**IJPSR (2020), Volume 11, Issue 6** **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 02 September 2019; received in revised form, 10 January 2020; accepted, 21 January 2020; published 01 June 2020

# NANOEMULSION: A PROMISING AND NOVEL NANOTHERAPEUTIC VEHICLE FOR TRANSDERMAL DRUG DELIVERY

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**Keywords:**

Nanoemulsion, Skin, Bioactives, Transdermal, Drug delivery, Bioavailability

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**ABSTRACT:** Transdermal delivery of therapeutics has been identified by scientific researchers as an alternative choice of drug administration, owing to its unique and tremendous benefit over conventional and oral administrations, but its exploration has been limited because of the "skin barricade" as its major challenge. A special formulation that is capable of meeting up and overcoming its associated challenges is required. Nanotechnology is already established as one of the developing areas of technology, and its application in drug delivery has proven overwhelming success. Nanoemulsions are unique nanotechnological formulations that represent a novel drug delivery system towards resolving pharmaceutical challenges as well as improves dermal and transdermal drug delivery. Since the majority of novel drug candidates, especially those phyto-pharmaceutically discovered, are of less solubility and bioavailability, their pharmaceutical applications have been underexplored. This study aims at presenting nanoemulsion as a novel formulation capable of solving undesirable pharmaceutical challenges such as toxicity, first-pass metabolic effect, drug solubility, and bioavailability. Its potential as an exclusive nanocarrier that mobilizes and promotes transdermal therapeutic delivery is also reviewed. Improvement in drug potential and delivery using nanoemulsions as a recent advance with particular attention to the possibility of its journey through the skin and its consideration as a multiple delivery tool for the systemic circulation through the skin as a transdermal drug delivery route is also highlighted.

**INTRODUCTION:** Novel and promising drug candidates represent our therapeutic dependence in different health conditions, but the majority of these drug candidates are of reduced exploration because of their limited bioavailability.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(6).2636-48

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(6).2636-48

Also, in recent years, there has been an overwhelming interest in the dermal and percutaneous delivery of pharmaceuticals as well as bioactive. Fortunately, the use of nanoemulsion as the vehicle reflects a good future in both transdermal drug delivery [1] and bioavailability enhancement.

Transdermal drug delivery is an innovative research area that is becoming prominent globally as a result of its unique merits over other routes [2]. This system uniquely achieves the therapeutic concentration of drug through skin with proper

delivery at a controlled rate, making it very conducive for the treatment of both chronic and acute disorders [3, 4]. These delivery systems also constitute a novel research area of drug delivery as it helps to overcome drawbacks associated with parenteral routes [5]. Its ability to promote therapeutic efficacy can be based on its improving bioavailability of drug, non-invasive nature, overcoming gastrointestinal side effects, patient's accessibility, pain-free nature, ability to avoid hepatic first-pass metabolism and facilitation of self-medication in patients [6-8]. In addition, extensive investigation shows this route as a substitute to the oral route of drug transport because the rich supply of blood by the dermis ease the unswerving passage of drug into the blood for systemic circulation and effects [9, 10-12].

In contrast, the biophysical properties of the skin impose a barrier towards enhanced permeation of drug through the stratum corneum [13]. Also, limitations are associated with percutaneous delivery of semi-solid formulations as a result of their large particle size, slow skin entry, fast volatilization of highly vaporous compounds, environmental disintegration, etc. [8] In order to promote drug permeation through this significant barrier, chemical and physical methods such as iontophoresis, microneedle array, laser and thermal ablation including chemical penetration enhancers have been explored [9, 11, 14]. However, these techniques pose limitations such as irritation and damage to the skin barrier. A higher dosage of chemical enhancers could also lead to increased toxicity [14]. Extensive investigation has also been carried out in the area of nanotechnology to be able to deliver less soluble, highly volatile as well as photosensitive and charged surface [15].

In view of the best technique to display safe and improved drug bioavailability and drug delivery approach, as evident from the literature, Nanoemulsion-based technology is expected to fit in [16]. Nanoemulsion based technology allows the combined possibility of enhancing penetration across the skin by altering the lipid bilayer and at the same time, acts as a tiny storage channel for drugs [17]. Considering its flowing (fluidic) nature, notable interrelation with skin cells, adequate permeation ability, small globule size, ability to protect and deliver even irritant as well as the compound of high volatility and molecular weight makes it the best [1]. Nanoemulsion droplets are able to overcome the barrier posed by the skin by penetrating the skin pores and arrive at the systemic circulation, getting successfully channelized for effective delivery of drugs [18]. This delivery vehicle also offers advantages such as the great solubilizing ability of both hydrophilic and hydrophobic drugs, reduced cost of preparation, reduced viscosity with Newtonian behavior, thermodynamic and increased storage stability, and protection of bioactive ingredients against oxidation and hydrolysis [7, 13, 19].

