Comprehensive Review on Submicron Colloidal Particulate System

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Abstract: Submicron colloidal particulate systems, particularly nanoemulsions, represent a pivotal advancement in drug delivery and formulation. These systems, consisting of finely dispersed droplets ranging from 20 to 200 nm, possess unique properties that enhance solubility, bioavailability, and targeted delivery of various pharmaceutical compounds. Nanoemulsions typically comprise oil, surfactant, aqueous phase, and preservatives. The choice and ratio of these components play a crucial role in determining the stability, particle size, and drug release profile of the nanoemulsion. Nanoemulsions offer versatile routes of administration, including oral, topical, parenteral, and pulmonary, widening their applicability across different therapeutic areas. Several methods are employed for nanoemulsion preparation, such as high-energy emulsification and high-pressure homogenization, each offering unique advantages in controlling droplet size and distribution. Characterization techniques like dynamic light scattering, transmission electron microscopy, and zeta potential measurement are utilized to assess particle size, distribution, surface charge, and stability of nanoemulsions. Understanding the stability mechanisms involving Ostwald ripening, coalescence, and creaming is pivotal in ensuring the long-term stability of nanoemulsions. The future of nanoemulsions holds promise in diverse applications, from drug delivery to cosmetics and food industries, owing to their enhanced stability, solubility, and bioavailability. In summary, nanoemulsions represent a groundbreaking technology with immense potential for revolutionizing drug delivery and various other industries, promising a new era of enhanced therapeutic efficacy and product development.

Keywords: Nanoemulsion, colloidal particle, preservative, antioxidant, chemoprotectants, phase inversion, zeta potential, stability, dermatitis, rheumatoid arthritis.

INTRODUCTION

Basically, Emulsion is a Biphasic Liquid Dossage form in which two phases (Oil Phase & Aqueous Phase) are mixed together by using suitable emulsifying agent is called as Emulsion. Emulsions, also called as macroemulsions, are generally described as two immiscible phases dispersed within another[1]. There are two main differences between conventional emulsions and nanoemulsions which results from size and shape of the particles in the continuous phase. Firstly, particle sizes in nanoemulsions (5-200 nm) are very smaller than conventional emulsions (0.1-100 μm). Secondly, in emulsions there are roughly spherical droplets of one phase dispersed into another. However, nanoemulsions consist of various structures such as droplet like swollen micelles and bicontinuous structures [2;3].

Nanoemulsion is an isotropic, transparent/translucent, heterogeneous system of two immiscible liquids consisting of a fine dispersion of drugs in nanodroplets. It is stabilized by an interfacial layer of emulsifiers and co-emulsifiers [4-6]. They are thermo-dynamically and kinetically stable [7] systems (without any apparent flocculation or coalescence during long-term storage) with extremely small droplet size (20 to 400 nm), uniform size distribution [4, 8] and different physicochemical and biological properties than that of other emulsions (>500 nm) [9]. The two immiscible phases are usually oil and aqueous in nature which are enriched with the oil and aqueous soluble ingredients, respectively. Mixing oil and aqueous phases forms coarse emulsion in the presence of emulsifier that may change in to nanoemulsion spontaneously or by applying high energy [10]. Based on the components, nanoemulsions are categorized in three types i.e. Oil in water (O/W); where oil phases are dispersed in continuous aqueous phases [11], Water in oil (W/O); where water phases are dispersed in continuous oil phases [12] and Bi-continuous/multiple emulsion where micro domains of oil and water phases are inter-dispersed within the

