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Nanoemulsion and Nanoemulgel as a Topical Formulation

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Abstract: *Nanoemulsion is referred type of emulsion with uniform and extremely small droplet size in the range of 20-200 nm. Nanoemulsion provides numerous advantages over other carrier such as polymeric nanoparticle and liposomes, including low cost preparation procedure, high hydrophilic and lipophilic drug loading system to enhance the longer shelf live upon preserving the therapeutic agents. Incorporating the preparation of nanoemulsion with hydrogel matrix to produce nanoemulgel exhibited by the two separate systems that forming it. Nanoemulgel possesses the properties of thixotropic, non-greasy, effortlessly spreadable, easily be removed, emollient, not staining, soluble in water, longer shelf life, bio-friendly, translucent and agreeable appearance.*

Keywords-*Nanoemulsion, Nanoemulgel, Emulsifying method, Liposomes, Thixotropic, Hydrogel*

I. Introduction

Emulsion as a dispersed system, which consists of small droplets which is well distributed in to immiscible vehicle [1].The types of emulsions which classified in according to their droplets size, are Macroemulsion (droplet of 1 to 100 µm of diameter) also known as the conventional emulsion/colloid. It is commonly unstable with droplets sediment or float with the dispersing phase and medium phase basically, unstable with absorption of solid particles on the surface [2]. Whereas, microemulsion (droplet between 10-100 nm) is an isotropic liquid system with more uniform size and good physiochemical properties [3] and nanoemulsion (droplet size 20-200 nm diameter) is more stable and requires less emulsifying agent.

Nanoemulgel is known as the formation of nanoemulsion based hydrogel by the addition of the nanoemulsion system intergraded into hydrogel matrix which influences a better skin penetration [4].

II. Nanoemulsion

2.1 Nanoemulsion in Topical Application

Nanoemulsion is a promising alternative to increase drug delivery system penetration and targeting poorly soluble drugs, by increasing its absorption through the skin, better retention time of drug in the target area and eventually result in less side effects [5]. The benefits of nanoemulsion with globules in nano-scale size of an emulsion does not relay on the emulsion physical properties itself [6], yet encounter the bioavailability of therapeutic drugs in whole. Apparently, there have been researches on the bioavailability of lacidipine via transdermal route was 3.5 times higher than that of oral route which believed to be due to avoidance of first-pass metabolism [7].

Besides that, nanoemulsion improves the permeation of drug through skin, which intergrade the interest of researchers. In addition, the small size of particles, the more amount of drug is able to be incorporated in the formulation, which subsequently increases the thermodynamics towards the skin. Moreover, the drug affinity for partitioning increases permeation into the skin [7].

One of the studies consequently narrates the implications of Nile red (NR) dye loaded in lecithin nanoemulsion was able to penetrate the skin 9.9-fold greater than the NR-loaded general emulsion [8]. Besides that, ingredients used in the formulation consisting of ethyl oleate and propylene glycol, also act as permeation enhancers [9].

The greatest obstacle upon transdermal drug delivery refers to barrier properties of stratum corneum a 10 µm to 20 µm thick tissue layer with great composed structured lipid/protein matrix [10]. On recent study, of topical delivery lipophilic flurbiprofen in nanoemulsion proves an increase in bioavailability by 4.4 times compared to oral administration [11]. Hence, the nanoemulsion as spontaneous emulsifying method which

provides numerous advantages over other carrier such as polymeric nanoparticle and liposomes, including low cost preparation procedure, high hydrophilic and lipophilic drug loading system to enhance the longer shelf live upon preserving the therapeutic agents [11].

2.2 Limitation of Nanoemulsion as Topical Applications

In the formulation of nanoemulsion as a topical drug delivery faces many challenges in delivering drug effectively through the skin which rates controlling barrier for topical drug delivery [12]. Small particle sized formulation yet concerned when delivering drug through the skin, the rheology properties of nanoemulsion is important. The nanoemulsion formulation, it is not convenient to be used due to low viscosity and spreadability is noted [13].