The prospect significance of this area of research has extended the hand of researchers into the challenging issues associated with the formulation of nanoemulsions and its applicability in the treatment of crucial and challenging issues associated with the transdermal delivery route. In this manuscript, some of the vital findings in various literature were represented, thereby discussing nanoemulsions and their association with the skin barrier. The skin physiology and mechanism of transdermal drug transport are also reviewed.

**2. Bioavailability of Orally Administered Drugs:**

Bioavailability includes drug absorption, drug distribution, drug metabolism, drug excretion, and drug toxicology despite the efficacy of such drugs. According to the U.S. Food and Drug Administration (FDA), bioavailability is defined as "the rate and extent to which an active drug ingredient or therapeutic fraction is absorbed from a drug product and becomes accessible at the site of drug action. It can further be said to be the absorption of a drug from the gastrointestinal tract after administration of an oral dosage form. The journey of an orally administered dosage form is majorly through the site of first-pass metabolism (Intestine and Liver) where metabolism of the drug takes place before reaching the systemic circulation. Low bioavailability is also due to poor aqueous solubility especially with oral dosage forms of lipophilic (poorly water-soluble) which displays slow absorption, hence, insufficient time for absorption in the GI tract. If the drug does not dissolve readily or cannot penetrate the epithelial membrane, the time required at the absorption site may be insufficient, thereby altering its bioavailability.

**TABLE 1: THE STEPS INVOLVED IN THE DISTRIBUTION OF ORALLY ADMINISTERED DRUG**

| Steps | Distribution |
|---|---|
| Step 1 | Oral dosage form gets to stomach/intestine |
| Step 2 | Undergo disintegration into small particles |
| Step 3 | Dissolution occurs in gastrointestinal (GIT) fluids and reaches GIT wall/membrane |
| Step 4 | Drug returns to GIT lumen by P-glycoprotein efflux pump |
| Step 5 | Metabolism of drug by intestinal enzymes |
| Step 6 | Absorption of drug into the hepatic circulation |
| Step 7 | Drug reaches systemic circulation |
| Step 8 | Excretion of drug through the urine |
| Step 9 | Drug is metabolized |
| Step 10 | The active metabolite approaches its site of action, causing a pharmacological response unrelated to desired therapeutic activity |
| Step 11 | A Response related to desired clinical response is produced |

## 3. Nanoemulsion Basics:

**3.1. Nanoemulsion and its Classification:** Nanoemulsions or submicron emulsions are optically isotropic system composed of a mixture of two immiscible liquids (mainly oil and aqueous medium) resulting in a fine dispersion of drugs in nanodroplets with small size distribution [20-22]. They are kinetically stabled colloidal particulate systems with uniform size distribution stabilized by an interfacial layer of suitable surfactant [8, 23].

Nanoemulsions can be classified based on their 'components' and 'surface charge' over the nanodroplets. For the former, nanoemulsions can be grouped into:

**(a) Oil-in-water (O/W) nanoemulsions:** It is a type of nanoemulsion formed when an oil phase is dispersed into an aqueous medium

**(b) Water-in-oil (W/O) nanoemulsions:** It is a type of nanoemulsion formed when water is dispersed into an oil medium

**(c)** Bicontinuous nanoemulsion *i.e.* interdispersion of microdomains of oil and water phase [19, 24]. The latter classifies nanoemulsions into Neutral nano-emulsions, Anionic nanoemulsions and Cationic nanoemulsions - where, neutral, anionic and cationic surfactants are used respectively [21, 25].

Recent research has proven O/W nanoemulsion to be of high popularity in medicine than the W/O counterpart owing to its compatibility with water, safe and wide use in drug delivery [26, 27].

**3.2 Nanoemulsion Composition:** Basically, nano-emulsions comprise oil, surfactants /emulsifiers including co-surfactants/co-emulsifiers and the aqueous phase [28]. **Fig. 1** represents an illustration of an O/W nanoemulsion, including the general composition of a nanoemulsion. Oil Phase is one of the important adjuvants in nanoemulsions, where its solubilizing ability in relation to drugs (phytoactive or synthetic drugs) of choice is an important factor in choosing oil. Depending on the chain lengths, long-chain triglycerides and medium-chain triglycerides are used either alone or in combination for nanoemulsion formulation. Recent studies have reported that nanoemulsion can be employed to improve the bioavailability of drugs with poor water solubility, such as curcumin by solubilizing [29]. Also, the permeability of cytotoxic drugs such as piplartine can be enhanced [30] into cancer cells.

