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A SMALL REVIEW ON THEPROPERTIES OF NANOEMULSIONS

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ABSTRACT

Drug delivery systems are designed in order to achieve maximum therapeutic efficacy of the drugs while reducing their toxicity. The modern drug dosage forms have been the result of a long scientific research in the field. Using sophisticated technologies and exploring novel excipients with outstanding physicochemical characteristics have led to the development of modern novel drug delivery systems from simple pills and mixtures. Emulsions are biphasic systems having one phase dispersed in the other phase in the form of droplets ranging in diameter from 0.1 to 100 µm. Thermodynamically, they are unstable in nature, but can be made stable with the applications of emulsifiers or emulgents. , the surfactants used as emulsifiers are termed as interphaseor intermediate The "Nanoemulsion" term is used for thermodynamically stable isotropically clear dispersion of two immiscible liquids like water and oil stabilized through the surfactant molecules interfacial film. They are novel drug delivery systems in which oil is emulsified in an aqueous system in the form of droplets with a mean diameter 100-500 nm. Nanoemulsions have found wide spread applications as drug delivery vehicles due to some of their distinguished characteristics. There is a growing interest for using of Nano/sub-micron particles in the technology of pharmaceutical, cosmetic and also food industries. Nanoemulsions are also preferred due to their administration through multiple routes. They are used for efficient drug delivery through skin because of the large surface area they provide for the drug penetration. Moreover, they have been nontoxic and nonirritant to the mucous membrane and skin tissues. Their fluidity and avoidance of thickeners in theirformulations make them transparentwithaestheticphysicalappearance. In this paper, a comprehensive review is presented to give basic ideas about properties of Nano emulsions, their preparation methods, and evaluations.

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INTRODUCTION

The "Nanoemulsion" term is used for thermodynamically stable isotropically clear dispersion of two immiscible liquids like water and oil stabilized through the surfactant molecules interfacial film. They are novel drug delivery systems in which oil is emulsified in an aqueous system in the form of droplets with a mean diameter 100-500 nm. Furthermore, they can be as water-in-oil (w/o) or oil-in water (o/w) type having water or oil as internal core, respectively. In case of water-in-oil emulsion, water is dispersed as droplets in the continuous oil phase, while in oil-in-water type emulsions, oil is dispersed in the aqueous continuous phase. They can also be formed in the form of bicontinuous Nanoemulsions. Nanoemulsions have been ideal drug delivery vectors due to their compatibility and ability to dissolve increased amount of lipophilic drugs along their protection from enzymatic degradation and hydrolysis [1,2,3.]

Nanoemulsions have found wide spread applications as drug delivery vehicles due to some of their distinguished characteristics. They can easily and uniformly deposit on the surfaces of the substrates. Similarly, they have enhanced spreading, wetting, and penetration capabilities due to low surface tension of the whole system and decreased interfacial tension between the oil and water phases. The small size of the nanoemulsion droplets also considered to play vital role in their stability. The Brownian motion of the nanoemulsions is strong enough to overcome the gravity force of the system. This results in the prevention of creaming and sedimentation in the systems during storage. The droplets flocculation is prevented by their small size, thus making the systems stable and evenly dispersed. The small droplet size plays also important role in the prevention of coalescence in the nanoemulsions. This is because of the surface elasticity resulting in the decreased surface fluctuations. Nanoemulsions are also preferred due to their administration through multiple routes. They are used for efficient drug delivery through skin because of the large surface area they provide for the drug penetration. Moreover, they have been nontoxic and nonirritant to the mucous membrane and skin tissues. Their fluidity and avoidance of thickeners in their formulations make them transparent with aesthetic physical appearance[2]

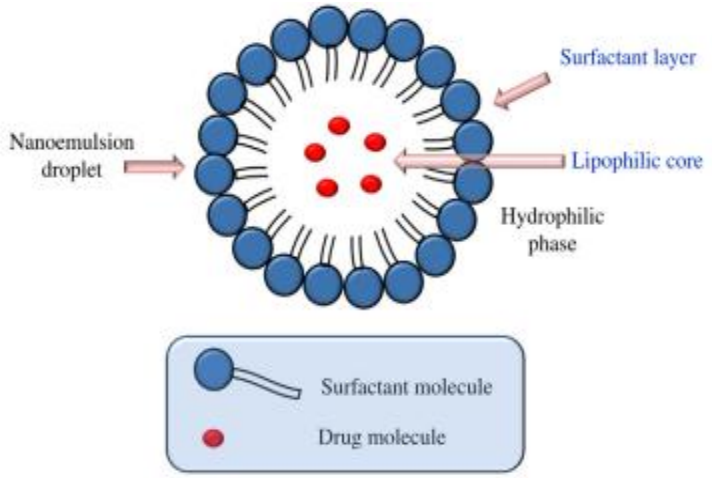

Figure 1: Image showing the structure of o/w nanoemulsion.

ADVANTAGES OF NANOEMULSIONS IN DRUG DELIVERY:

Nanoemulsions are prepared with surfactants that have already approved for use in human. They require a decreased concentration of surfactants as compared to that of micro emulsions. A surfactant concentration of about 5%10% is enough for a stable formulation of a 20% o/w nanoemulsion. They may be used as best alternative to the less stable liposomes. They can also be used in the form of lamellar liquid crystalline phases around the nanoemulsion droplets, leading to unique drug delivery properties. Nanoemulsions have been advantageous in terms of development of different dosage forms like liquids, foams, and creams. The higher biocompatibility of the constituting blocks of nanoemulsions makes them good delivery vehicles for human use. Nanoemulsions are widely used for solubilizing lipophilic drugs and masking their unpleasant taste. They have been found to enhance the absorption, bioavailability, and abolish variabilities in absorption. They are administered through a wide variety of routes, thus can be used for achieving prompt or delayed therapeutic effects of the drugs. Interestingly, the oil-soluble active substances show increased cellular uptake. Similarly, they protect the unstable drug molecules from the light, oxidative, and enzymatic degradation. Controlled release of drugs and their targeted delivery to specific cells or tissues can be achieved with nanoemulsions. They can be used for a wide variety of drugs having varied chemical structures and physical properties [2,4,5].

