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Nano Emulsion Type, Theories, And Factors Influencing: A Review Of Nano Emulsion Formulation

[1]Rajesh Saini, [2]Lalit, [3]Jennifer Gay, [4]Sneha Adhikary*

[1]Assistant professor, [2]Lecturer, [3]Lecturer, [4]Research Scholar

[1]Yogendra Nath Saxena College of Pharmacy & Research Center, Rampur bhood road Hasanpur, Amroha - 244241

[2]YNS College of pharmacy & Research Centre, Rampur bhood road, Hasanpur, Amroha 244241

[3]BIU College of Pharmacy, Campus, Rohilkhand Medical College, Chandpur Bichpuri, Bareilly, Uttar Pradesh 243006

[4]Asutosh College, Shyama Prasad Mukherjee Road, Bhowanipore, Kolkata, West Bengal 700026

Abstract: The Nano emulsion takes into account a novel medication delivery method that permits a regulated or prolonged drug release. It is regarded as a dispersion made up of oil, surfactant, and a transparent, kinetically or thermodynamically stable aqueous phase with droplet diameters ranging from 10 to 100 N. Nanotechnology is used to improve the solubility and bioavailability of lipophilic medications; nano emulsions offer a variety of benefits for drug delivery. It can be used in a variety of delivery methods, offering a consistent result in a wide range of industries, including biotechnology, therapy, and cosmetics. Oil and water dispersions known as nano emulsions allow for the stabilisation of dispersed phase droplets (20–500 nm) by an active surface coating composed of non-ionic surfactants. Nano emulsions have been proposed as a super solvent vehicle that can dissolve both lipophilic and hydrophilic medications. To some extent, a system based on nano emulsion can pass via hepatic metabolism because it has been observed that nanoparticles can enter the bloodstream directly through the paracellular pathway and absorb into the blood, indicating a systemic drug sequence.

***Index Terms* – Nano emulsion mellitus; Nanotechnology; Nanoparticle; NDDS.**

1. Introduction

Nano emulsions / Sub-micron emulsions (SMEs)/Mini-emulsions /Ultrafine emulsions are dispersions of oil and water where the dispersed phase droplets are in nanosized range and stabilized with surface active film composed of surfactant and co surfactant, Nano emulsions are transparent or translucent systems that have dispersed phase droplet size range of typically 20-500 nm.[1] The terms sub-micron emulsion (SME) and mini emulsion are used as synonyms. [2]

Nano emulsions are attractive as pharmaceutical formulations because they form spontaneously, are kinetically and thermodynamically stable, and optically transparent. The nanosized of the droplets prevent creaming or sedimentation form occurring on storage and droplet coalescence. Nano emulsions provide much longer oil- water contact area due to the nano size droplet compared to classical emulsions, which facilitates drug release from the dispersed droplets. The droplet size is very small that the interaction of matter with light is negligible and they appear transparent or translucent with bluish coloration.[3]

The design of effective formulations for drugs has long been a major challenge, because drug efficacy can be severely limited by instability or poor solubility in the vehicle. One of the most promising technologies is the nano emulsion drug delivery system, which is being applied to enhance the solubility and bioavailability of lipophilic drugs.[4] The bioavailability of drugs was reported to be strongly enhanced by solubilization in small droplets (below 0.2μm), for example, submicronic emulsions were found to increase the bioavailability of cefpodoxime proxetil from 58 to 98 %, compared to other oral formulations. The nanosized droplets leading to an enormous increase in interfacial areas associated with nano emulsion would influence the transport properties of the drug.

Three types of Nano emulsions [3] are most likely to be formed depending on the composition:

- Oil in water Nano emulsions wherein oil droplets are dispersed in the continuous aqueous phase;
- Water in oil Nano emulsions wherein water droplets are dispersed in the continuous oil phase;
- Bi-continuous Nano emulsions wherein microdomains of oil and water are interspersed within the system.

In all three types of Nano emulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants.

Emulsions and nano emulsions vary primarily in that the former have intrinsic thermodynamic instability and will eventually phase separate, even though they may show good kinetic stability. Emulsions and nano emulsions differ significantly in appearance, with the former being hazy and the latter being transparent or translucent. Furthermore, there are notable distinctions in the ways that they are prepared; emulsions necessitate a substantial energy input, whereas nano emulsions don't.