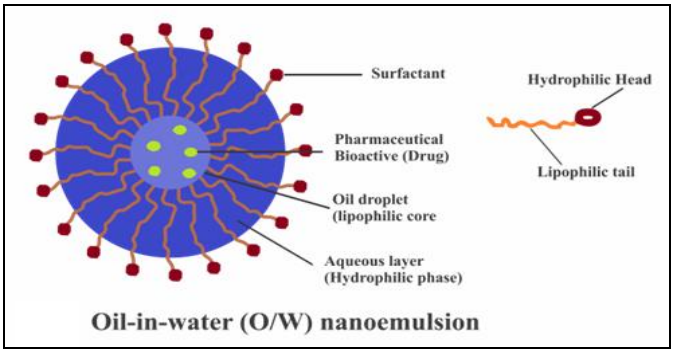


**FIG. 1: SIMPLE ILLUSTRATION OF AN O/W NANOEMULSION ENCAPSULATING A PHYTO-PHARMACEUTICAL**

An increased interest has aroused in the use of natural products in the field of drug delivery due to their preferred advantages. These include low toxicity and widespread therapeutic benefits [31]. The use of essential oils as oil phase in nanoemulsion formulation is not only safe and biocompatible but are volatile natural compounds that are susceptible to oxidation, thermal and photodegradation [32] with complex fatty acids composition known to have diverse benefits [33].

Da Silva Gundel *et al*., 2018, recently developed nanoemulsion that contains Basil oil. The objective is to determine its stability as well as cytotoxicity in healthy cells of humans with the antioxidant, including potential antimicrobial evaluation. Result indicated reduced activity of the free oil and the antioxidant. Also, cytotoxicity was not represented but the antimicrobial activity proves effective [32].

Ge *et al*., 2018, prepared a complex comprising a phospholipid and dabigatranetexilate (DE) nano-emulsion matrix. The formulation displayed an improved dissolution in simulated intestinal fluids. This is carried out by containing DE into an oil phase. DE, (a direct thrombin inhibitor for treatment of thromboembolism) in a phospholipid complex (DE-PC) showed a significant reduction ($p<0.05$) in drug leakage. Relatively, the bioavailability of DE-PC was found to increase to 147.3% and 606.6% [34].

Tumtibsri *et al*., 2018 also carried out recent research on spearmint oil (SMO), which was incorporated into a nanoemulsion. Spearmint oil acts as a cytotoxic agent to adverse oral carcinoma cell line using MTT assay. SMO is mostly used in oral hygiene products, and it has numerous interesting potentials, especially its anticancer property. Unfortunately, its application in combating cancer is reduced because it is naturally insoluble in water. In this study, nanoemulsion was chosen as an alternative vehicle for SMO to impede oral cancer cells. Surfactant amount and type, oil loading as well as the proportion of SMO in relation to virgin coconut oil (VCO) were studied. The SMO-VCO nanoemulsions showed a notable cytotoxic effect against oral carcinoma (KON) cell line using MTT assay. The investigation reveals the improved feasibility of SMO-VCO nanoemulsions as a potential unique carrier for oral cancer treatment [35].

Mohd. Aqil, 2015 investigated the development and optimization of clove oil with olmesartan nanoemulsion formulation in a transdermal application using the Box-Behnken design. The result suggested that the developed nanoemulsion carrier of the olmesartan provides 53.11 ± 3.13 nm as the particle size, 0.335 ± 0.008 as the polydispersity index with a transdermal flux of 12.65 ± 1.60 µg/cm$^3$/h. Confocal laser scanning microscope unveiled an improved entry of the Rhodamine - B loaded nanoemulsion, extending far down into the deeper layers of the skin 36.

Barabbas *et al.*, 2017, developed and characterized o/w hydrogel thickened nanoemulsion (HTN). The transdermal delivery of 8-methoxsalen (8-MOP) encapsulated in an HTC comprising sweet fennel oil as well as clove essential oil as the oil phase was studied. The incorporation of 8-MOP into two nanoemulsions that encompasses either sweet fennel or clove essential oil as oil phase led to the development of a formulation that brings possibility in the modulation of drug delivery transdermally and skin retention. This formulation proves to be promising for photo-chemotherapy and also guaranteed increased efficacy and reduced systemic exposure [37].

Surfactants are amphiphilic molecules that absorb readily at oil and water interface, thereby providing steric or electrostatic stabilization [17]. Surfactant renders a repulsive surface force while stabilizing the droplets against aggregation and coalescence [38, 39]. In nanoemulsion, a lower concentration of surfactants is required, exposing nanoemulsions to thermodynamic instability [7, 40, 41]. Still, they end up being more kinetically stable due to a reduction from macroemulsion to nanoemulsion after the external application of shear/energy [42]. Since lower surfactant concentration is required, little or no toxicity is accompanied by the generated nanoemulsion.