PROPERTIES OF NANOEMULSIONS (NE):

NE is biphasic mixture comprising of oil and aqueous phase stabilized by surfactant molecules. The structure generated as a result of orientation of surfactant molecules attributes NE with exceptional properties. Due to the unique properties of NE which are highly useful in drug delivery, these are one of the prime Nano carriers in pharmaceutical field. NEs have number of sensible properties including optical clarity with simplest method of preparation, nanosized droplets giving increased surface area and ultimately effective drug release. NEs are formed using lower surfactant concentration which makes it prone to thermodynamic instability[6,7, 8]. However, external application of considerable energy reduces the size of macroemulsion into nanoscale making them more kinetically stable.

Kinetic stability is one of the most important properties of NE which can result into formation of more stable formulation for pharmaceutical drug delivery. Gibbs free energy change in NE is positive which necessiates external energy application during NE manufacturing[7].NE, as described earlier, is mainly manufactured using low surfactant concentrations making it necessary to apply external shear for generation of nanosize droplets as spontaneous formation is not possible at low surfactant concentrations. This point is accompanied with the benefit of less toxicity or no toxicity with NE as surfactant concentration is very low theoretically as compared to NE[9,10,11] Looking to the thermodynamic instability and practical approach, NE is prone to destabilization, temperature fluctuations and even to dilution due to limited amount of surfactant which cannot resist film formed on the large surface area for longer time[15] . However, literature suggests that NE is very robust carrier against temperature changes and even on dilution [6]. This point is always a matter of doubt about the exact molecular phenomena in influence of environmental stressful condition on stability of NE[9].Due to their nanoscale droplets, NEs appear either transparent or translucent with slightest bluish tint. Their bluish tint is due to the phenomena called as Rayleigh scattering. It occurs when droplet size of NE is smaller than wavelength of incident light. As a result, light bluish color or reddish color is seen in media, when it is visualized from light source or toward light source respectively. This phenomena clearly differentiates NEs from their counterparts, such as MEs[9,12]. Their constant brownian motion due to nanosize leads to impede their dormancy thereby preventing gravitational force to destabilize them by virtue of sedimentation, creaming, and coalescence. Such improved stability is useful for storage of NE-based products for prolong period of time.[13]. However, the only mechanism which destabilizes NE is Ostwald ripening process which is the growth of NE droplets at the cost of smaller droplets. Ostwald ripening process is highly attributable to the molecular diffusion of oil between droplets across continuous phase which is identified as Kelvin effect and it is due to the difference in Laplace pressure which can lead to significant droplet growth. Ultimately, it leads to phase separation at latter stage. When particular oil has considerable solubility in water, then the NE prepared from it faces higher risk of Ostwald ripening as smaller droplets will get easily solubilized[14.15,16,..]

PREPARATION OF NANOEMULSIONS:

THEORY OF EMULSIFICATION:

The theory of emulsification describes emulsions as the thermodynamically unstable dispersions of two immiscible liquids due to the positive Gibbs free energy of formation (ΔG)[17].This Gibbs free energy is expressed as

$$\Delta G = \gamma \Delta A - T\Delta S$$

γΔA represents surface contribution, while γ donates interfacial tension and ΔA denotes created surface area. As γ is positive, the energy needed for the expansion of interface is large and positive. Gibbs free energy (ΔG) becomes positive as the energy term is not compensated by the entropy of the system TΔS (positive but small). Therefore formation of emulsion is a nonspontaneous method and requires energy along with surfactants so that one phase gets dispersed into another. In comparison with micro- or macro emulsions, nanoemulsions require a much higher amount of energy for their formation. The difference in the pressure outside and side droplets, termed as Laplace pressure, makes it evident that nanoemulsion formulations require increased amount of energy. If the volume fraction of the dispersed phase is small, the droplet would exist as a sphere with radius r. Surfactants along with cosurfactant decrease the interfacial tension and consequently the Laplace pressure. Hence use of surfactants reduces the stress needed for preparation[18].

COMPONENTS FOR NANOEMULSIONS:

The preparation of nanoemulsions requires drugs, oil and aqueous phases, surfactants/cosurfactants, and additives. The chemical nature and physical characteristics of these components play vital role in the formulation in vitro and in vivo stability and their performance. All these components are discussed in detail.

Oil phase:

Oils may be used to solubilize the lipophilic drugs and increase the drug transport through intestinal lymphatic system. The oils are selected on the base of their ability to solubilize drug molecules. The drug solubilizing property of the oil phase of the nanoemulsions is of greater importance when nanoemulsions are intended for oral administration. The oil can be used as individually or in combinations. Long and medium chain triglyceride oils with different degree of saturation have been used as oil phase, although the latter are preferred and are safe.

A mixture of oils and triglycerides may be used to emulsify the drug. Semisynthetic medium chain derivatives possessing surfactant like properties are used nowadays as oil phase. Commonly used oils in formulating nanoemulsions are: soyabean oil, ethyl oleate, sesame oil, castor oil, arachis oil, corn oil, lanolin, jojoba oil, Capryol 90, triactin, isopropyl myristate, olive oil, oleic acid, isopropyl palmitate, LabrafilMM44CS, palm oil esters, corn oil, LabrafacLipophile WL1349, Maisine 35-1, Captex 200, Captex 355, Captex 8000, Miglyol 812, Sefsol 218, Witepsol, Myritol 318, and Capmul MCM[18,19,20].

Surfactants

The oil and water mixture results in the formation of a temporary emulsion, which separates in its distinct phases after some time upon standing. This phenomenon occurs due to the coalescence of the dispersed globules. Surfactants are used for the stability of such systems. Surfactants contribute significantly in the formulation of nanoemulsions by lowering the interfacial tension between two immiscible liquids and make them miscible. They decrease the stress required to break the drop by lowering the Laplace pressure. Further, they prevent coalescence of newly formed drops. For the preparation of stabile nanoemulsions, the selection of a suitable surfactant is the most important step. Nonionic surfactants are highly preferred due to their less toxic nature and lower critical micellar concentration as compared to ionic surfactants. Moreover, nonionic surfactants are believed to enhance the in vivo stability of an o/w nanoemulsion used for oral or parenteral applications. Hydrophilelipophile balance (HLB) and critical packing parameter must also be taken into account for surfactant selection. Surfactants with high HLB values (8-18) are used to prepare o/w nanoemulsions. Surfactants having low HLB (3-6) may be used for the preparation of w/o nanoemulsions. Commonly used surfactants for o/w and w/o type emulsions are given in Table 1. The right blend of low and high HLB surfactants leads to the formation of a stable nanoemulsion upon dilution with water. Surfactants used in preparation of nanoemulsions must be nontoxic and its taste, odor, and chemical stability should be compatible with the product. They are also required to develop an adequate zeta potential and viscosity in the system so as to impart optimum stability[21].