system [13]. Based on surface charge over the nano-droplets, nanoemulsions are categorized as neutral, anionic and cationic nanoemulsion [14]. Several modifications have also been done i.e. primary, secondary and ternary emulsions. In primary nanoemulsion, oil phase is emulsified with water phase using an emulsifier while in secondary nanoemulsion oppositely charged electrolyte is deposited over single layer nanoemulsion. In ternary nanoemulsion, secondary nanoemulsion is coated with oppositely charged or hetro polymer [15]. The oil phase plays a vital role in nanoemulsion formulation as it solubilizes lipophilic drugs meant to be used for treatment of range of ailments. In o/w type nanoemulsion, the amount of oil may vary from 2 to 20% w/w based on site of administration. Choudhury et al. 2013 claims that the drugs that belong to BCS class II and IV are the preferred choice for the development of o/w nanoemulsion, as it helps enhance the solubility of the drugs [16]. FDA approved and GRAS certified oils viz. Isopropyl Myristrate (IPM) [17], Triacetin (Glycryl triacetate), Sefsol 218 (Propylene glycol mono ethyl ether) etc. are preferred over conventional high density fixed oils such as castor oil, coconut oil, sesame oil, cottonseed oil, fish oil,linseed oil, mineral oil, olive oil, peanut oil, sunflower oil etc. [18]. The best emulsifier systems are selected from a pool on the basis of their solubility and emulsification ability [16]. In many instances, non-ionic surfactants are used because they are less toxic and irritant than that of their anionic and particularly their cationic counterparts [19]. Emulsifier selection is done on the basis of their solubility in oil and aqueous phases, HLB value, and lesser toxicity profile etc. In the preparation of o/w nanoemulsion, nonionic surfactants having HLB value 8-16 are preferred [20]. Sole use of single chain emulsifiers is less likely to reduce the o/w interfacial tension to an appreciable extent and therefore, a coemulsifier with an amphiphilic nature is used with the emulsifier system. The penetration of coemulsifiers into the emulsifier interfacial film at the o/w interface helps in further reduction of the fluidity of the interface and thereby increase the entropy of the entire colloidal system [21]. Generally C3-C8 alcohols such as Transcutol IP, glycerine, ethylene glycol, propylene glycol, ethanol, propanol are used as co-emulsifiers [22]. It further stabilizes the interface and increases the mobility of the hydrocarbon chains. Area of the stable nanoemulsion region under phase diagram is used as assessment criteria for the evaluation of strength of co-emulsifiers [23, 24]. As per the report published by Azeem et al. 2009, at fixed emulsifier and coemulsifier (1:1) ratio and concentration, the area of the existence of the nanoemulsion is increased with increase in the chain length of co-emulsifiers i.e. from C2 to C3 however; the area of the existence of the nanoemulsion is decreased with increase in the number of hydroxyl groups, as we move from isopropyl alcohol to propylene glycol [19].

Nanoemulsions have unique properties such as small droplet size, exceptional stability, transparent appearance and tunable rheology. These properties make nanoemulsions an attractive candidate for applications in the food, cosmetic, pharmaceutical industries and in drug delivery applicati. Furthermore, they can serve as the building blocks for designer advanced materials with unique properties.

COMPONENT OF NANO-EMULSION

1. Oil
2. Surfactant
3. Co- Surfactant
4. Aqueous phase
5. Preservative, Antioxidant & Chemoprotectants

1. Oil: -

The oil selection used in Nanoemulsion formulation considers as an important factor since the drug will be incorporated as a droplet in the oily phase that dispersed in the aqueous phase. So, the oil which is selected should able to dissolve the substances used in dosage form to get a higher % of drug-loaded, also oil selected must be compatible with other Nanoemulsion component. The oil used in Nanoemulsion either natural, synthetic, or semi-synthetic.[26]

2. Surfactant (Surface-active Agent): -

Surfactants are substances that decrease interfacial tension or surface tension occurring between a solid and a liquid. Surfactants function as emulsifiers, wetting agents, foaming agents, detergents, and dispersants, depending on the hydrophilic-lipophilic balance (HLB) ratio. The use of surfactant in preparation of Nanoemulsion to stabilize the system and chooses it to depend on Nanoemulsion type to be prepared Hydrophilic Surfactant with HLB value more than 10 used for o/w nanoemulsion, while hydrophobic Surfactant with HLB value less than 10

used for w/o Nanoemulsion. The use of Surfactant combinations with low and high HLB value leading to the formation of good stability Nanoemulsion upon water dilution.[27]

HLB Value	*Surfactant Property*
(0-3)	Anti-foaming agent
(4-6)	Water in Oil (W/O) emulsifier
(7-9)	Wetting agent
(8-18)	Oil in Water (O/W) emulsifier
(13-15)	Detergents
(> 15)	Solubilizing agent

Table 1: Surfactant property according to HLB value[28]

3. Co- Surfactant: -

These materials added to Nanoemulsion formulation to decrease the interfacial tension that occurs between oil and water when the surfactant failed to decrease it. In addition, it provided some fluidity to the interfacial tension of Surfactant when it has high rigidity, through penetrating into a monolayer of surfactant and disrupting its crystalline liquid phase, an example of Co-Surfactant propylene glycol, poly glyceryl oleate, PEG 400.[29]

4. Aqueous phase: -

Deionized water used in Nanoemulsion formulation as an aqueous phase since its pH 7 and has no electrolytes. The stability of Nanoemulsion and its droplet size influenced by the nature of aqueous phases like ionic content, electrolytes, and pH. The electrolyte decreases the repulsion force between droplet due to zeta potential reduction and pH changing of formulation leading droplet flocculation in the formulation.[30]