Surfactants used in nanoemulsion are collected considering their toxicity profile, solubility in nanoemulsion phases, *i.e.*, the oil and water, together with their emulsification ability, *i.e.*, hydrophile-lipophile (HLB) value. Non-ionic surfactants are the preferred choice of surfactants for therapeutic purposes because of their reduced toxicity as well as less irritant compared to the ionic counterparts [8, 28]. Also, the use of O/W nanoemulsions for medicinal purposes requires non-ionic surfactants, and this is likely to render *in-vivo* stability [43]. Choosing a suitable surfactant is a critical factor. To improve the stability of nanoemulsions, a right blend of low and high HLB surfactants should be considered upon dilution with water. The selection of a surfactant blend not only shows a great effect on the size and stability of

nanoemulsion but sometimes also determines its toxicity, pharmacokinetics including pharmacodynamics [44, 45]. Surfactants that have their HLB values between 4 and 6 generally find application in stabilizing W/O emulsions, while surfactants that have their HLB values between 8 and 18 stabilizes O/W nanoemulsions. Recently, sugar-based natural surfactants are employed because of their skin and environmental friendliness [46].

Co-surfactants in nanoemulsion could also be added in low concentration to further reduce the interfacial tension by complementing structurally weaker areas [47]. Independent use of single-chain emulsifiers might not prove enough ability to bring down the interfacial tension to a large extent; hence, it's used with a co-surfactant that possesses an amphiphilic character is also encouraged. A co-emulsifier is able to further penetrate the interfacial layer, thereby reducing the fluidity and elevating the entropy of the emulsion system [48].

Pengon *et al*., 2009, investigated the role surfactants play in the physical properties of a nanoemulsion prepared with coconut oil. Different amount of surfactants that includes, polyoxyethylene sorbitanmono stearate (POS), polyethylene glycol hydrogenated castor oil (PHC), polyethylene glycol phenyl ether (PGO), sodium lauryl sulfate (SLS) and poloxamer 407 (PLX) were used. From the result, it was indicated that Coconut oil nanoemulsion exhibited a small percent creaming index when the surfactants employed were: POS, PGO, and PHC [26]. Yin *et al*., 2017 also conducted research on biocompatible nanoemulsion using hemp oil with less surfactant for the oral delivery of baicalein with enhanced bioavailability [49]. Aside from the major role of surfactants in the preparation and stability of nanoemulsions, surfactants can also upset the skin barrier function and play a penetration enhancing role to these systems [46].

**3.3 Method of Nanoemulsion Preparation:** Formulation of nanoemulsion is an important and crucial aspect that needs to be considered before the formation of a nanoemulsion. Various methods of nanoemulsion development are discussed in this review in order to help scientists for proper selection of the suitable method of formulation. Numerous methods have been developed for nanoemulsion formulation but can be grouped into High and Low energy methods [27, 50, 51].

**3.3.1 The High Energy Methods:** Here, high shear forces are required. The nanoemulsion prepared using this technique requires external energy in the form of high shear stress to generate a nanosized emulsion [41, 52]. These methods employ specially designed mechanical devices to break the intermolecular forces that exist between the liquids [16] by intense shear turbulence and cavitational flow profile [50]. The most common techniques employed in the high energy/intensity emulsification are Microfluidization; High-Pressure Homogenization (HPH); Sonication Method and production with High Magnitude Ultrasound [53-55].

In the Sonication method, a sonication mechanism is employed to reduce the droplet size of conventional emulsion to form small batches of nanoemulsions [56]. Here, the system is exposed to the substantial amplitude of sound waves in the presence of a sonicator probe. Cavitation occurs, and during this process, there exists a generation of sound waves and energy is supplied to the emulsion droplets, which are coarse. Due to these sound waves, globule size becomes reduced to nanosized droplets with optimum frequency and time [41].

In High-pressure Homogenization (HPH), very intense pressure is supplied into the emulsion system that contains oily phase, aqueous (water) phase, surfactants, and co-surfactants with the aid of high-pressure homogenizer. O/W nanoemulsion that contains less than 20% oil can be prepared with this method [57]. And the fluid is finally discharged as a homogenized nanoemulsion58. Limitation of this method aside, its selectivity also includes the deterioration of active ingredients due to exposure of the emulsion system to a large amount of heat [17, 54, 55, 59].