Co-surfactants:

The addition of co-surfactants in low concentration is necessary for the formation of nanoemulsions. Alcohols of short and medium chains (C3-C8) are mostly used as cosurfactants. They are indeed for reducing the interfacial tension and increasing fluidity of the interface of the nanoemulsion system. They are also expected to enhance the hydrocarbon tail mobility, thus resulting in the increased penetration of the oil in this part. As alcohols get partitioned between the oil and aqueous phase, they also increase the miscibility of these two contrast phases. Most commonly used cosurfactants include isopropyl alcohol, propylene glycol, ethanol, and butanol. Carbitol and PEG 400 are also used as cosurfactants because they are tolerable and their presence in the formulations increases their permeation.

Fabricating nanoemulsions:

Fabrication of any complex drug delivery system plays a crucial role in successful development and efficient outcomes. Quality attributes of that delivery system are altered significantly when there are flaws in the fabrication. As a consequence of this, the delivery system does not deliver as hypothesized leading to either inefficient or exaggerated therapy of targeted disease, both of which are unwanted for optimal treatment of patient illness. The well-established. The understanding of each method will help the scientist to select the best method for NE fabrication with required product characteristics. Selection of fabrication methods for NE is of paramount importance as NE produced by different methods has varied attributes (droplet size, stability including in process stability, composition) which can be its base for selection in pharmaceutical drug delivery. The high energy methods use the application of external energy of higher mechanical amplitude via suitable devices to reduce the size of coarse droplets. These methods are very efficient in generating nanosize product due to high shear applied externally. High disruptive energy may be applied in the form of shear forces, or sound waves or pressure. This approach uses intense disruptive forces that act to break the coarser droplets of dispersed phase to the fine droplets within the nano-range. Methods such as high shear/pressure homogenization, ultrasonication, or microfluidizer follow this principle to generate nanoscale droplets. The droplet size of NE mainly depend upon the type of disruptive forces used, exposure time and the environmental conditions, that is, temperature or pressure of the system. In-fact these methods control the desired size of NE by controlling the amount of applied external energy. Further, this method utilizes the sophisticated instruments and high energy to get desired output which adds to the cost of NE.

However, excess of high energy in any form can destabilize the NEs generated by these methods. Moreover, the efficiency of these methods might be lower, as stated in literature that B99% of energy applied externally, is dissipated in the form of heat. Alternatively, only 1% energy is utilized in producing nanodroplets while remaining is wasted completely. This is the reason of extreme temperatures generated, when these methods are in process[13,22.] On the contrary, the low energy methods, as the name suggests work on the principle of stored energy of NE rather than external energy to get nanoscale droplets. In-fact, these methods rely upon the change in the inherent physicochemical properties of components of NE and phase transition process due to the alteration of temperature or NE composition rather than using destructive power to generate nanoscale droplets. These utilize the intrinsic physicochemical properties of surfactants and co-surfactants to spontaneously generate the nanoscale droplets. The inherent property mentioned here means the change in solubility/miscibility of surfactants/co-surfactants due to alterations in environmental conditions or solution composition [23.24]. Due to change in the curvature of surfactant molecules as a result of change in temperature or composition, phase transition takes place at interface leading to growth of nanodroplets. The low energy methods have currently gained popularity as NEs are not exposed to hostile experimental conditions and thus facilitate longer stability to NEs[25.26].Figure 2 shows the details about methods of fabrication of nanoemulsions.

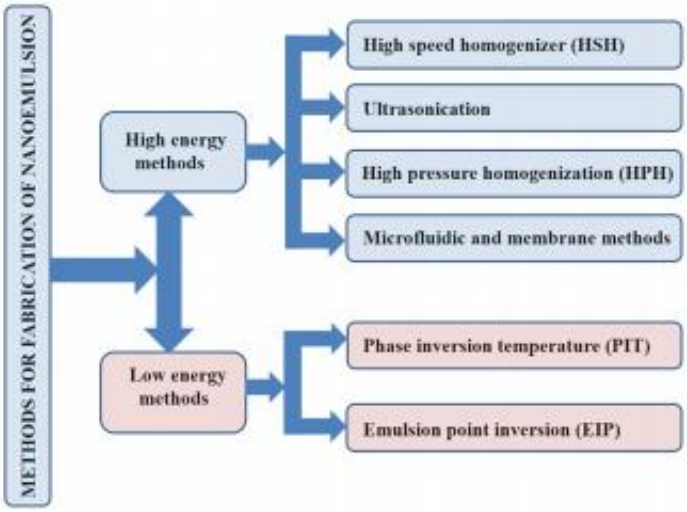

Figure 2 the details about methods of fabrication of nanoemulsions.

High energy methods:

The process of NE fabrication utilizing the high energy methods involves the manufacturing of coarser emulsion called as premix followed by treating it with external energy to reduce the droplet size. The first step involves the simple mixing of aqueous phase (water) into the lipophilic phase (oil) already comprising of surfactant, which leads to the formation of interfacial film of surfactant at the oil-water interface, resulting in generation of stable coarser droplets. The final step involves the reduction of size of coarser droplet to the nanoscale using suitable high energy application devices based on the application of NE. As new surfaces are created by application of external energy, simultaneously surfactant already present on coarser droplets manages to form interfacial films to stabilize newly created surfaces, if it is present in sufficient concentration to cover the new surfaces[27]. The interfacial film of surfactant plays very crucial role in stabilizing the nanodroplets[28]

High speed homogenization/high shear stirring (HSH/HSS):