5. Preservatives: -

Preservatives employed in nanoemulsion should meet criteria like low toxicity, stability to heat and storage, physical and chemical compatibility, reasonable cost, ease of availability, acceptable odor, taste and colour and should have a broad antimicrobial spectrum. Microorganisms thrive in both oil and water, and consequently selected preservative should attain effective concentration in both the phases. Because of their hazardous potential, preservatives are generally avoided in parenteral nanoemulsions. Acid and acid derivatives viz. benzoic acid, sorbic acid, propionic acid, dehydroacetic acid can be used as antifungal agents in formulation. Alcohols like chlorobutanol and phenoxy-2-ethanol are routinely used in ophthalmic. Broad-spectrum preservatives include phenols and quarternary ammonium compounds [31].

Various Routes of Administration of Nanoemulsion: -

1. Nanoemulsion for Oral Route: -

The poorly water-soluble drugs have low bioavailability because they have a low rate of dissolution; therefore o/w Nanoemulsion for these drugs lead to increase its solubility, absorption, and bioavailability after oral administration.

2. Nanoemulsion for Ocular Delivery: -

For improvement, lipophilic drugs delivery to the eye, o/w Nanoemulsion used such as pilocarpine, erythromycin.

3. Nanoemulsion for Nasal Delivery: -

The nasal route possesses many advantage comparing with the perioral and parenteral route, such as by pass first metabolism in the liver, increasing the contact time between nasal mucosa and Nanoemulsion droplet leading to increase drug absorption. [Ref. 28,32,33,34]

METHODS OF PREPARATION

Nanoemulsions may be made utilizing both high and low energy processes. Mechanical devices provide the requisite huge disruptive forces in high energy approaches. Low energy approaches, on the other hand, do not require an external force. The intrinsic physiological features of the system are used to produce nanoemulsions. In this nanoemulsion preparation method, stored energy of the system is utilized by alteration of parameters such as temperature, composition of the system [35].

1) High-Energy Emulsification Methods: -

Nanoemulsion are non-equilibrium systems that cannot form on their own. As a result, mechanical or chemical energy is required to produce them. High energy techniques are commonly used to create nanoemulsion, with mechanical energy input provided by high pressure homogenizers, high shear stirring, and ultrasonic generators [36]. These mechanical devices generate significant forces that disrupt the oil and water phases, resulting in nanoemulsion. The input energy density in high energy technologies is around 108 -1010 W kg-1 [37]. The system receives the necessary energy in the least amount of time in order to produce homogenous tiny sized particles. Because high-pressure homogenizers can achieve this, they are the most often utilized machines for preparing nanoemulsion [38]. Moreover, producing emulsions

using ultrasound is a cost-effective process which needs less surfactant use [39].

2) High Pressure Homogenization: -
It is the most widely used method for producing nanoemulsions. This approach uses a high-pressure homogenizer or a piston homogenizer (Figure) to create nanoemulsion with particle sizes as small as 1 nm. During the method, the macroemulsion is forced to pass through in a small orifice at an operating pressure between 500 to 5000 psi [40]. Because to the interaction of numerous forces throughout the process, such as hydraulic shear, severe turbulence, and cavitation, extremely tiny droplet sized nanoemulsions are generated.
This process can be repeated until the final product reaches the desired droplet size and polydispersity index (PDI). The uniformity of droplet size in nanoemulsions is specified by PDI [42]. Higher PDI means lower uniformity of droplet size in nanoemulsions. Monodisperse samples have PDI lower than 0.08, PDI between 0.08 and 0.3 states a narrow size distribution, whereas PDI greater than 0.3 indicates broad size distribution [43]. However, obtaining tiny submicron droplets needs a significant amount of energy [44]. This amount of energy and increasing temperatures during high pressure homogenization process might cause deterioration of the components [35].