Hence, the limitation has restrained the application of nanoemulsion clinically [14]. Therefore, the approach of incorporation of nanoemulsion with gelling system can help in overcoming this problem.

III. Nanoemulgel

Nanoemulgel which known as the formation of nanoemulsion based on hydrogel is the addition of nanoemulsion system intergraded into hydrogel matrix which influences a better skin penetration [4]. This mixture of nanomulgel has attracted the attention of many scientists for the development of numerous drugs that function to treat various kinds of skin disorders.

Emulgel is not a new type of formulation and are already present in the market as shown in Table 1. On the other hand, Table 2 shows the example of nanoemulgel or microemulgel formulations that had been prepared before.

The formulation of nanoemulgel for the topical delivery system acts as drug reservoirs which, influence the release of drugs from the inner phase to the outer phase and then further onto the skin [14]. These release mechanism depends on the composition of the network polymer chains and the crosslink density [15].

Besides that, the ability of a drug to permeate the skin and successfully release of therapeutic agent is influenced by drug affinity to diffuse out from the vehicle and permeate through barrier [16].

Nanoemulgel on intact with skin will release the oily droplets from the gel network. The oil droplets then will penetrate into the stratum corneum of the skin and directly deliver the drug molecules without a transfer via hydrophilic phase of nanoemulsions [14].

Table 1: Product of Emulgel Present in the Current Market

Name of product	Manufacturer	Formulation
VoltarenEmulgel©	Novartis Consumer Health	Active ingredient: 100 g Diclofenac diethylamine corresponding to 1g diclofena sodium, propylene glycol. Base: Fatty emulsion in an aqueous gel to which isopropanol and propylene glycol have been added.
ReumadepEmulgel©	ErbozetaEnergia Verde	Arnica, Ashwagandha, Myrrh, Ginger, Rosemary, Cloves, Mint.
EmulgelLevoragMonodose©	THD LAB Farmaceutici	
MeloxicEmulgel©	Provet	Meloxicam
BenzolaitAzEmulgel©	Rordermal	Benzoylperossido 10%
Coolnac Gel Emulgel 1 %©	Chumchon	Diclofenac Diethylammonium

Table 2: Researches on Nanoemulgel or Microemulgel Formulations

Authors	Year	Formulation
Huabing*et al.*	2007	Microemulsion-based hydrogel formulation of ibuprofen.
Mou*et al.*	2008	Hydrogel-thickened nanoemulsion system (HTN) of mixture of camphor, menthol and methyl salicylate.
Gannu*et al.*	2010	Lacidipine microemulsion-based gel
Fouad *et al.*	2013	Poloxamermicroemulsion-based gel
Khurana*et al.*	2013	Nanoemulsion-based gel of meloxicam
Eid *et al.*	2014	*Swietenia macrophylla* Nanoemulgel.

3.1 Advantages of Nanoemulgel

A stable nanoemulsion formulation is enhanced through nanoemulgel, by decreasing surface and interfacial tension and which leads the viscosity of the aqueous phase to be increased [18]. Emulsifier and thickeners been added to hold the gelling capability of hydrogel serves a better stability, permeation and suitable viscosity for the delivery of topical drug-loaded nanoemulsion.

In Nanoemulgel system, the stability of nanoemulsion is enhanced by the distribution of oily droplets in gel network [14]. These oily droplets function as carrier for drugs, such as lipophilic drug. The stability of drugs loaded in the system is determined by the affinity of the drug to be solubilized in the oil phase. Nanoemulgel attained a good adhesion property on the skin together with high solubilizing capacity leads to larger concentration gradient towards the skin that influence further skin penetration of drug as it move down the gradient.

Moreover, the Nanoemulgel formulation is known to support better delivery of lipophilic and poorly soluble drugs as shown in Table 3. It also promotes improve patient compliance because the formulation is not sticky and easily spread as compared to other topical delivery system such as ointment and cream which are very sticky, troubled upon application and have reduced spreading coefficient, hence they require the mechanism of rubbing. Besides that, nanoemulgel helps in controlling the release of drugs by extending the effect of drugs having shorter half-life [19].