This method belongs to the group of methods utilizing flow fields for droplets size reduction. This method generates larger droplets as compared to other methods of high energy application. The simplest understanding of this method is the vigorous mixing of the contents constantly thereby providing constant shear to coarser droplets. Various rotor/stator devices with different dimensions are used to apply shear to the coarse emulsion and generate small sized droplets. As the distance between the rotor and stator becomes shorter, the shear force is intensely generated, thereby helping the reduction of the size of coarser droplets in the field flow area [29.]The coarse emulsions are exposed to very high shear with speeds ranging from hundreds to several thousand rotations per minute. Generally, the process is carried out at room temperature bu27t there is also provision to control temperature using thermostat. At such high speed of rotor leading to high rarefaction in the stator, the NEs get sucked in the rotor-stator unit and they are expelled out in periphery (between rotor and stator) with the force enough to reduce the size of droplets. When compared with other methods, HSH enjoys popularity as being the only method with considerable high energy for nanodroplets generation with minute rise in temperature. Hence, this method has been of choice for many NE formulations consisting of thermolabile components. However, ultra nanosize droplets are difficult to obtain and highly viscous media are difficult to process by this method as HSH is not able to generate violent disruptive forces[30,31] have used HSH method to develop and optimize the NEs. These authors have compared the high speed stirring method with high-pressure homogenization (HPH) method.

Ultrasonication:

Sonication is exposure of the system to the considerable amplitude of sound waves. It is executed with the help of sonicator probe, which when touches the liquid, mechanical vibration created and cavitation occurs. Cavitation is the generation and collapse of vacuum cavities in liquid. As a result of cavitation, sound waves are generated that supply energy to the coarse emulsion droplets. Due to these sound waves, the droplet size will reduce to nanosized droplets till optimum frequency and time of sound waves. Ultrasonication utilizes similar mechanism of flow field to generate nanodroplets. Simpler sonication equipment has very less frequency and amplitude. For generation of nanosized droplets, high frequency sound waves with considerable amplitude are required. The use of high frequency sound waves in generating nanosized droplets is termed as ultrasonication. This system propagates the turbulence in the solution with actuator generating pressure fluctuation which helps in vibration at specific frequency[21.29]. By tuning the experimental conditions such as temperature, amplitude, frequency, and sonication time, one can get NE with suitable nanosized droplets. However, this technology is not supposed to be suitable for industrial applications because of varied size difference of particles during large scale manufacturing. The effect of ultrasound is superior in immediate vicinity of probe leading to improper emulsification in areas far away from the sonicating probe. This can have very high polydispersity in large batch. Also, high frequency sound waves are responsible for compromised stability of surfactant-based formulations as these are capable of decomposing surfactants[33.34.36]

Some research also depicts the nonproportional size reduction using ultrasonication which forms unstable formulations after optimal conditions[33, 34.] Usage of ice-cold water or placing the solution filled beaker in ice can decrease the temperature of system which otherwise increases due to high frequency sound waves. Jafari et al., Hashtjin and Abbasi, and Singh et at [37,38]. have manufactured NEs utilizing this technology and considerably stable systems were generated. However, an adjunct method has to be supported with ultrasonication for industrial scale applications.

High-pressure homogenization:

HPH is also a flow field type of system where the sample under treatment is subjected to moderate to extensive pressure which is pumped across very small orifice/gap. As a result, the system comprised of very small droplets of dispersed phase that have very good stability is generated. Exposing to samples to various pressures concomitantly with pumping through orifice will break up larger droplets into extremely smaller ones in nanometer scale. This technique, used to generate nanosized globules, is accomplished by the equipment called as high-pressure homogenizers[29]. Unsatisfactory product, in terms of microsized globules, can be resubjected to the homogenizer at higher pressure and cycles for getting desired globule size. Suitable combinations of pressure and cycles will generate optimum sized NE which can be immediately cooled for maintaining surfactant orientation[39]. Modern homogenizers are equipped with heat exchanger devices for temperature control throughout the process. The reduction in particle size occurs a result of combination of forces acting viz hydraulic shear, intense turbulence, and cavitation [40 41 42.43]The most important output of using HPH is that it gives very uniform homogenized NE as indicated by polydispersity index of the formulation. It produces uniform sized globules with narrow particle size distribution which if not in range, can lead to instability of the NE. This method requires preparing of premix or coarser emulsion by spontaneous emulsification method which, when subjected to different pressures and homogenization durations, leads to generation of NE of desired size. It is extensively utilized method/technique for reduction in particle size of NE. Disadvantage of high-pressure homogenizer is that it is not suitable for thermolabile systems (drugs/components of NE). Drastic rise in the temperature of system appears due to usage of high pressure. The temperature of the system can increase by the rate of 2C per every cycle at 500 bars. This can have serious impact on the attributes of the product. Some of the labile drugs or oils/surfactants cannot tolerate high temperature and may get degraded leading to opaque or milky emulsion as a size reduction output. Rise in temperature can be minimized by protecting the flow pipe by ice-cold water or specifically by heat exchange phenomena. Heat exchanger can be used to exchange the heat and to bring down the temperature as low as 4°C5°C. In spite of the limitation, most of the research work on NE utilizes homogenization as a primary tool to generate nanoscale droplets. Various groups [31 44 45] have worked on manufacturing NE utilizing HPH as primary or comparative tool to reduce size to nanoscale. NEs prepared by such methods have shown adequate stability for longer period during storage.

Microfluidic and membrane methods:

Microfluidization uses the mechanism of flow through microchannels for generation of nanosized droplets, hence, the name microfluidics and the equipment is called microfluidizer. The mechanism is considered as a modified high-pressure homogenization which works using high-pressure positive displacement pump which forces the liquid to pass through the microchannels arranged in it. The product passing through the microchannels collides with each other in the interaction chamber causing breakdown of the droplets. This method is also called as direct emulsification technique because no preemulsification step is required [27]. Initially, the two phases are mixed in an inline homogenizer to get coarse emulsion which is then subjected to microchannels at various pressures to generate nanosized droplets. Like high-pressure homogenizer, repetitive passes can be made for the product to achieve desired globule size. It works on the simple principle of generation of shear forces, when the streams get collide with each other at high velocity. The shear forces are responsible for reduction in size of globules[28.29] Various microchannels can be arranged in different geometry such as T-junction, cross junction, flow focusing geometries, concentric junction, and any suitable geometry can be adopted for experimentation. The limitations of this method are that the microchannels may get clog in process thereby impeding the process and it has prolong emulsification time which ultimately disturbs the emulsification efficiency leading to coalesce of globules