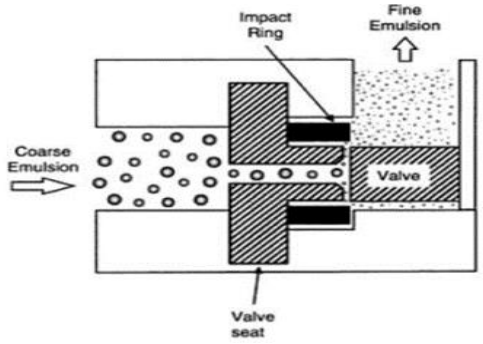

Fig.1: Schematic representation of high pressure valve homogenizer.[41]

3) High-Shear Stirring: -
High-energy mixers and rotor-stator systems are employed in this approach to prepare nanoemulsions. By raising the mixing intensity of these devices, droplet sizes in the internal phase may be greatly reduced. It is, however, difficult to generate emulsions with average droplet sizes smaller than 200-300 nm [45]. [PDF 11 P 3,4]

4) Low–energy emulsification method: -
This method provided more uniformly and smaller droplets through using physicochemical characterize of the system.[46] There is some limitation for this method about using some oil and emulsifier types such as polysaccharides and proteins. To solve this problem, synthetic surfactants at high concentrations are used with techniques at low energy, but this is narrowing its application space, especially for food processing.[47]
5) Spontaneous Nanoemulsion: -
It utilizes the chemical energy released upon processes of dilution with a continuous phase, which happens at a constant temperature throughout the emulsifications procedure, without any phase transition in the system.[48] This method produces Nanoemulsion without special device at room temperature. In this system, an oil phase with a hydrophilic substance mixed with water, oil droplet immediately formed, this mechanism depends on water-dispersible material movement from oil to water phase as red arrows which lead to spontaneous oil droplet formation.[47]
6) Phase Inversion Composition (PIC): -
The composition is modified at a steady temperature in this procedure. Nanoemulsions are created by constantly adding water or oil to an oil-surfactant or water-surfactant combination. The PIC approach is more suited for large-scale manufacturing than the PIT method since adding one component to an emulsion is easier than generating sudden temperature changes [36]. When water is added to the system, the amount of water increases, resulting in a transition composition. In other words, when the amount of hydration of the surfactant's polyoxyethylene chains grows, the surfactant's spontaneous curvature changes from negative to zero. As in the HLB temperature, in the transition composition a balance is obtained for the surfactant hydrophilic–lipophilic properties. When this transition composition is exceeded, small sized metastable oil in water droplet are composed due to the separation of the structures that have zero curvature [49].

Characterization and Evaluation: -
• Droplet size: - In this case, light scattering or electron microscopy may be used to determine the droplet size distribution of nanoemulsion vesicles. However, this method is thought to be the best at predicting the stability of nano-emulsions.

• Zeta potential: - The zeta potential is used to determine the surface charge of particles while they are submerged in liquid. The zeta potential of a pharmaceutical polymer or vehicle is a physicochemical parameter that is used to predict dispersion stability. The presence of electrolytes and their adsorption influence its value. It is measured using Malvern Zetasizer equipment. The nanoemulsion is diluted to compute the zeta potential, which is based on the electrophoretic mobility of oil droplets. A zeta potential of 30 mV is regarded to be sufficient for assuring physical stability of nano-emulsions. Making use of the Malvern Zetasizer.

• Viscosity measurement: - The viscosity of formulations was examined to identify their rheological qualities. This was accomplished using a Brookfield Rheometer viscometer (DV-+version 10) at 30°C with a CPE 61 spindle spinning at 100 rpm. After the findings were obtained in triplicate, the average was considered.

• Drug content: - Using a spectrophotometer or HPLC, the pre-weighed nano-emulsion is extracted by dissolving it in an appropriate solvent. The extracted material is then compared to a drug reference solution.

• pH: - A pH meter was used to check each nano-emulsion compostion. The pH meter was calibrated using pH 4 and pH 7 standard buffer solution before use in formulation. PH was measured using a pH meter electrode immersed in 10% nano-emulsion.

• Refractive index: - RI is an optical property that may be utilized to explain the isotropic character of nano-emulsions and, more crucially, the chemical interaction between the drug and the excipients. The refractive indices of formulations created by each technique were not substantially different (p 40.05). All nanoemulsion formulations had refractive indices closer to 1.42, the refractive index of water. The same refractive index value indicates a homogeneous nano-emulsion structure. These findings suggest that the enhanced nano-emulsion formulations were not only stress stable, but also isotropic.

