudhary SP (2014) Transdermal drug delivery: An overview, Drug Del. Ind. Pharm., Vol. 3, no. 4, pp. 321-327.
19. Dev A, Chodankar R, Shelke O (2015), Emulgels: a novel topical drug delivery system. Pharmaceutical and biological evaluations, Vol. 2, no. 4, pp. 64-75.

20. Patel D, Patel B, Thakkar H (2021) Lipid based nanocarriers: Promising drug delivery system for topical application. european Journal of lipid science and technology, Vol. 123, no. 5, pp. 2000264.
21. Annakula D (2010) Provesicular drug delivery systems: An overview and appraisal. Arch Appl Sci Res, Vol. 2, no. 4, pp. 135-146.
22. Reddy YK, Reddy DM, Kumar MA (2014) Transdermal drug delivery system: a review. Indian Journal of Research in Pharmacy and Biotechnology Vol. 2, no. 2, pp. 1094-1999.
23. Date A, Naik B, Nagarsenker M (2005), Novel drug delivery systems: potential in improving topical delivery of antiacne agents. Skin pharmacology and physiology, Vol. 19, no. 1, pp. 2-16.
24. Ali S, Shabbir M, Shahid (2015) The structure of skin and transdermal drug delivery system-a review. Research journal of pharmacy and technology, Vol. 8, no 2, pp. 103-109.
25. Akombaetwa N (2023) Current advances in lipid nanosystems intended for topical and transdermal drug delivery applications. Pharmaceutics, Vol. 15, no. 2, pp. 656.
26. Gopi S (2016) Introduction of nanotechnology in herbal drugs and nutraceutical: a review. J. Nanomedine. Biotherapeutic Discov, Vol. 6, no. 2, pp. 143-150.
27. Yaqoob Khan A (2006) Multiple emulsions: an overview. Current drug delivery, Vol. 3, no. 4, pp. 429-443.
28. Yoshida K (1999) Stability of vitamin A in oil-in-water-in-oil-type multiple emulsions. Journal of the American Oil Chemists' Society, Vol. 76, no. 2, pp. 1-6.
29. Mataumoto S, Kang W (1989) Formation and applications of multiple emulsions. Journal of Dispersion Science and Technology, Vol. 10, no. 4-5, pp. 455-482.
30. Zhang, J., et al., Facile fabrication of cyclodextrin-modified magnetic particles for effective demulsification from various types of emulsions. Environmental science & technology, 2016. 50(16): p. 8809-8816.
31. Sarathchandra Prakash N (2013) Emulsions and emulsifiers. The Asian Journal of Experimental Chemistry, Vol. 8, pp. 30-45.
32. Vandamme TF (2002) Microemulsions as ocular drug delivery systems: recent developments and future challenges. Progress in retinal and eye research, Vol. 21, no 1, pp. 15-34.
33. Alexander A (2013) Recent expansions in an emergent novel drug delivery technology: Emulgel. Journal of Controlled Release, Vol. 171, no. 2, pp. 122-132.
34. Warisnoicharoen W, Lansley A, Lawrence M (2000) Non-ionic oil-in-water microemulsions: the effect of oil type on phase behaviour. International Journal of Pharmaceutics, Vol. 198, no. 1, pp. 7-27.
35. Sapra B (2013) A critical appraisal of microemulsions for drug delivery: part I. Therapeutic delivery, Vol. 4, no. 12, pp. 1547-1564.
36. Silva HD, Cerqueira MA, Vicente AA (2015), Influence of surfactant and processing conditions in the stability of oil-in-water nanoemulsions. Journal of food engineering, Vol. 167, pp. 89-98.
37. Mason, T.G., (2006) Nanoemulsions: formation, structure, and physical properties. Journal of Physics: condensed matter, Vol. 18, no. 41, pp. R635.
38. Poré J (1992), Émulsions, micro-émulsions, émulsions multiples: Les agents de surface. 2, Balance hydrophile. Éd. techniques des industries des corps gras.
39. Wang Z (2015) Lower irritation microemulsion-based rotigotine gel: formulation optimization and in vitro and in vivo studies. International Journal of Nanomedicine, Vol. 2, no. 3, pp. 633-644.
40. Hua L (2004) Preparation, evaluation, and NMR characterization of vinpocetine microemulsion for transdermal delivery. Drug development and Industrial Pharmacy Vol. 30, no. 6, pp. 657-666.
41. Syed HK, Peh KK (2014), Identification of phases of various oil, surfactant/co-surfactants and water system by ternary phase diagram. Acta Pol Pharm, Vol. 71, no. 2, pp. 301-309.
42. Rai VK (2018) Nanoemulsion as pharmaceutical carrier for dermal and transdermal drug delivery: Formulation development, stability issues, basic considerations and applications. Journal of controlled release, Vol. 270, pp. 203-225.
43. Reza KH (2011) Nanoemulsion as a novel transdermal drug delivery system. International journal of pharmaceutical sciences and research, Vol. 2, no. 8, pp. 1938-1945.
44. Eqbal A (2021) Recent applications of nanoemulsion based drug delivery system: A review. Research Journal of Pharmacy and Technology, Vol. 14, no. 5, pp. 2852-2858.
45. Choudhury H (2017) Recent update on nanoemulgel as topical drug delivery system. Journal of pharmaceutical sciences, Vol. 106, no. 7, pp. 1736-1751.
46. Salim N (2016) Nanoemulsion as a topical delivery system of antipsoriatic drugs. RSC advances, Vol 6, no. 8, pp. 6234-6250.
47. Singh Y (2017) Nanoemulsion: Concepts, development and applications in drug delivery. Journal of controlled release, Vol. 252, pp. 28-49.
48. Nor Bainun I, Alias NH, Syed-Hassan SSA (2015) Nanoemulsion: formation, characterization, properties and applications-a review. Advanced Materials Research, Vol. 1113, pp. 147-152.
49. Kumar N, Verma A, Mandal A (2021), Formation, characteristics and oil industry applications of nanoemulsions: A review. Journal of Petroleum Science and Engineering, Vol. 206, pp. 109042.
50. Gupta A (2016) Nanoemulsions: formation, properties and applications. Soft matter, Vol. 12, no. 11, pp. 2826-2841.
51. de Oca-Ávalos JMM, Candal RJ, Herrera ML (2017), Nanoemulsions: stability and physical properties. Current Opinion in Food Science, Vol. 16, pp. 1-6.
52. Jiang SP (2013) Preparation and characteristics of lipid nanoemulsion formulations loaded with doxorubicin. International journal of nanomedicine, Vol. 3, no. 4, pp. 3141-3150.
53. Sari T (2015) Preparation and characterization of nanoemulsion encapsulating curcumin. Food Hydrocolloids, 43, pp. 540-546.
54. Liu F (2014), pH-responsive nanoemulsions for controlled drug release. Biomacromolecules Vol. 15, no. 3, pp. 968-977.