Low energy methods:

These methods of NE fabrication are relatively simpler ones as compared to former methods. Unlike high energy methods, the low energy methods are based on phase transitions of emulsion system due to changes in temperature or composition of system[23.13]Surfactants are wonderful molecules which alter their physicochemical properties when exposed to temperature fluctuations or subjected to change in concentrations. Alteration in physicochemical properties leads to change in curvature of surfactant which forces phase transition from water-based to oil-based NE leading to generations of nanodroplets. Such phase transition results due to shifting of hydrophilic lipophilic balance (HLB) of surfactants to extremes making them either oil loving or water loving molecules. There are mainly two most significant methods which use this concept for fabrication of NE; phase inversion temperature (PIT) and emulsion inversion point (EIP)[21.46.36]

Phase inversion temperature:

This method is based on the critical property of nonionic surfactants which changes their HLB with temperature fluctuations or sometime electrolyte concentrations. It was first disclosed by Shinoda et al. in their research activities [47 48 49].Some specific surfactants behave in different manner in the presence of electrolyte, and change their affinity quickly as electrolyte concentration changes. However, electrolyte alterations are rarely used for fabricating NEs as these even can destabilize the whole system[28] Polyethoxylated surfactants are highly preferred for this application as these are temperature sensitive. When particular composition of NE is exposed to temperature changes without altering its composition, it leads to change in affinity of surfactant from water to oil and vice versa. This will accommodate the water phase or oil phase in large amount based on HLB of surfactant which subsequently is based on temperature fluctuations. At low temperatures, the majority of surface of surfactant is covered by hydrated polar groups which favor hydrophilicity leading to O/W system while at high temperature, due to dehydration of polyox ethylene groups, hydrocarbons chains dominate the surfactant surfaces, thereby favoring W/O system. This is the basis of NE fabrication with PIT[50.36.51]However, at HLB temperature, it has similar affinity for water and oil as interfacial tension or curvature of surfactant is ultralow or close to zero. Thus, by immediate change in temperature either on higher side or lower side, one can get NE droplets with low polydispersity and good kinetic stability as HLB temperature also attracts coalesce of droplets. In general, when system is cooled at 25C30C below HLB temperature, then stable NE with low polydispersity can be formulated [52]. Main drawback of this method is that the thermolabile agents including excipients cannot be used as temperature plays crucial role in PIT[28. 36]

Emulsion inversion point:

This method works on similar mechanism like that of PIT method for nanodroplets generation but by using concentration alterations rather than temperature fluctuations. Hence, it is also called as phase inversion composition (PIC) as composition of surfactant plays significant role in phase inversion of system. It works on using such components which alters the HLB of surfactant and most probably uses concentrations of surfactants only with rare use of alcohols or electrolytes [52] This method works on the dilution of dispersed phase to convert or transit the system from O/W to W/O. As percent of dispersed phase increases above the threshold levels, there is auto transition of phase. However, at the time of phase transition, interfacial tension needs to be very low for successful transition. For example, when O/W is diluted with oil above its threshold level, breakdown of current system occurs due to decrease in the degree of hydration to great extent making it lipophilic substance, while further dilution converts oil phase as continuous phase leading to formation of W/O system. During this process, temperature is constant at particular value, thereby altering the HLB of system and affinity of surfactant alters till it reaches minimum average curvature. At the initial stage, thermodynamically stable system is formed when the nearly equal proportions of phase co-exist in the system. Beyond this proportion, moderate change in composition of any phase, breakdowns the thermodynamic system to form kinetically stable nanodroplets thereby forming NE[13.47. 22.51]. It has received enough attention of scientists globally as this method avoids the use of any organic solvent or heat application which makes it favorable for any type of drugs and excipients. Moreover, EIP is not restricted to temperature sensitive surfactants; in-fact it can use castor oil derivatives, nonionic mixture of surfactants, even anionic and cationic surfactants. One of the disadvantages of EIP method is that this process can be executed only once for particular system (concentration cannot be changed frequently) while in PIT temperature can be fluctuated as many times as required by scientists for desired outputs[28.52].

Nanoemulsion in drug delivery:

Applications in routes of drug delivery:

Drug delivery in pharmaceutical field is considered as the most important part of research activity for a successful development of pharmaceutical drug product. Understanding of the type of disease and its progression, therapeutic options used to treat the disease, physicochemical properties of drug molecules and in vivo behavior of drug (ADME) altogether form the basis for selection of type of drug delivery methods used for delivering the active agent. By selecting suitable drug delivery method, drug behavior in vivo can be improvised to get efficient therapeutic treatment. There are number of drug delivery systems which can facilitate the delivery of active agents to the target region with improved bioavailability and efficiency. Oral, parenteral, and topical drug deliveries are the oldest systems which have been preferred due to their simplicity and well-established applications. Some newer, interesting and attention demanding delivery systems include intranasal, ophthalmic, transungual etc. However, of all these systems intranasal drug delivery is researched extensively due to its critical application in brain targeting. Section 29.4 will brief out the applications of NE in various drug delivery systems which are of significant importance in pharmaceutical drug delivery. The usefulness of NEs in particular drug delivery system is depicted by various peer reviewed publications in that area. In depth explanation of NE applications in each drug delivery system is out of scope of this chapter while authors have tried to restrict it to some of the critical and well-established systems only.

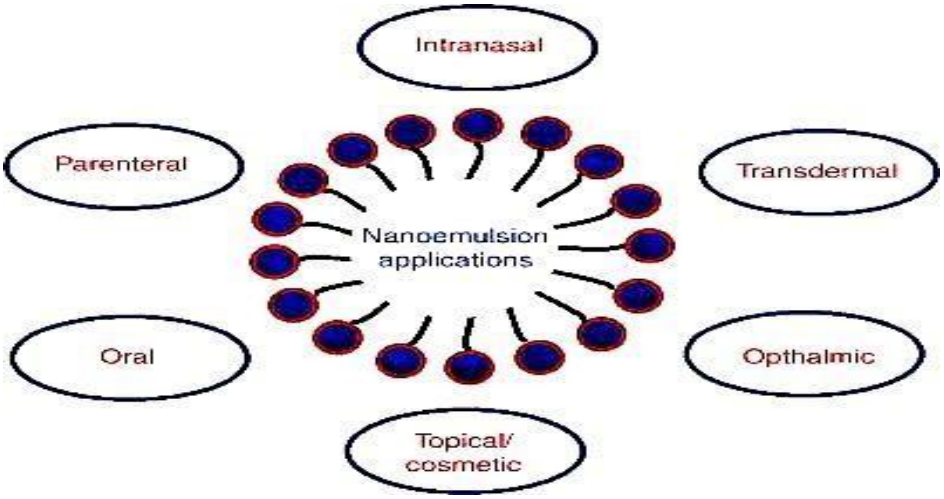

Figure no: 3 Applications of nanoemulsions.