• Phase behaviour study: - The goal of this study is to characterize and optimize surfactant, oil phase, and aqueous phase constitutions. In general, research is required in the case of nano-emulsion formulations created by phase inversion temperature method and self-emulsification method in order to determine the phase of nano-emulsion and dispersibility. The experiment is carried out by thoroughly homogenizing various nano-emulsion ingredients in glass ampules at a specific temperature for a period of time until equilibrium is reached. The anisotropic phase can be revealed by polarized light.[50]

STABILITY OF NANOEMULSION

The role of surfactants, their composition, and the distribution of droplet size all affect the stability of the emulsion. Surfactants play a crucial role in the preparation of nanoemulsions by reducing the interfacial tension between two phases, which allows for the production of small droplets [51]. The kind of emulsifier affects the stability of the nanoemulsion under various conditions, including pH, ionic strength, heating, and long-term storage [52]. There are various ways that surfactants can promote stability. For example, ionic surfactants can provide an electrical charge, while non-ionic surfactants can create a steric barrier by forming bulky molecular groups [53]. Furthermore, the gravitational pull of larger particles is greater than that of smaller ones [2]. Because of their unique particle size, nanoemulsions are very stable against creaming, flocculation, coalescence, and sedimentation [38]. Creaming or coalescence are typically not an issue for nanoemulsions because of their extremely small droplet size, which subjects them to Brownian motion rather than gravitational forces [54]. Additionally, smaller droplet sizes offer better stability against flocculation and less adhesion, along with steric stabilization, which acts as a natural nanoemulsion preventive mechanism [55; 56]. However, because of the way their droplet sizes are, Ostwald ripening serves as their primary destabilizing mechanism their droplet sizes are, Ostwald ripening, therefore, severely restricts their use in developing applications [57].

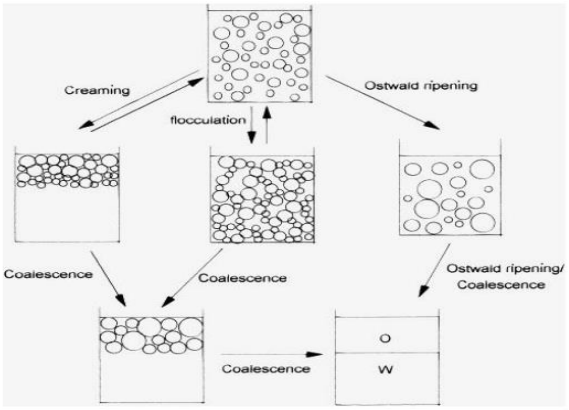

Fig.2: Physicochemical mechanisms cause instability [58].

Mechanism of Nanoemulsion: -

- Percutaneous Absorption: -

Dermal and transdermal drug delivery requires efficient penetration of active compounds through the skin barrier basically by a passive diffusion process. A molecule applied on the skin surface may use two diffusional routes to penetrate: the transappendageal and the transepidermal routes. Transport through skin shunts, such as sweat glands and hair follicles with sebaceous glands connected, is a part of the transappendageal pathway. Furthermore, there is a correlation between the sebaceous glands and hair follicles and a number of dermatological conditions, including alopecia, acne, and several skin tumors. Therefore, there is a great interest in the pilosebaceous units as targets for localized drug delivery, as well as shunts for transdermal delivery, even if the specific role of the follicular pathway in dermal drug absorption is difficult to elucidate due to the lack of an adequate animal model to distinguish follicular to non-follicular transport [59]. However, the main route to penetrate the skin barrier is considered the transepidermal passage, following which molecules can cross the intact, unbroken horny layer by using two different pathways: the transcellular, across the corneocytes and the lipid matrix and the intercellular across the lipid domains between the corneocytes [60]. Structure and barrier function of the skin have been extensively described in the literature [59,61] and it is generally accepted that the tortuous but continuous intercellular route provides the principal pathway for the permeation of most drugs [62,63]. However, hydrophilic compounds would preferably follow the transcellular route because of the aqueous environment due to the great amount of hydrated keratin inside the corneocytes. The most common methods for evaluating in vitro skin penetration employ diffusion cells, and a rich literature confirms the suitable performance of these experiments. Since the in vivo sink circumstances cannot be perfectly replicated, one possible drawback of the in vitro investigations is the absence of information regarding impacts of blood flow on drug penetration [64,63].

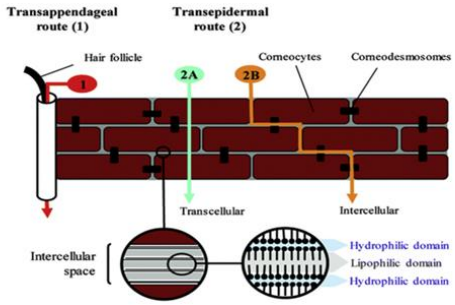

Fig.3: The brick and mortar model for stratum corneum. [60]

