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Nanoemulsion as Pharmaceutical Carrier for Topical and Transdermal Drug Delivery

Vinay Kumar[1], Ankita Vishwakarma[2], Prerna Gupta[3]

Abstract: ***The use of nanoemulsion for topical and transdermal delivery systems is now well proven to improve the therapeutic effectiveness of drugs. Current research is focused on the design of nanoemulsion-based semisolid dosage formulations and describes the advancements made in the delivery of therapeutics using nanoemulsion, with a focus on topical and transdermal administration. Finally, this review discusses the fundamental concepts and issues of nanoemulsion manufacturing, the use of nanoemulsion-based semisolid dosage forms in medicine, and basic considerations during nanoemulsion absorption into and through the skin.***

Keywords: Nanoemulsion, topical drug delivery, transdermal drug delivery

1. Introduction

Even though numerous therapeutics/new chemical entities have been identified every year, only a few have been conquered clinical success. Low "bioavailability" and insufficient site-specificity are often imputed to the decreased success rate. The route of drug administration, the physiology of the body, and metabolism are the key properties to achieving greater bioavailability [1]. Parenteral administration of drugs requires frequent dosing and causes pain at the injection site as well as rapid plasma drug concentration level fluctuations. As a result, drug administration via the systemic route can be painful and uncomfortable [2]. Although the enteral route is the most convenient and conventional route of administration, it can be associated with drug and food interactions, first-pass metabolism, and other issues [3]. Concurrently, the skin's versatility makes it the ideal site for drug administration. It's been used to treat many different types of skin problems, including inflammation, microbial infections, psoriasis, dermatitis, and more. transdermal route has long been used to treat various systemic ailments like pain, hypertension, cancer, diabetes, and others. The problems related to intravenous and oral routes are prevented by topical and transdermal routes [4]. Topical and transdermal routes give a higher surface area for drug absorption, and as per need, drug therapy can be withdrawn at any time [4, 5]. Drug administration through the skin aids in the treatment of both topical and systemic illnesses [5]. It is painless drug delivery system that allows self-medication, is favored for long-term treatment of diseases such as neuropathic pain [6], and prevents first-pass metabolism [7]. Drugs that fall under Biopharmaceutical Classification System (BCS) classes II and IV that have unfavorable physiological characteristics such as rapid degradation in the gastric medium [8], high first pass metabolism [9], and may be good drug candidates for topical and transdermal drug delivery.

According to the literature, nanoemulsion formulation is expected to be the best formulation because of its fluidic nature, small droplet size, efficient penetration power, and protection ability to deliver even irritant, volatile, and high molecular weight molecules. It also has good interaction with the skin cells.

2. Nanoemulsion

Nanoemulsion is a novel drug delivery system that contains two immiscible liquids that impart a uniform distribution of drugs in nanodroplets, forms an isotropic, transparent, heterogenous, thermodynamically and kinetically stable system. In this system, both phases are combined together with the aid of surfactant and co-surfactant [11–13]. It forms very small droplets in the nano-range, i.e., 20–400 nm [14]. These two immiscible phases generally comprise the oil and aquous miscible ingredients which are solubilized in the oil and aquous phases. Combining the oil phase and aquous phase, it forms a coarse emulsion with the help of emulsifiers and co-emulsifiers, which is transformed into the nanoemulsion by using the high-energy emulsification method [15].

Nanoemulsion can be classified into three categories, as per their composition, they are: water in oil (w/o); here, aquous phase is dispersed in oil phase [17]. oil in water (o/w); oil phase dispersed in water phase [16]. bi-continous phase or multiple emulsions. Furthermore, nanoemulsions are categorized into three categories as per nanoparticle surface charge: neutral, anionic, and cationic nanoemulsions [7]. Lipid soluble drugs easily get dispersed in the oil phase and form a nanoemulsion formulation that cures various kinds of illnesses. As per the route of drug administration, the quantity of oil may range from 2 to 20% w/w in o/w nanoemulsion. Chaudhury et al. (2013) described, BSC class-II and class-IV drugs have the solubility problem. To overcome this problem, formulate the O/W nanoemulsion [18]. Select the surfactants with high aqueous and oil solubility [18]. In many instances, non-ionic surfactants are mostly used because they are less toxic and less irritating as compared to anionic and cataionic surfactants [19].

2.1 Method of preparation

Some key points that are considered before the development of a quality product are the selection of ingredients, their desired concentration, order of addition, appropriate method of preparation, and ideal stirring speed or shear stress. To

date, various methods have been used to develop nanoemulsion (size range 20–200 nm), some of which are summarized below.

2.1.1. High energy emulsification methods

Nanoemulsions are extensively formulated utilizing high-energy methods. High mechanical energy is employed to produce strong disruptive forces that break down the large particles into nano-sized particles, resulting in high-kinetic-energy nanoemulsions. Mechanical devices such as ultrasonicators, microfluidizers, and high-pressure homogenizers are used to create disruptive forces [42]. By employing high-energy methods, we can attain better control over partice size with a desired formulation composition. With high-energy methods, the stability, rheology, and color of nanoemulsion can be easily attained (Graves et al., 2005; Gursoy and Benita, 2004). The following methods are used in high-energy emulsification methods.