Oral drug delivery:

Oral drug delivery is the most preferred route of drug delivery of pharmaceuticals encompassing number of diseases which have been successfully treated. Owing to its potential advantages including well-established delivery system, patient friendly, convenient, cost effective, and noninvasiveness, it has been the most favored drug delivery system in pharmaceutical field.[53,54]. While the oldest drug delivery route is enjoying its monopoly in drug delivery area of pharmaceutical field, associated with it are some of the serious drawbacks which hinder its applicability in some of the specific populations, namely, pediatric, geriatric, and mentally ill patients. Oral dosing to these populations is sometimes restricted as the patient is unable to swallow the product. Also, there are many pharmaceutical agents which are not stable in varied environmental conditions which oral dosing encompasses (from acidic stomach condition to basic intestinal conditions). A prerequisite for oral delivery is sufficient aqueous solubility of drug in gastrointestinal conditions, which when not achieved, leads to drug accumulation or instability of product in vivo. Drug molecules not fitting to above criteria are having low bioavailability leading to the partial treatment of the disease.[13,28,53].

To protect the drug from earlier mentioned drawbacks, several approaches (related to drug modifications and drug product modifications) have been suggested to improve the bioavailability of the drug in oral delivery. These approaches may include micronization, complexation strategy with polymers cyclodextrins, and the use of particulate drug delivery systems.[55]. As a part of this approach, NE is the most convenient route of oral drug delivery to improve the bioavailability of the drug. Being colloidal liquid formulation, it is conveniently administered to populations of all the ages. The dispersed phase of NE can encapsulate the drug molecules which can protect them from the external environment of gastrointestinal tract, thereby imparts stability to the drug which helps in efficient treatment of disease [56,57]. Further, surface engineering of the NE can help to target the specific sites in some disease thereby limiting unwanted side effects. Chhabra et al. [58].had worked on amlodipine besylate to improve its oral bioavailability using NE-based delivery system. The drug has poor water solubility and low permeability leading to low bioavailability of orally administered drug. NEs by virtue of its properties can improve its water solubility and its oil phase can lead to enhanced permeation across biological membrane thereby improving the drug availability to the target site to treat hypertension. Labrafil M (15%), tween 80 - ethanol (35%), and water (50%) were used as NE components as they showed highest solubility of drug as compared to other competitors in their respective categories. From phase diagram studies, 2:1 ratio for surfactant and co-surfactant was used for optimization of NE. The globule size of all the formulations were equal or less than 100 nm. In vitro drug release of all the formulations showed higher release (. 70.00%) from NE-based formulations than marketed formulation (B54.00%) under similar environmental conditions. Moreover, in vivo biodistribution in mice showed the enhanced concentrations of drug in blood and heart after oral administration of solution and NE of amlodipine. The improved pharmacokinetics of drug encapsulated in NE was also disclosed in publication. Direct drug transport was 44.1% which clearly depicts the potential of NE-based system as a carrier for oral drug delivery. The earlier finding supports the fact that oral delivery of such insoluble drug can be improved using NE-based formulations for efficient treatment of hypertensive patients. Wan et al.[59] have reported the improved characteristics of insoluble herbal medicament, curcumin by using NE-based lipid nanosystems. Curcumin is herbal drug with multiple pharmacological actions but has major limitation as it is highly hydrophobic agent which impedes it oral bioavailability.

This research has tried to improve the oral bioavailability of curcumin and subsequent pharmacological action. Curcumin is delivered using lipidic systems encompassed in NE base which were prepared using spontaneous hydration and thin film hydration methods. Ethyl oleate, hydrogenated 35 castor oil-poly ethylene glycol 400 and water were used to form NE and their subsequent addition in lipid to form lipidic systems. The size of this stable system (negative zeta potential) was below 200 nm with high entrapment efficiency. In vitro drug release and in situ absorption from gastrointestinal tract showed improved output of curcumin novel system as compared to free curcumin solution. In vivo pharmacokinetic studies of curcumin novel system and free curcumin solution showed encouraging results for curcumin novel system. All the pharmacokinetic parameters were at least three times higher than parameters of free curcumin solution. It is well supported with the fact of tumor suppressing rates of A549 cells by curcumin novel systems and free curcumin solution which was significantly higher for the former than with the latter.

Thus, earlier presented findings indicated strongly that the problem of aqueous solubility of hydrophobic agent for oral delivery has been alleviated using NE-based lipidic systems. It converts the drug into oily droplets embedded in lipid matrix thereby facilitating the permeation of drug across biological membrane leading to enhanced bioavailability. Another research is as a result of burning problem of curcumin's hydrophobicity and its ultralow bioavailability that makes the formation of aqueous formulation impractical. Borrin et al. [60]. have worked on method to improve the use of curcumin as food additive by enhancing its bioavailability using NE-based system. The NE was manufactured by EIP method using soybean oil (20%), tween 80 (10%), and glycerol (20%) as NE components. The size of curcumin NE manufactured using EIP method was below 200 nm, even after 2 months of manufacturing. However, as loading of drug dose increases, there was subsequent increase in size of NE droplet. This study supports the fact that the NE may have upper hand in benefits as compared to the other nanoencapsulation system. Their oily components have ability to preserve the curcumin for extended period of time. It may lead to the improvement in permeability of curcumin thereby enhancing the bioavailability leading to improve usage of curcumin as food additive. Shi et al.[61]have explored the NE-based systems for other herbal agent, emodin, which is also very hydrophobic agent. The hydrophobicity limits its development in the liquid preparations and extensive glucuronidation limits its absorption from oral route. NE was prepared using ultrasonication and was optimized using suitable experimental design. Capryol 90 (B12%), cremophore RH 40-transcutol P (B20%), and water were used as NE components at 24 min operating time of ultrasonication. The formulated NE was quite stable with nanoglobule size below 50 nm and low polydispersity index. The formulation was compared with emodin nanosuspension for in vitro drug release which indicated that sustained release property was obtained with emodin NE. Thus, it can be used for long-term treatment or study by incorporating it into nanocarrier system, that is, NE. Thus, by virtue of NE and its properties, hydrophobic drug like emodin can be incorporated into the aqueous phase, improve its permeability across biological membrane and successful delivery to the target site is feasible. Baspinaret al.[62]have reported the successful delivery of NE-based pitavastatin produced using microfluidization method at varied temperatures and pressures for hypercholesterolemia. Pitavastatin has ultralow solubility which impedes its bioavailability and thereby its successful treatment for hypercholesterolemia. An attempt was made to improve the drug delivery of pitavastatin using NE-based drug delivery containing oleic acid, lipid-based surfactants, and water phase with additional hydrophilic surfactants as NE components. The size of NE was below 500 nm with low polydisperity index.