- Oral Absorption: -

Upon oral administration, nanoemulsion enter gastrointestinal tract and are subjected to variety of environmental conditions [65]. Stimulation of 'lipidsensing' mechanism in GI tract leads to secretion of gastric lipases which start fractional digestion of LCT or MCT making up the nanoemulsion, to yield simpler di-glycerides, mono-glycerides and free fatty acids. In other cases, the medication may simply partition out of the oil droplet into the surrounding aquatic environment. The presence of oils and oil digestion products in the GI tract stimulates bile production and slows GI tract motility. Components of bile aid in solubilization of nanoemulsion by acting as endogenous surfactants and may form colloidal structures known as mixed micelles. Additionally collisional absorption also occurs, which involves accidental impact absorption of nanoemulsion droplet. Due to flexible nature of droplets, nanoemulsion tend to stick and squeeze through absorption barrier, bending and changing their contours according to gaps available in the packed bilayer [66]. Certain excipients such as tocopheryl polyethylene glycol 1000 succinate [67] and Labrasol [68] used in formulating nanoemulsion have unique ability of inhibiting ATP dependent p-glycoprotein transporter and have been exploited to increase oral bioavailability of poorly soluble anticancer drugs like paclitaxel [69]. After absorption, nanoemulsion droplets may either enter systemic circulation via hepatic portal vein or alternatively be trafficked into perforated lymphatic endothelium[66]. Consequently, when medications are delivered as nanoemulsions, many processes combine to provide multiple paths that change the oral bioavailability of poorly accessible pharmaceuticals.