Table 3: Research on Bioavailability of Lipophilic Drug in Nanoemulgel and Microemulgel through Skin Penetration

Author	Year	Research	Outcome
Gannu*et al.*	2010	Enhanced availability of lacidipine via microemulsion based transdermal gels.	The study on bioavailability of lacidipine (LCDP) was found to be C_{MAX} = 110.0 ng mL^{-1} (microemulgel) and 97.4 ng mL^{-1} (oral suspension). It was revealed that LCDP penetrated well by transdermal route.
Azeem*et al.*	2012	To investigate the pharmacokinetic and biochemical of the oil based nanocarrier system for transdermal delivery of ropinirole.	Through nanoemulsion gel formulation, ropinirole exhibit improved penetration through the skin and extended release. Furthermore, the bioavailability of ropiniroleis twice improved than gel formulation available in the market.
El –Hadidy*et al.*	2012	Microemulsions as vehicles for topical administration of voriconazole: formulation and in vitro evaluation.	Results also indicated that in nanoemulgel formulations (BG4-BG6) as the surfactant co-surfactant mixture concentration was decreased from 55% to 35% the skin permeation rate was increased to two-fold. The reason attributed to the situation could be an increase in thermodynamic activity of drug in nanoemulgel at lower content of surfactant.
Khurana*et al.*	2013	Formulate nanoemulsion based gel for transdermal delivery of meloxicam.	The study on bioavailability of meloxicam nanoemulsion (MLX-NE) gel and MLX solution, via skin permeation, give outcome of 344.061 +/- 1.49 µg and 186.34 +/- 1.66 µg respectively. MLX-NE has higher penetration ability than solution formulation. Skin permeation of lipophilic meloxicam showed better penetration in nanoemulsion gel when analysed through confocal laser screening microscopy (CLSM). The nanoemulsion gel incorporated with Rhodamine 123 (lipophilic fluorescent marker) showed deeper penetration into the rat skin which can reach up to 130µm compared to solution formulation of only 20µm.

Arora *et al.*	2014	The aim of the present study was to investigate the nanoemulgel as transdermal delivery system for poorly water soluble drug, ketoprofen, in order to overcome the troubles associated with its oral delivery. Different nanoemulsion components(oil, surfactant, and cosurfactant) were selected on the basis of solubility and emulsification ability.Pseudoternary phase diagrams were constructed using titration method to figure out the concentration range	Transdermal permeation of ketoprofen from nanoemulgels was determined by using Franz diffusion cell. Nanoemulgel containing 6% oleic acid as oil, 35% Tween 80, and Transcutol P as surfactant cosurfactant mixture, 56.5% water, 2.5% drug, and 0.6% carbomerwas concluded as optimized formulation (NG6). The ex vivo permeation profile of optimized formulation was compared with nanoemulsion and marketed formulation (Fastum).

IV Summary

Nanoemulsions are non-equilibrium, thermodynamically stable optically transparent, metastable dispersion of nano-sized particles having defined surface tension formed by certain shear, comprises of a suitable oil and definite blend of surfactants and co-surfactants and having capacity to dissolve large quantities of hydrophobic drugs. The stabilization system possesses the stability sedimentation or creaming.

In addition, breakdown of the particles into nano-scaled sizes, the system has the ability to attain low polydispersity. The physicochemical and biological properties of nanoemulsion deviate from the classical emulsion properties.

Nanoemulsion system can be achieved through homogenizers, low energy emulsification and phase inversion temperature methods. On top of that, there are so many conflicts regarding suitable method of preparation of nanoemulsions and later on it was proved that nanoemulsions can be formulated by low-energy emulsification method along with high shear homogenizer method.

Nanoemulgel is also known as hydrogel-thickened nanoemulsion (HTN) since the system is showing an increment in viscosity compared to the nanoemulsion system. A stable nanoemulsion formulation is enhanced through nanoemulgel, by decreasing surface and interfacial tension which leads viscosity of the aqueous phase increased.

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