The prepared formulations having good permeability and nontoxicity on in vitro cell lines indicated to be safer to use with improved transport across physiological barrier. The permeability coefficient and efflux ratios were significantly higher with drug loaded NE than drug solution indicating suitability of NE-based systems for hydrophobic agents. This work successfully delivers pitavastatin by oral route using stable NE-based delivery system with enhanced permeability and absorption, thereby improved bioavailability. Further studies, have shown the improved applicability of NE-based drug delivery systems for drug candidates having compromised solubility, bioavailability, stability, or limited absorption on oral administration. Moreover, scientists globally have utilized the fantastic properties of NE for improvement of various pharmaceutical agents. Further, ample of studies [63,65,64] have reported the success in delivering the pharmaceutical active agents accompanied with some or other drawbacks that were limiting their development in one of the most convenient route of drug delivery (oral drug delivery).

Parenteral drug delivery:

It is the most primitive route of drug delivery, often has been placed by scientific community after oral route of delivery. It is the first nonoral route of drug delivery which enjoys the advantage of being the fastest acting route for emergency or related conditions in treatment of several disorders. Injecting the drug solution directly into the blood pool avoids the rate limiting step of oral delivery, that is, absorption. This difference in drug delivery makes the parenteral route most successful route in case of crisis. This route is most preferable for drug candidates needing faster onset of action, having compromised behavior and less bio-availability with oral administration. However, limitations of the drug molecules as mentioned in Section 29.4.1 including lower solubility and aqueous stability, impede the development of parenteral delivery for such agents.[53]. NEs in such cases, are ideal alternatives for alleviating the problems with drug molecules and can facilitate the successful development of parenteral drug delivery. A prerequisite for success of parenteral drug delivery is the complete solubility of drug molecule in the solvent used, which is mostly aqueous-based. The hydrophobic drugs could also be delivered by parenteral route unless a single particle of drug does not exist insoluble. This can be achieved using oil-based NE in which drug molecules are dissolved in oily globules and dispersed in aqueous phase .[84]. As discussed in section 29.2, NEs can improve the solubility of drug molecules, and protect them from unstable conditions by improving stability. Furthermore, their nanosize structures provide substantial benefits of improved brain targeting potential leading to higher brain concentration of drug at targeted site. The praiseworthy research reports of utilization of NE-based systems in parenteral drug delivery have supported the fact that NE can be final alternatives for compromised drug molecules having drug delivery issues in the simpler aqueous solutions1.[13,28]. Zahra et al. [66]have reported development of intravenous NE for treatment by antineoplastic agent suffering from limitation of hydrophobicity. Sorafenib is highly hydrophobic molecule used for treating advanced renal cell carcinoma and to some extent hepatocellular and thyroid carcinoma.

Owing to its hydrophobicity, bioavailability of drug is as low as 35% leading to sub-optimal treatment of cancer. The NEs were prepared using high energy application methods and were optimized using experimental design. The formulated NE consists of medium chain triglyridelecithin, polysorbate 80, and glycerol as NE components. All the formulation batches prepared were having particles size equal to or below 100 nm. The developed NE was stable for 3 months at 4% oC with minor change in particle size indicating that it can be used for long term treatment. The incorporation of sorafenib in NE-based system has proved its worth as it can inhibit the tumor proliferation at application of low dose without affecting the normal cell proliferation. The MTT [3-(4,5-dimethylthiazol-2-Yl)-2,5-diphenyltetrazolium bromide] assay results confirmed that the effective treatment in cancer with sorafenib was possible with NEbased system and higher concentration of drug could be achieved in the target sites.

Dordevic et al.[75].Had developed NEs for parenteral delivery to investigate the pharmacokinetics of diazepam in laboratory animals. To execute faster action in related disease condition, parenteral NEs were prepared using pressure homogenizers within controlled temperature. These NEs contained triglycerides and soybean oil as oil phase, lecithin, and polysorbate 80 as surfactants and buffer solution as aqueous phase. Various NE batches having particle size within 250 nm and polydispersity below 0.15 were prepared. Stable NEs were obtained with negative zeta potential for the period of 2 months. An in vivo study revealed the higher pharmacokinetic parameters and immediate distribution of diazepam in animal brain after parenteral administration of diazepam loaded NEs. This study supported the fact that the NEs can be helpful in the emergency situations of diseases which provides the immediate relief in critical situations. Prabhakaret al.[67].have reported novel NE contaningindinavir for treating HIV (Human immunodeficiency virus) infection. Indinavir is protease inhibitor which is used to eliminate HIV but as it is a substrate of P-glycoprotien (P-gp), its concentration in brain is compromised by rapid efflux. The researchers had worked on developing tween 80-based lipid NE for efficient treatment of HIV infection with improved concentrations of drug in target areas. The NE consists of soybean oil, egg phospholipids and glycerol as prime component and tween 80 or cholesterol as co-emulsifier. All the batches of NE were below 400 nm size and with polydispersity index below 0.3.