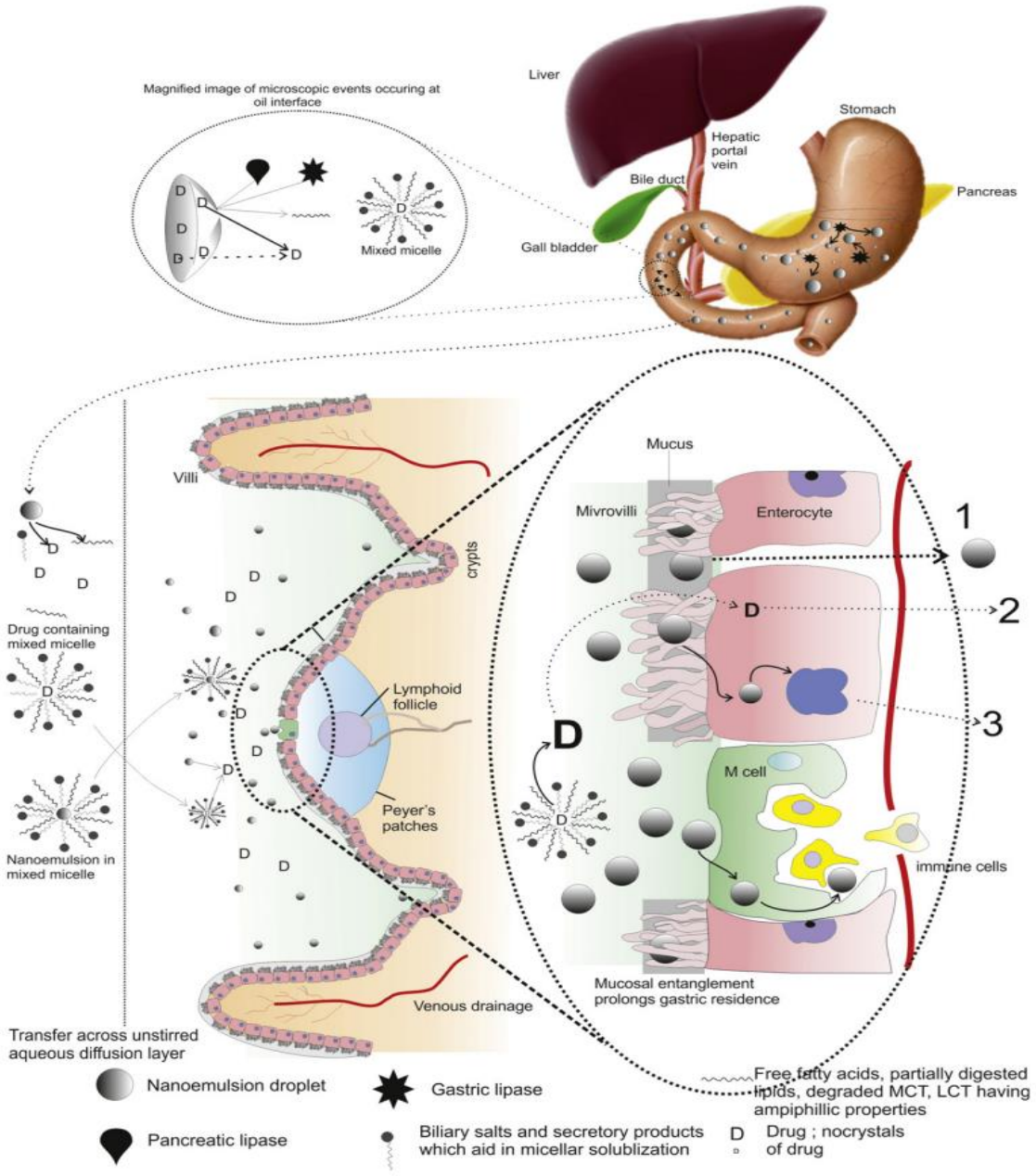

Fig.4: (1) Thereafter a drug may be directly absorbed via conventional lipid solubilization and partitioning phenomena and become systemically available as per its biopharmaceutical properties which dictate preferential venous or lymphatic entry. A partially digested nanoemulsion droplet, or in cases where the oil is lipase resistant, an intact droplet might also be solubilized in a mixed micelle. (2) The droplet may exploit specific or non specific uptake mechanisms like paracellular or trancellular pathways, mucosal entanglement or enter M cells or other absorptive cells. (3) Once inside the absorptive cell, nanoemulsion droplet may be processed into apolipoproteins and channeled into lymphatic drainage.

FUTURE PROSPECTS AND OPPORTUNITIES

- Despite different types of nanoemulsion have been widely explored as the drug delivery carriers, the expansion of investigation in dermal and transdermal delivery of drugs through engineered nanoemulsion technology is highly desirable to widen its outstanding applications.

- In near future, the issues related with nanoemulsion delivery over the skin, suitability of nanoemulsion formulation containing semisolid dosage forms, toxicity and regulatory aspects are to be addressed properly. The main reasons for low industrial scalability of transdermal nanoemulsion are their short term stability, scale-up problems, lack of interaction studies between nanoemulsion and human skin, and lack of clinical data on human skin.
- Extensive investigations in the fundamental research like the role of surfactants/protein/lipid in nanoemulsion development are to be done which will offer the optimum emulsifier system as well as their concentrations that would be more economical.
- Forthcoming scenario of nanoemulsion in the field of dermatology and trans-dermal applications seem to be very opportunistic where the potential of nanoemulsions in dermal and trans-dermal delivery of several novel phyto-pharmaceuticals are to be explored.
- Elimination of the absorption and miscibility related problems of flavonoid, exploitation of the role of lipid interfaced nanoemulsion in dermal delivery and their usefulness over other transdermal delivery modalities such as iontophoresis and sonophoresis should be emphasized.
- We recommend that more emphasis is to be given to the research efforts to exploit the potentials of emulsion nanotechnology in drug delivery of therapeutics. It is evident from the in process clinical trials, there is a great future for dermal and transdermal delivery of drugs by nanoemulsion. [70]

APPLICATION OF NANOEMULSION IN VARIOUS DISEASES

1) Dermatitis: -

Atopic dermatitis is defined as a dry skin disorder caused by trans-epidermal water loss in which the stratum corneum feels a lack of barrier function; hence, the main focus in atopic dermatitis is to restore skin moisture and preserve homeostasis. To ensure that ceramide was available to the lipid lamellae, the surface of the nanoemulsion was modified with positively charged phytosphingosine, allowing ceramide to stay in touch with the skin cells for an extended period of time. As a result, the amount of ceramide in the stratum cornium was maintained, and therefore the skin barrier's homeostasis was preserved [71]. The inflammatory situation was alleviated, and the amount of ceramide in the stratum corneum was returned to normal, restoring skin homeostasis [72]. Because of its vasoconstrictor, anti-inflammatory, immunosuppressive, and antiproliferative properties, CP is clinically useful in the treatment of atopic dermatitis[73]. A low energy emulsified nanoemulsion of rice bran oil shown remarkable usefulness in the treatment of atopic dermatitis and increased skin moisture [74].