Microfluidization of an emulsion system is a technique that also generates nanosized droplets through its mechanism of flow that occurs through microchannels [41]. It is a modified or revised high-pressure homogenization that works with a positive displacement pump of high pressure (500 – 20,000 psi) that pressurizes the liquid to pass along microchannels arranged in it. The materials passing

through the micro-channels breaks down [60] into very fine particle. The liquid phases (oil phase and aqueous phase) give a coarse emulsion in an inline homogenizer after processing. This coarse emulsion then undergoes further processing in the microfluidizer for the generation of stable nanoemulsions of submicron range [7, 56].

High Amplitude Ultrasound is a technique that requires high-frequency sound waves supported with significant amplitude; hence, the process "Ultrasonication". The system creates uneven air current in the solution with pressure fluctuation being generated for vibration at specific frequency [19, 61]. In this technique, adjusting of experimental conditions such as temperature, amplitude, frequency as well as sonication time, nano-emulsions with appropriate nanosized droplets can be obtained. However, this technique is not acceptable for industrial application because of variation in particle size during large scale manufacturing. Also, the technique is capable of decomposing surfactants in surfactant-based formulations due to the effect of the high-frequency sound waves [42, 62, 63].

From this review, the advantages and disadvantages of high energy method can be summarized. High energy methods can be said to be of advantages in respect to the fact that nanoemulsions are produced from a flexible sample of materials, and they can easily be scaled to industrial quantities. However, their limitations can be associated with their exposure to intense external energy input requirements and hence, highly expensive to operate. Also, newly created interfaces suffer from stabilization due to insufficient surfactant [38].

**3.3.2 Low Energy Methods:** This method, unlike high intensity (energy) methods, relies on the spontaneous generation of small droplets whenever the system composition experience a phase change or inversion as a way of responding to alterations generated from changes in the composition of surfactants or temperature of the system [64, 65]. In this method, significantly less input of energy density is needed since energy required can readily be attained in a simple magnetic stirring system [64]. These methods are typically named as 'Phase inversion" method because it usually involves the generation of thermodynamically-stable nano-emulsion by altering the conditions (temperature and composition) which affects the HLB of the emulsion system [66]. Alteration in physicochemical parameters could lead to changes in properties of surfactants that enforce phase transformation, making them either fat-loving or hydrophilic molecules. The two most important low energy methods include Phase Inversion Composition or Emulsion Inversion Point (PIC or EIP respectively) and Phase Inversion Temperature (PIT) [19, 60].

In the PIT method, the solubilization pattern of the surfactants (hydrophilic to lipophilic) is changed by increasing the temperature of the emulsion system which forms bicontinuous microemulsions followed by emulsion inversion [7]. The principle of this technique is dependent on the specific properties of temperature-sensitive surfactants, which have the capability of changing its distribution affinity towards water and oil (HLB) with temperature change. Non-ionic surfactants, usually the polyethoxylated surfactants, are mostly chosen in this regard because of their temperature sensitivity. At low temperatures, the surfactant tends to be hydrophilic because of the presence of hydrated polar groups, leading to O/W system. When temperature increases, the dehydration of the polyoxyethylene group makes it hydrophobic because of the presence of aliphatic groups [7, 67]. At HLB temperature, there is a common affinity for water and the oil, hence, kinetically stable nanoemulsion with narrow droplet size distribution and low polydispersity [42]. The main challenge associated with this particular method is that thermolabile agents and other excipients cannot be employed as temperature plays a major role in PIT [60, 68].

Emulsion Inversion Point (EIP) is also known as the Phase Inversion Composition (PIC) method since the composition of the surfactant plays an important role in the phase transformation of the system [42]. At a constant temperature, phase transitions are produced by the composition of dilution of dispersed phase to convert [69]. In PIC, W/O macroemulsions are generated at ambient temperature, followed by slow dilution using water. In the process of dilution, what happens is that the system undergoes a transition where inversion from W/O to O/W emulsification occurs.

At this inversion point, the interfacial tension of the oil-water interface becomes greatly reduced; therefore, nano-droplets having a high specific surface area is obtained without significant energy or pressure required [70, 71].

## 4. Nanoemulsions through Transdermal Route: Basic Considerations:

**4.1 The Skin:** The Skin is the most extensive multilayered organ of the body, having a surface expanse of 1.7 - 2.0m$^2$ [72]. The skin not only covers the body surface but also serves as a shield for the internal organs against direct exposure to the external environment. Amongst its numerous functions are: immunity against microorganisms, electrolytic balance, protection against and from physical injuries, temperature regulation ability UV radiation and harmful chemical substances [73]. Additionally, the skin serves as a route of absorption for drugs as well as an avenue for the expression of drug efficacy [73-75].