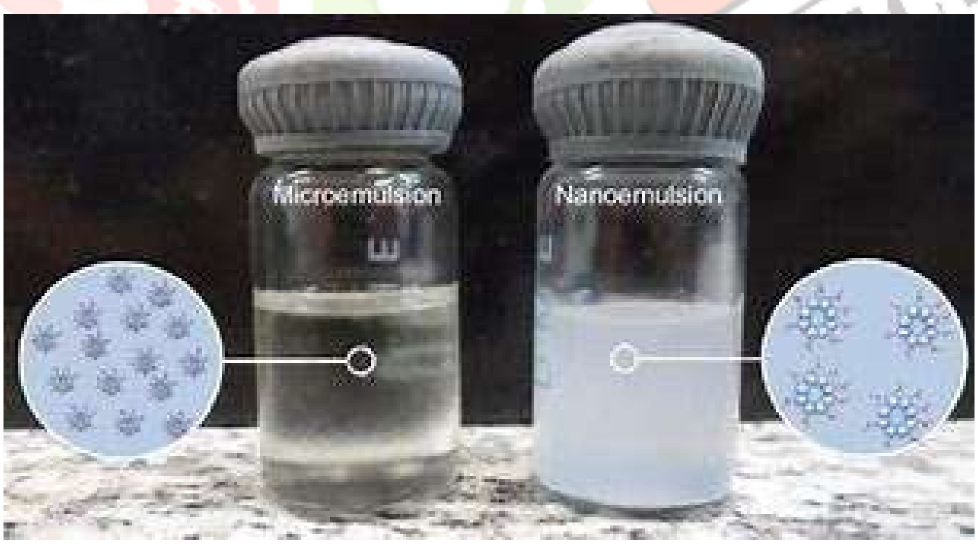

Fig. 1. Nano emulsion and Microemulsion with Droplet Diameters of Less Than 100 Nm and More Than 1000 Nm, Respectively

ADVANTAGES OF NANOEMULSIONS

The attraction of nano emulsions for application in personal care and cosmetics as well as in health care is due to the following advantages:

- Reduce the concentration of surfactants; 3–10% might be sufficient.
- The droplets for topical application are small enough to distribute evenly on the skin.
- They are suitable for efficient delivery of active ingredients through the skin.

- The emulsion system's wide surface area, the system's overall low surface tension, and the O/W droplets' low interfacial tension all contribute to the active agents' enhanced penetration.
- Due to their small size, nano emulsion can penetrate though the rough skin surface and this enhances penetration of actives.
- They may have a pleasing aesthetic aspect and skin feel due to the system's fluidity (at low oil concentrations) and lack of thickness
- Fragrant can be delivered by nano emulsion, which can be used in a variety of personal care products. This might also be used to perfumes, since it's preferable for them to be made without alcohol.
- The first stage in the manufacture of nanocapsules and nanospheres involves the creation of nano emulsions by the use of interfacial polycondensation, nanoprecipitation, and spontaneous emulsification. These methods call for the same ideal circumstances for the spontaneous emulsification stage.
- The small droplet size prevents any flocculation of the droplets. Weak flocculation is prevented and this enables the system to remain dispersed with no separation.[5]
- Nano emulsion may be applied as a substitute for liposomes and vesicles (which are much less stable) and it is possible in some cases to build lamellar liquid crystalline phases around the nano emulsion droplets.
- Improve the solubility of lipophilic substances.
- Because of the extremely small droplet size, which reduces the force of gravity, Brownian motion may be enough to overcome gravity, which is why nano emulsions do not cream during storage. This makes it possible to create sprayable liquid items that don't phase separate in storage
- Use the administration of medicines through different routes such as I.V, oral, and topical.
- It provided efficient and fast medication penetration through the skin and GIT.[6]

DISADVANTAGES OF NANOEMULSIONS

- The cost of creating a nano emulsion is high.
- Ostwald ripening may cause an instability issue for nano emulsion.
- SG and HG capsules are not suitable for encasing nano emulsions.
- Due to their high lipid content, nano emulsions are not very palatable.[5]

Classification of o/w nano emulsions-

There are three classes of Nano emulsion:

i. First-generation nano emulsions, also known as peripheral NE.

ii. Second-generation nano emulsions, including as oral, aerosolized, stargate, and sustained release DDS.

iii. Third-generation nano emulsions (gene therapy applications).