55. Miastkowska, M, Śliwa P (2020), Influence of terpene type on the release from an O/W nanoemulsion: Experimental and theoretical studies. Molecules, Vol. 25, no. 12, pp. 2747.
56. Abbasi S (2020) New design strategies for controlling the rate of hydrophobic drug release from nanoemulsions in blood circulation. Molecular Pharmaceutics, Vol. 17, no. 10, pp. 3773-3782.
57. Sun W (2014) Nano composite emulsion for sustained drug release and improved bioavailability. Pharmaceutical research, Vol. 31: p. 2774-2783.
58. Alam MS (2015) Stability testing of beclomethasone dipropionate nanoemulsion. Tropical Journal of Pharmaceutical Research, Vol.14, no. 1, pp. 15-20.
59. Kong M, Park HJ (2011), Stability investigation of hyaluronic acid based nanoemulsion and its potential as transdermal carrier. Carbohydrate polymers, Vol, 83, no.3, pp. 1303-1310.
60. Ali MS (2014) Preparation, characterization and stability study of dutasteride loaded nanoemulsion for treatment of benign prostatic hypertrophy. Iranian Journal of Pharmaceutical Research Vol. 13, no. 4, pp. 1125-1130.
61. Delmas T (2011) How to prepare and stabilize very small nanoemulsions. Langmuir, Vol. 27, no. 5, pp. 1683-1692.
62. Makidon PE (2010) Characterization of stability and nasal delivery systems for immunization with nanoemulsion-based vaccines. Journal of aerosol medicine and pulmonary drug delivery, Vol. 23, no. 2, pp. 77-89.
63. Rahn-Chique K (2012) Nanoemulsion stability: experimental evaluation of the flocculation rate from turbidity measurements. Advances in colloid and interface science, Vol. 178, pp. 1-20.
64. Ding B (2023) On the stability of pickering and classical nanoemulsions: Theory and experiments. Langmuir, Vol 39, no. 20, pp. 6975-6991.
65. Nishitani Yukuyama M (2017) Challenges and future prospects of nanoemulsion as a drug delivery system. Current pharmaceutical design, Vol. 23, no. 3, pp. 495-508.
66. Ganta S (2014), Nanoemulsions in translational research—opportunities and challenges in targeted cancer therapy. Aaps Pharmscitech, Vol. 15, pp. 694-708.
67. Wani TA (2018) Safety of nanoemulsions and their regulatory status in Nanoemulsions Elsevier. pp. 613-628.
68. Rana S, Yadav KK, Jha M (2024), Environmental, legal, regulatory, health, and safety issues of nanoemulsions, in Industrial Applications of Nanoemulsion Elsevier. pp. 219-247.
69. Özoğul Y (2019) Nanotechnological Applications. Innovative Technologies in Seafood Processing, pp. 279-301.
70. Maali A, Mosavian MH, (2013), Preparation and application of nanoemulsions in the last decade (2000–2010). Journal of dispersion science and technology Vol. 34, pp. 1, pp. 92-105.

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