As represented in **Fig. 2**, the skin comprises three layers microscopically, namely: Epidermis, Dermis and Subcutaneous Layer, *i.e.*, the Outer, middle, and the inner layer respectively [59]. The Epidermis, which is composed of several cell layers, can be subdivided into viable Epidermis (VE) and non-viable epidermis. The non-viable epidermis is also known as stratum corneum (SC) where the SC represents the outermost layer of the epidermis while the viable epidermis represents the beneath layer [76, 77]. The stratum corneum (SC) consists of keratin filled corneocytes that are surrounded by a lipophilic matrix, which comprises of esters, ceramides, cholesterol, and fatty acids [72]. Corneocytes are flat dead cells that contain a huge amount of water, including keratin filaments. The Corneocytes further have interconnections with some special juncture called Corneodesmosomes [76]. The complexity of the SC can, therefore, be summarized as described by Menon *et al*., 2012 as 'brick and mortar' structure with the corneocytes representing the bricks stuffed in a mortar (the surrounding lipophilic matrix), hence, the barrier of this layer for transdermal drug permeation especially hydrophilic drugs [78].

The dermis represents the thick layer of the skin with 500-3000 µm depth. This layer contains lymph vessels, blood vessels, sweat glands, and nerve endings. It is the middle layer of the skin [79]. The subcutaneous fatty layer forms the most inner layer of the skin. It lies below the dermis, and it contains adipose tissue (fat). It is responsible for providing support such as nutrition, temperature regulation, and physical protection [79].

**Nanoemulsion:**

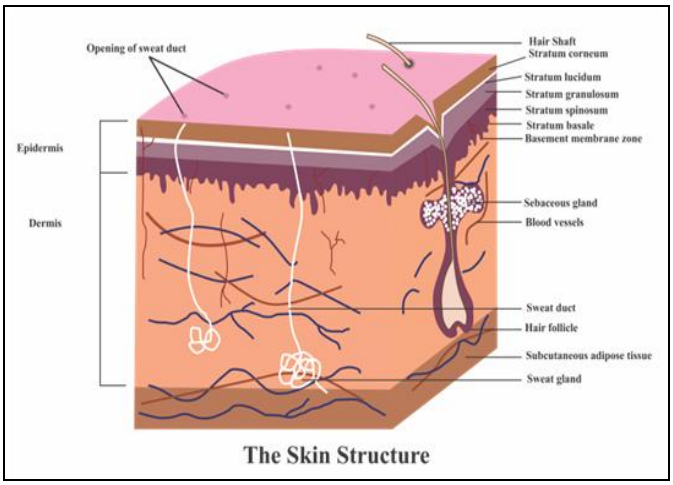


**FIG. 2: THE SKIN AS A DRUG DELIVERY VEHICLE**

**4.2 Position of the Skin in Transdermal Delivery:** Transdermal drug delivery systems refer to the delivery of drugs across the skin in order to accomplish local and systemic therapeutic effect [80]. Transdermal drug delivery is an attractive alternative to conventional administration of drugs owing to its numerous advantages [81] including the convenient administration route of the drug, ease of accessibility, non-invasive nature, and increase in patience compliance [82]. This mode of drug administration increasingly becomes a research focus in pharmaceutical preparation. It's numerous potential and features also include the reduction in the fluctuation of drug concentration in the blood, easy drug detection, reduced chances of an overdose, provision of steady plasma levels and escape from the gastrointestinal environment: pH and enzymatic reactions [83]. Most importantly is its ability to shelve the first-pass effect, increases the therapeutic efficacy of the drug, and increases their long-time stability because there will be little or no drug interference [84]. Despite its long list of advantages, drug absorption through the skin seems to be a bit difficult. Drug permeation through the skin can be a little bit challenging [85]. Its transport through the skin to systemic circulation can be divided into three steps:

**(a) Penetration:** Release of drug from the vehicle/dosage form and passage into the external layer of the skin.

**(b) Permeation:** Passage of the drug from one layer of the skin to the other.

**(c) Resorption:** Penetration of the drug into systemic circulation through the blood and lymph vessels within the dermis.

The transepidermal (across SC) or the transappendageal are the two potential pathways for drug permeation through the skin [72]. The SC route can take place as intra or intercellular penetration where the intracellular route passes through the corneocytes allowing hydrophilic substances to be transported in and out of the cell membrane. On the other hand, intercellular transport allows the transportation of lipophilic drugs around corneocytes in the lipid-rich extracellular regions. For the transappendageal route, transportation of substances is granted through the sebaceous glands across hair follicles and sweat glands [9, 86]. Animal models are usually explored in assessing penetration properties of drug candidates for human consumption. This is because ethical as well as practical issues have made specimens associated with human skin to be very less available. Hence, alternative models, especially models of animal skin, have been developed [87].