➢ THEORIES OF NANOEMULSION FORMULATION

1. Mixed film theories

According to Schulman, the surfactant and co-surfactant formed a complex layer at the oil-water interface, which is what caused the spontaneous creation of nano emulsion droplets. The oil-water interfacial tension decreases as a result, reaching extremely low values (from almost zero to negative). This is represented by the equation below-

$y_i = y_{0/w} - \pi_i$

Where, $y_{0/w}$= Oil-water interfacial tension without the film present

π_i =Spreading pressure

$y_{i=}$ interfacial tension [8]

2. Solubilization Theories

It is believed that the nano emulsion is getting closer to thermodynamically stable monophasic solutions of spherical micelles that are swelled in water (w/o) or oil (o/w). Phase diagrams were used to show the connections between reverse micelles and w/o nano emulsion. The areas consist of reverse micelles that have been dissolved in water. [9]

3. Thermodynamic Theories

Oil, surfactant, and energy are required for emulsion preparation. This can be understood by looking at the energy needed to widen the interface, or ΔAY (where y represents the interfacial tension and ΔA is the increase in interfacial area when the bulk oil area A creates a lot of droplets with area A2: A2>> A_1). The energy to enlarge the interface is significant and positive since y is positive. The tiny positive entropy of dispersion TΔS and, consequently, the total free energy of emulsion formation, cannot offset this energy factor. ΔG is elevated,

$\Delta G\text{-}A\Delta Y\text{-}T\Delta S$

Thus, emulsion formation is non-spontaneous and energy is required to produce the droplets The high energy required to form nano emulsions can be understood in terms of the LaPlace pressure p (the difference in pressure between inside and outside the droplet).

$P=y\ [1/R1+1/R2]$

Where Rl and R2 are the principal radii of curvature of the drop. For a special drop, R1-R2 and

$P=2\ y/R$ [09]

A drop needs to be severely damaged in order to split into smaller ones, and this distortion raises "P". As a result, for a smaller drop, more stress is required to deform it. Higher stresses require more violent agitation, which requires more energy to create smaller droplets because stress is typically conveyed by the surrounding liquid through agitation (Tadros et al, 2004).[10]

➢ FACTORS INFLUENCING TYPE OF NANOEMULSION

Packing ratio

This balance between hydrophilicity and lipophilicity (HLB) influences surfactant behaviour. via considering the relative contributions of hydrophilic and hydrophobic surfactant molecule fragments, the HLB defines the type of nano-emulsion via affecting film curvature and molecular packing. The amphiphilic molecule (polar head and hydrophilic tail) results in film geometry that depends on their intrinsic geometry, according to the packing ratio or critical packing parameter notion.

Critical packing parameter, CPP - V/al

Where, V is Volume of surfactant, a, is Head- group surface area and I length.
If CPP= between 0-1, interface curves towards water (positive curvature): o/w system favoured.
If CPP>1. interface curves spontaneously towards oil (negative curvature): w/o system favoured.
If CPP-1, either bi-continuous or lamellar structure (zero curvature) HLB is balanced.[11]

Property of surfactant, oil phase and temperature

The kind of surfactant determines the kind of emulsion. When hydrophilic surfactants are used, oil-swollen-type or oil-in-water (O/W) nano emulsions are created, but water-swollen-type or water-in-oil (W/O) nano emulsions are created when lipophilic surfactants are used. When hydrophilic and lipophilic surfactants are used, an oil phase and surplus water coexist in a nano emulsion. The greatest solubilization capacity of the three-phase system is achieved by the use of both ionic and non-ionic surfactant systems.

Temperature

When establishing the effective head group size of a non-ionic surfactant, temperature is a critical factor. They come from a typical out-of-womb system and are hydrophilic at low temperatures. They originate from the w/o system and are lipophilic at higher temperatures. Nano emulsion formed by carbonate structure and coexists with surplus water and oil phases at an intermediate temperature.