- High pressure homogenization
- Microfluidization
- Ultrasonication

2.1.2 Low energy emulsification methods

This method requires low energy for the fabrication of the nanoemulsion system. In phase inversion methods, phase transition occurs when the temperature is changed while the composition remains constant, or when the temperature remains constant while the composition changes. At room temperature, the mixture of oil, water, and nonionic surfactant has a positive curvature. Rapid temperature changes in the phase inversion temperature approach prevent coalescence and fabricate stable nanoemulsions. Low energy emulsification methods are mostly preferred by manufacturers because they do not require expensive instruments. The following methods are used in low-energy emulsification methods.

- Phase inversion method
- Spontaneous emulsification method
- Solvent displacement method

3. Role of topical and transdermal route in drug delivery

According to the USFDA, more than twenty transdermal and ten topical products are currently available in the US market [41]. Delivery of drugs via topical route can be dependent on their molecular size and independent of hydrophilicity and lipophilicity. The use of topical drug administration helps patients to self-medication without pain. Topical route reduces the frequent dosing and keeps a steady drug plasma level for a longer period of time in comparison to oral or parenteral routes [5, 20]. In 2013, Khurana et al. designed a meloxicam transdermal nanoemulsion to avoid the gastrointestinal adverse effects [21]. A number of drugs have been formulated in the form of nanoemulsion to alter their physiochemical properties for the treatment of topical and systemic diseases. drug delivery via these routes has become widely accepted [22].

4. Mode of topical and trandermal drug delivery by nanoemulsion

Topical delivery of nanosized globules/particles is achieved by interaction with skin cells, followed by the release of medicaments at the stratum corneum or in the deeper epidermis layer [33, 34]. On the other hand, the transdermal route is a well-known route for systemic drug delivery because it allows the drug enter to the blood capillaries [22]. To increase the penetration of drugs through the epidermal layer or stratum corneum, modify the physiochemical properties of nanoemulsion and emulsifiers. Surfactants affect the skin's cellular integrity in a number of ways, resulting in skin hydration. Due to the presence of a thicker stratum corneum layer in human subjects, skin hydration duration can be extended. The fluidic and elastic properties of nanoemulsions assist in changing the spherical morphologies of the nanoemulsions in a stressed state, allowing larger droplets to penetrate even narrower intercellular gap junctions [35, 36]. Due to its rigidity, larger droplet sizes may not be easily penetrated. Nanoemulsion regarded as ultra-flexible and is likely to form any shape while administered on the skin. On the other hand, lipidic nanoemulsions with droplet sizes greater than 50 nm are less likely to penetrate through passive diffusion and will require a concentration gradient or external assistance to push the droplets into the deeper layers of the skin [35]. If the lipid nanoemulsion droplets are smaller than 50 nm, transdermal absorption may be achieved. The size of nanoemulsion droplets has an inverse relationship with skin permeability [31]. Surfactant-based emulsion droplets larger than 150 nm may not penetrate skin well and require topical application [10, 37].

5. Role of surfactants and co-surfactants in topical and transdermal nanoemulsion preparation

Nanoemulsions have unique characteristics that may change the stratum corneum layer and assist drug distribution into the deeper layers of the skin. The size of the droplets, the charge of the nanoemulsion, the composition of the nanoemulsion used, and the type of animal model all help to speed up the rate, extent, and mechanism of absorption via skin. When topical or transdermal nanoemulsions are developed for human usage, special attention must be devoted to skin irritation or toxicity issues. When formulating the nanoemulsion with the aid of surfactants, then it must have the most suitable mean droplet size range for topical administration is 150 to 350 nm [12]. Somagoni et al. 2015 suggested that nanoemulsions have maximum droplet size of 1000 nm while topical application is needed. When a surfactant-based nanoemulsion is employed in large quantities, it temporarily disrupts the configuration of the cells

in the stratum cornium and forces para-cellular and trans-cellular drug absorption.

Table 1: The topical and transdermal nanoemulsion formulations:

S. No.	Drug	Route of drug delivery	Surfactants and co-surfactants	advantages	Reference
1	Ropinirole	Transdermal	Tween 20 (surfactants) and Carbitol (co-surfactatns)	In comparison to the conventional gel, nanoemulsion-based nanoemulgel showed 7.5 times increase in skin permeation rate and 2 times increase in relative bioavailability.	[22]
2	Apomorphine	Transdermal	Pluronic F68 (surfactants) and PEG 400 (co-surfactants)	The formulated nanoemulsion showed huge augmentation in permeation fluxes, up to 11 times bigger than the drug alone. That means a higher concentration of drug enters the systemic circulation.	[23]
3	Menthol, and methyl salicylate	Topical	Tween 80 (surfactants) and propylene glycol (co-surfactants)	The nanoemulsion droplet size was 60 nm, and shows better interaction with the skin.	[24]
4	Clobetasol propionate	Topical	Tween 20 (surfactants) and ethanol (co-surfactants)	Formulated o/w nanoemulsion showed better interaction with the skin and provided a safe and effective treatment of psoriasis and atopic dermatitis.	[25]
5	Amphotericin B	Topical	Tween 80 (surfactants) and Transcutol-P (co-surfactants)	The developed nanoemulsion has a mean droplet diameter of approximately 76–78 nm, which was safe and very effective for topical treatment.	[26]
6	Meloxicam	Transdermal	Tween 80 (surfactants) and propylene glycol (co-surfactants)	In comparison to meloxicam solution, nanoemulsion-based gel significantly increased meloxicam permeation.	[29]
7	Econazole nitrate	Topical	Pluronic F68 (surfactants) and PEG 400 (co-surfactants)	Positively charged emulsion showed slower permeation but increased drug retention in the skin in comparison to negatively charged particles.	[27]
8	Meloxicam	transdermal	cremophor RH 40, Tween 60 (as surfactants) and PEG 400 (as co-surfactant)	In comparison to meloxicam solution, negatively charged meloxicam UF-SNEDDS showed an 11.89-times increase in skin permeation.	[28]
9	Curcumin	Transdermal	cremophor RH 40 (surfactants) and PEG 400 (as co-surfactant)	The formulated nanoemulsion improved the permeation flux and increased the relative bioavailability of the drug.	[30]
10	Caffeine	transdermal	Transcutol-HP (surfactant) and isopropyl alcohol (co-surfactant)	The W/O nanoemulsion is a good vehicle for transdermal delivery of caffeine and other anti-cancer drugs.	[32]

6. Applications of nanoemulsion in topical and transdermal drug delivery

6.1 Nanoemulsion in topical drug delivery

Topical drug delivery is a site-specific drug delivery system that can be used to deliver drugs to the skin, ophthalmic, rectal, and vagina as topical routes. The skin provides the major surface area for topical administration of drugs and its easily accessible organs. Local and systemic effects are achieved by topical drug application to the skin. Skin disease (dermatological problems) affects a large segment of the population and is one of the top 15 health issues for which recurrence and healthcare spending significantly soared in the previous ten years. Table 2 depicts Number of studies have important outcomes of the nanoemulsion used in the field of dermatology to cure various illnesses, such as wound healing, psoriasis, acne, cancer, and dermatitis.

Table 2: Nanoemulsion for topical drug delivery

S. No.	Drug	Disease	Preferred route of administration	Ref.
1.	Menthol, methyl salicylate and camphor	Arthritis, and muscle pain	Topical	[24]
2.	Clobetasol propionate	Psoriasis	Topical	[25]
3.	Amphotericin B	Fungal infection	Topical	[26]
4.	Naringenin	wound	Topical	[38]
5.	Econazole nitrate	Fungal infection	Topical	[27]

6.2. Nanoemulsion in transdermal drug delivery

Transdermal drug delivery system has always been difficult because of the subcutaneous barrier; as a result, umpteen methods have been employed form time to time. It has several advantages, like the ability to easily withdraw drug delivery while needed and prevent hepatic first pass metabolism. Table 3 shows several sorts of nanoemulsions with transdermal administration of drugs and their uses for the treatment of cancer, rheumatoid arthritis, hypertension, and other diseases.

Table 3: Nanoemulsion for transdermal delivery

S. No.	Drug	Disease	Preferred route of administration	Ref.
1.	Meloxicam	Inflammation	Transdermal	[29]
2.	Ropinirole	Parkinson's disease	Transdermal	[22]
3.	Caffeine	cancer	Transdermal	[32]
4.	Nitrendipine	hypertension	Transdermal	[39]
5.	Rifampicin	Tuberculosis	Transdermal	[40]

7. Conclusion

Currently, topical and transdermal drug delivery systems are the most acceptable routes for treating various local and systemic illnesses. Drug administration through the skin tends to be simple to apply and less expensive, researchers are leaning toward the development of nanoemulsion-based formulations. Nanoemulsion has been shown to be a versatile drug delivery vehicle for topical and transdermal administration of a number of drugs. It has been recognized as a novel approach to tackling solubility and bioavailability constraints, and it may provide greater therapeutic flexibility than semisolid dosage forms. Due to the extended stability of nanoemulsion inside the polymer-based gel base, nanoemulgel confers a novel nanoemulsion-based dosage form. Finally, nanoemulsion appears to be a more profitable option for topical and transdermal use than currently available marketed dosage forms and have an emerging future for delivering existing or newly developed therapeutics in a safe and effective manner.

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Author Profile

Vinay Kumar, Advance Institute of Biotech & Paramedical Sciences, Kanpur, 209217, U.P., India.

Ankita Vishwakarma, Advance Institute of Biotech & Paramedical Sciences, Kanpur, 209217, U.P., India.