**4.3 Nanoemulsions and Transdermal Drug Delivery: Means of Operation:** As earlier discussed, the delivery of drugs through the skin experiences high resistance against diffusion into the blood pool because the upper layer of the skin is the most restricted layer, thereby making diffusion across the SC a rate-limiting step for drugs [41]. To overcome this difficulty, nano-formulations seem to be the required choice. Amongst the most favorable nanoformulations for improvement of transdermal permeation and delivery of drugs is nanoemulsion technique [88]. Dermally applied nanoemulsion penetrates the stratum corneum and firmly exists in the whole horny layer altering both lipid and polar pathways [89]. Their small particle size brings better results on 'drug retention,' 'drug specificity,' and 'drug targeting' with these three making an ideal transdermal drug delivery [90].

Nanoemulsion, a unique aspect of nano-formulations are an isotropic, low viscous mixture with extremely small droplet size comprising of clear or translucent oil globules that are dispersed in an aqueous phase with stability offered through an interfacial surfactant or co-surfactant film [17]. Since the droplet or particle size of nanoemulsions exists below 25% of the wavelength of visible light, they tend to come out clear or transparent [91]. Due to these unique particle sizes, large surface area and low surface tension, nanoemulsions show great wettability, which makes them maintain close contact with the skin. They also give shorter transdermal time and better percutaneous absorption [75].

Bakshi *et al*., 2018, reported the topical delivery of nanoemulsion-based formulation containing heparinoid, an anticoagulant derived from heparin. Its potential in delivering a transdermal therapy towards the treatment of superficial thrombo-phlebitis was studied. Results indicated that the developed O/W nanoemulsion transported a greater amount of heparinoid (91.25 ± 25.75 µg/sq.cm and 62.29 ± 5.66 µg/sq.cm) respectively after 72 h [92].

Aqil, 2015 also developed a clove oil-based nanoemulsion for the transdermal supply of olmesartan, a lipophilic, and an anti-hypertensive drug. The optimized formulation revealed a small droplet size of 53.11 ± 3.13 nm with an enhanced bioavailability of Olmesartan proven by an improved penetration through the rat skin [36].

Transdermal delivery of Diacerein that was formulated with glucosamine sulfate laden oil in water nanoemulsion as the homing carrier was reported by Chattopadhyay and Datta, 2018. The nanoemulsion system was reported to contain an oleic acid oil phase with Tween 20 and PEG 400 as the surfactants. The result revealed a powerful permeation ability and good stability, thereby identifying nanoemulsion as a potential carrier to achieve an enhanced topical transport of lipophilic diacerein [93].

The success of nanoemulsion in promoting drug penetration transdermally as well as achieving therapeutic success can be traced to its channel of operation. The first agent that can be considered is the nanoemulsion composition: the oil and the

surface-active agents [94]. According to Shakeel, 2008, increased solubility of the drug in the oil phase, surfactants and co-surfactants efficiently improve the extent at which the nanoemulsion system maintains the drug in the solubilized form. This leads to a better permeability for improved permeability and successful delivery. Also, since nanoemulsion contains both lipids and aqueous phase, it is expected that if the drug gets dissolved in the lipid domain of the nanoemulsion, direct penetration of the lipid layer of the SC can take place, causing destabilization of its bilayer structure [94]. This interaction leads to a high increase in the drug permeability through the transdermal lipid pathway. In contrast, the hydrophilic aspect of nanoemulsion can largely serve as a source of hydration to the SC, resulting in transdermal uptake of drugs. Possibility of this can be explained that when the aqueous fluid of nanoemulsions migrates into the polar pathway, the interlamellar volume of the stratum corneum lipid bilayer increases, thereby resulting in a disarrangement of its interfacial structure [95]. The oil component of nanoemulsion finds compatibility with the sebum, an oily secretion from the sebaceous gland found in the follicular openings. These openings are alternate entry point that opens up chances of leading and trapping drugs with therapeutic capabilities to clinically active skin lesions [17].

The presence of surfactants in nanoemulsions increases skin permeation by altering the cellular integrity of the skin in several ways making the stratum corneum become hydrated [96]. Both oil and surfactants interact readily with different layers of the skin and assist in the distribution of loaded moiety to the deeper part of the skin [97].