The oil phases

By penetrating the tail group region of the surfactant monolayer and causing it to swell, the oil components also affect curvature. Because short chain oils—like alkanes—penetrate the lipophilic group more deeply than long chain alkanes do, swelling in this area causes an increase in negative curvature. [11]

- **FORMULATION OF MICROEMULSION AND PHASE BEHAVIOR**

Phase diagram

Nano emulsions are one of several association structures that form when oil, water, and surfactant are combined. Other association structures include regular emulsions, cubic and different gels, mesomorphic phases gels, and oily dispersions. These formations depend on the chemical makeup and concentration of each component at the current temperature and pressure. Many factors must be taken into account in order to prepare a stable, isotropic, homogenous, transparent, and nontoxic nano emulsion. Phase diagrams are useful for locating the nano emulsion area in ternary or quaternary systems as well as the surfactant minimum required for the development of nano emulsions.

Ternary system

The ternary diagram provides the best explanation of the phase behaviour of surfactant-oil-water (SOW). The phase diagram assists in determining the ratio of oil to water and surfactant to co-surfactant at the border of the nano emulsion zone. In this case, two composition variables are sufficient, as the third one is complemented to 100% [12]. A conventional tetrahedron made up of comparable triangles can be used to represent the composition of a four-component system, but creating the quaternary diagram takes effort and is frequently challenging to understand. Thus, it is more typical to use a pseudo ternary phase diagram to study the planner sections of a tetrahedron. That means either by Keeping the composition of one component fixed and varying the other three, or by using a constant ratio of two component (Surfactants and co-surfactants or co-solvent).

Winsor's phase diagram

Winsor documented the connection between the nature of the various ternary systems and the phase behaviour of amphiphile, oil, and water. He divided the phase behaviour into the categories listed below [13-15]

- **Winsor's type 1:** System (o/w nano emulsion), in which oil is solubilized within micelles in an aqueous continuous phase**.**
- **Winsor's type 2:** System (w/o nano emulsion), in which the aqueous phase is solubilized within micelles in an oil phase.
- **Winsor's type 3:** System (nano emulsion), in which the aqueous and oil phase are in equilibrium with a third, surfactant-rich, phase called the middle- phase nano emulsion, which can contain bi-continuous emulsion.
- **Winsor's type 4**: System shows single phase with oil, water and surfactant, which are homogenously mixed.

Quaternary phase diagram.

In general, nano emulsions are quaternary systems. to research the behaviour of their phases. Pseudo-ternary phase diagrams with an oil-water amphiphile—a surfactant/co-surfactant ratio—are frequently depicted. Utilising a pseudo-ternary diagram for optimisation results in inaccurate results. For such systems, it is therefore preferable to utilise quaternary phase diagrams

➢ FORMULATION OF NANOEMULSION

Compared to regular emulsions, nano emulsions are more difficult to create because of the formulation's extremely specialised composition and spontaneous interactions between the constituent molecules.

The general composition of nano emulsion includes the following:

a) An oil phase: Oils such as Caprylic/Capric triglycerides (Miglyol 812, Myritol 318). castor oil, Cremophore EL etc can be used as oil components.

b) An aqueous phase: This phase may contain hydrophilic active ingredients and preservatives for example, ethanol, tetrahydrofuran, purified water etc. Buffer solutions for example, Dulbecco's phosphate buffered solution, have been used as aqueous phase by some researchers.

c) A primary surfactant: The surfactant is generally ionic, non-ionic, or amphoteric, but the non-ionic surfactants are generally preferred because they can be rapidly absorbed in the alimentary canal. Rest both are for specific cases. For example, Span. 80, Span 85, Tween 20, Tween 80, Pluronic F68

➢ Conclusion

The Nano emulsion takes into account a novel medication delivery method that permits a regulated or prolonged drug release. It is regarded as a dispersion made up of oil, surfactant, and a transparent, kinetically or thermodynamically stable aqueous phase with droplet diameters ranging from 10 to 100 N. Nanotechnology is used to improve the solubility and bioavailability of lipophilic medications; nano emulsions offer a variety of benefits for drug delivery. It can be used in a variety of distribution methods, giving it a reliable impact in a wide range of industries, including biotechnology, therapy, and cosmetics. Oil and water dispersions known as nano emulsions allow for the stabilisation of dispersed phase droplets (20–500 nm) by an active surface coating composed of non-ionic surfactants. Nano emulsions have been proposed as a super solvent vehicle that can dissolve both lipophilic and hydrophilic medications. Because it has been observed that nanos particles may be directly absorbed into the blood by a paracellular pathway and enter the blood circulation, indicating a sequence systemic medication, a system based on the nano emulsion is capable of passing hepatic metabolism to some extent

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