2) Cancer: -

Nanoemulsion enhances drug delivery into and across the skin primarily by modulating concentration gradient across skin and skin barrier function by virtue of the presence of emulsifiers and proved its utility in chemotherapy [75]. O/W nanoemulsion of dacarbazine comprising soyabean oil, polysorbate-80, DAC and water improved anti-tumor efficacy of DAC significantly in epidermoid carcinoma xenograft mice. Tween 80 emulsified nanoemulsion ensured reduced oxidation and degeneration of DAC into 4-diazoimidazole-5-carboxamide in water dispersion. This strategy ensured local availability of DAC and maximum possibility to be taken up by tumor tissue after topical application. DAC nanoemulsion circumvented its side effects viz.skin discoloration and ulcers [76]. Zn phthalocyanine and foscans which is a known photosensitizer were incorporated in to the magnetic nanoemulsion for photodynamic therapy of skin cancer topically. Phosphate-coated magnetite, soy phospholipids Epikuron 170, and Poloxamer 188 constituted biodegradable o/w magnetic nanoemulsion of foscans administered locally at tumor site.[77].

3) Rheumatoid arthritis: -

Nonsteroidal anti-inflammatory drugs are the most commonly used drugs to reduce pain and inflammation of rheumatoid arthritis. Transdermal gel of etoricoxib nanoemulsion has been found to be active in maintaining the effective drug plasma concentration without portraying the adverse effects associated with its oral delivery. This transdermal gel was credited due to the smaller droplet size and fluidic nature that has improved the anti-inflammatory efficacy of etoricoxib [78]. Frequent oral intake of these drugs is not comfortable as they cause

discomfort to the gastric mucosa. Oleic acid that is used in the development of nanoemulsion and constituted oil phase is thought to disrupt the cellular arrangement of the stratum corneum irreversibly and thereby allowed better penetration through the different skin layers. [79, 80].

4) Hypertension: -

Several classes of medications viz.thiazide-diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been used in the treatment of hypertension. However, the drugs like carvedilol, have several limitations like extensive first-pass metabolism and unpredictable or low bioavailability[81]. The findings demonstrated that oil globules in the nano size range penetrated epidermal barriers and attained effective medication concentration in blood. Water in oil nanoemulsion of nicardipine hydrochloride[82] and o/w nanoemulsion of amlodipine[83] and felodipine[84] have been developed for transdermal delivery and have been successfully assessed against the treatment of hypertension. The better penetration of these calcium channel antagonists through the skin was attributed to the higher flux (due to the presence of surfactant and co-surfactant) and small droplet size of nanoemulsion.

5) Diabetes: -

It is a consequence of defective or impaired insulin secretion and is treated by administering insulin and oral hypoglycemic [85]. Developing transdermal systems overwhelmed the shortcomings related with oral hypoglycemic like glibenclamide (GCL)[86]. In experimental animals, GCL transdermal nanoemulsion gel demonstrated better control of hyperglycemia and more efficiently cured diabetes mellitus problems than oral GCL treatment. Better result of the gel is attributed to the many factors such as larger amount of surfactant and cosurfactant carrying drug, high penetration into the skin, nanosized droplets, high solubilization of drug in nanoemulsion, high thermodynamic activity providing significant driving force for its release and permeation and lastly hydration of the stratum corneum due to external water phase of the nanoemulsion results in high diffusivity of lipophilic drug as droplet size approaches to molecular dispersion. Subsequently in 2015, Dina et al.[87] developed the nanoemulsion of essential oil of fennel which is highly recommended for diabetes owing to the presence of trans-anethole as one of the major constituent. Due to the presence of oleic acid and propylene glycol (PG), a co-surfactant that acts as a permeation enhancer for dermal delivery by increasing the fluidity of the liquid portion of the stratum corneum, this nanoemulsion demonstrated high potential in reducing the plasma glucose levels of rats when administered transdermally. Moreover, Tween 20 enhanced the flux of the materials permeating through biological membranes resulted in better penetration of oil and hence improved activity.

CONCLUSION

Nanoemulsion offer several advantages for the delivery of drugs and are thus receiving increasing attention as drug carriers for improving the delivery of active pharmaceutical ingredients. They are applicable for almost all routes of delivery and therefore hold promise for different fields, be it cosmetics, therapeutics or biotechnology. This new technology could be developed to overcome the poor absorption of some phytopharmaceuticals and poor miscibility of these compounds with the lipid contents of cell membrane linings. Nano-emulsions can be used as colloidal carriers for a variety of lipophilic drugs, diagnostic agent, and other substances. It is a good carrier for Nano-emulsions for drug administration via various transdermal routes. Due to the renewed interest in herbal drug formulation, nano emulsion may be the ideal delivery platform for these difficult-to-formulate phytopharmaceuticals. The prospects of nano emulsions lie in the ingenuity of formulation experts to utilize the advantages of nano emulsion carriers in overcoming peculiar problems of drug delivery such as absorption, permeation and stability of both orthodox and herbal drugs.

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