Moustafa *et al*., 2015 reported his study on transdermal cumin oil nanoemulsions for effective and increased systemic antioxidant and hepato-protective properties. The surfactant/co-surfactant used in this study was tween 20/ ethanol. Oleic acid /capryol was employed as the oil phase. From the results, phenolic content of Cumin oil showed increased encapsulation efficiency, including remarkable phenol permeation across the rat skin was recorded. From the different surfactant mix prepared, the formulation containing cumin/oleic acid as the oil phase Tween 20/ethanol (2:1) as surfactant/cosurfactant and distilled water as the aqueous phase showed the highest favorable formula. This was proven from the *in-vitro* and *in-vivo* antioxidant effect and a great hepatoprotective potential after 7 days of single transdermal application [98].

Elmateeshy *et al*., 2018 developed a novel nanoemulgel for enhanced transdermal permeability of terbinafine (TB), an antifungal drug with inadequate water solubility. The formulation, which comprises Peceol (oil phase) and Tween 80/propanol (Surfactant/co-surfactant mix) were prepared in different weight ratio which ranges from 1:9 to 9:1. From the pseudo ternary phase diagram, required formulae were obtained, followed by formulation and characterization of nanoemulsions. The thermodynamic stability studies including the *in-vitro* drug release studies were also carried out. The nanoemulsion formulae containing 10 or 15% w/w oil, 45% w/w Smix (1:2/1:3) and 45-40% w/w aqueous phase) were selected as the optimum formulae and incorporated into Carbopol 940 gel bases to form three groups of TB nanoemulsion formulated emulgel formulae (F1-F3). These were investigated for *ex-vivo* drug permeation as well as *in-vivo* antifungal activity. Results indicated that all the prepared nano-emulsion based gel formulae reveals significant ($p<0.05$) improvement when compared to the commercially prepared emulgel [99].

Rachmawati, 2015 also studied a curcumin nanoemulsion for transdermal evaluation. The nanoemulsion prepared by self nanoemulsification method includes glyceryl monooleate as oil phase, cremophor RH-40 and PEG 400 as surfactant/co-surfactant. In vitro permeation of curcumin was studied using casted (shed) snakeskin of a python reticulatus and a modified vertical diffusion cell. Evaluation of nanoemulsions was carried out using particle size analyzer, polydispersity index (PDI), zeta potential, physical stability, and Raman spectra. The overall study revealed improved curcumin permeability; it also protected curcumin from chemical degradation [100].

Another factor that contributes to the permeability effect of nanoemulsion through skin is the little particle size and high specific surface area of the nanoemulsion [101]. Transdermal delivery is made

possible when the size of the nanoemulsion droplet is low. Permeability of nanoemulsions through the skin is inversely proportional to the magnitude of the nanoemulsion droplet. A nanoemulsion with droplet size above 150 nm may find difficulty in penetrating the skin efficiently, limiting its application topically while a nanoemulsion droplet below 60 nm ensures great possibilities in transdermal delivery [102].

Other important factors could be associated with the special and unique structure of nanoemulsions which gives them the capability of solubilizing both lipophilic and hydrophilic drugs. When this occurs, a greater chance of deeper drug penetration is allowed since a high permeable concentration gradient will take place both in and out of the skin [103]. Also, nanoemulsion ability to act as tiny reservoirs for drugs gives them inner storage ability, thereby prolonging drug absorption. This is because diffusion of drug is constantly maintained because of the forceful pull from the external phase to the inner phase [102].

**CONCLUSION:** Nowadays, an alternative route of drug delivery is highly invested as the parenteral route seems challenging. The transdermal route of drug delivery is now embraced strongly as it has confidently reflected positivity and uniqueness. To resolve the challenges of drug bioavailability, improved solubility increased penetrability, and enhanced therapeutic effectiveness, nanoemulsions have been considered. The identity of nanoemulsions has advantageously playedan outstanding part in the improved transdermal delivery of drugs. In this review, the components and transdermal mechanism of nanoemulsions is summarized with the aim to improve understanding of the role of nanoemulsions in transdermal drug delivery systems. This review encourages further research in the field of drug delivery for improved transdermal treatment.

**ACKNOWLEDGEMENT:** Nil

**CONFLICTS OF INTEREST:** The authors have no conflicts of interest.

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2018; editor Transdermal delivery of Diacerein with homing carrier glucosamine sulphate laden in oil-in-water nanoemulsion. International Conference on Functional Nanomaterials; 2016 28-29 September; Shibpur, India: Materials Today Proceedings; 2018.
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**How to cite this article:**
Oyelaja OB, Dare EO, Katare DP and Oladoyinbo FO: Nanoemulsion: a promising and novel nanotherapeutic vehicle for transdermal drug delivery. Int J Pharm Sci & Res 2020; 11(6): 2636-48. doi: 10.13040/IJPSR.0975-8232.11(6).2636-48.