The prepared formulations were stable for 6 months at 4% ^{o}C and room temperature. Fluorescence microscopy revealed theimproved distribution of drug in brain after intravenous administration of lipid NE (cholesterol or tween 80-based) as compared to drug solutions. Pharmacokinetic study confirmed the above fact and proved that the higher concentrations of drug in the brain can be achieved with the tween 80-based NE system as compared to other NEs. This was achieved due to simultaneous enhancement and inhibition of endocytosis and P-gp at brain barrier due to tween 80 which improved the rapid uptake of drug molecules by brain. Zhao et al. [68].have reported the intravenous delivery of lycobetaine for anticancer activity against lung carcinoma. Lycobetaine has extremely shorter half-life in the blood and thereby frequent administration is required. This study found out novel lipid NE-based formulation for prolonging the half-life of the drug and improvising the treatment options. Drug was complexed with oleic acid and it was formulated to form NE altogether with its PEGylated and non-PEGylated forms. These were manufactured using thin film hydration and pressure homogenization methods. The encapsulation efficiency of all the formulations was above 96.00%. The globules size for all the formulations was within 200 nm and polydispersity index below 0.200 indicating formation of well-disciplined NE with this method. The in vitro drug release studies showed that the release can be prolonged for developed NE as compared to free lycobetaine. In vivo studies indicated that the area under curve (AUC) for PEGylated form was substantially higher than that of free lycobetaine after intravenous administration. Moreover, the PEGylated form facilitates the targeting of drug to specific areas, that is, lung while minor concentrations were found in other major organs. This was not the case with the free lycobetaine as it was widely distributed in every major organ. PEGylated form showed improved pharmacokinetics, and organ distribution due to enhanced lipophilicity of drug, effect of polyethylene glycol chains and prolonged drug release. It also improved the inhibitory effect and survival time in the tumor models as compared to free drug solution. Hence, lipid-based NE systems for such drugs bring significant improvement in the cancer treatment. Araujo et al.[69].Have tried to deliver effective amount of thalidomide encapsulating in NE carrier through parenteral drug delivery. Thalidomide is antileprotic agent and also used in multiple myeloma cases. This drug is associated with lower solubility as well as stability which hinder its successful use in the treatment of leprosy and myeloma. For administering it through parenteral route, it was formulated in NE-based systems which can have ability to solubilize the drug and disperse it in aqueous phase and also protect it from external sensitive environment. The NE consists of castor oil (10%) and soy lecithin (3%) as oil phase, while water and polysorbate 80 as aqueous phase. The formulations were having globule size in the acceptable range (around 200 nm) and polydispersity index below 0.250 which is encouraging for parenteral NE. The in vitro dissolution of developed NE revealed that the dissolution profiles of thalidomide NE were encouraging (more than 80% in 2 h). Improved pharmacokinetic parameters after intravenous delivery revealed that the doses required for parenteral administration were lower than oral route which is beneficial as dose dependent side effects may get minimized. In other words, maximum concentration (Cmax) for parenteral delivery after 25 mg dose was twice the value for oral delivery after same dose. This finding reveals that the NEbased system can enhance the drug delivery to target site via parenteral routes and makes it possible for compromised drug molecules to be delivered by parenteral route so as to impart efficient treatment for leprosy and myeloma. The earlier reported studies clearly highlight the significance of NE in improvising the delivery of compromised agents through parenteral route. The delivery through NE makes it possible to manufacture the aqueous dispersion of hydrophobic drugs, improve stability of drug molecules while in some cases suitable NE components can also provide prolonged release for long term treatment. Similar outcomes have been reported in support of the applicability of parenteral NE for compromised drug agents.

Intranasal drug delivery:

Intranasal delivery as stated previously, is latest advancement in drug delivery technologies. It has been known to the developing world since last not more than three decades. The history of intranasal delivery dates back to several years before 21st century and it is a part of serious development in drug delivery area.[72]. This delivery system is used for delivering the drugs systemically and in brain areas of which latter is of crucial importance.[73]. While Section 29.4.3 will focus on the latter part of intranasal drug delivery which is called as nose to brain delivery, it has ample of advantages including noninvasiveness, self-medication, protection of drugs from harsh gastrointestinal tract environment, and many more.[74]. The fascinating feature of intranasal route is its ability to deliver pharmaceutical agents to the central nervous system (CNS) by completely bypassing blood brain barrier (BBB). Interference of BBB in the treatment of neurologic.al disease by restricting the access of majority of compounds (endogenous or exogenous) in brain is the rate limiting step and may impede the successful treatment for such disease.[72,73,75]. Intranasal route has emerged as an alternative to this problem and it may be the future of CNS drug delivery if well-established preclinical or clinical trials are succeeded.

The intranasal delivery is a part of transmucosal delivery as therapeutic agents need to diffuse across nasal mucosa in olfactory region of nasal cavity which has direct access to brain areas. In such cases, nanoformulations are of prime importance as these can have faster diffusion across nasal mucosa owing to their nanosize and better targeting potential in brain areas with improved concentrations of drug in brain.[76]. NE-based systems are the ideal option for the delivery of therapeutic agent targeted to CNS due to their versatile benefits, stability and easy manufacturing.[74]. These system also facilitate the delivery of therapeutic agents across nasal mucosa, and can encapsulate the therapeutic agents in their oily core thereby supporting in their protection and faster diffusion across nasal mucosa, while their nanosize has ability to cross various biological barrier, if any.[74,76,77]. Jaiswal et al. [78]. worked on the development of NE-based gel for enhancing neuroprotective action of Centellaasiatica extract. The herbal agents are generally associated with the poor permeability across biological membranes while in conventional liquid formulations short residence time in nasal cavity is impeding sufficient levels of drug in brain areas. The gel part was responsible for adhering to the nasal mucosa thereby improving the residence time and absorption through the nasal cavity, while the NE was used to improve the permeability through its emulsifiers and faster diffusion across mucosa for efficient brain targeting in Alzheimer's disease. Calendula oil, tween 20-span 80, ethanol, and water were used to formulate NEs with globule size near to 200 nm and negative zeta potential. Later the developed NEs were converted into the gel state using carbopol polymer and were sufficiently stable. In vitro drug release showed controlled release from NE gel (up to 80% in 24 h) as compared to drug solution (almost 100% in 12 h). Even ex vivo permeation study showed 30% of permeation of NE gel in 24 h as compared to drug solution (3%). There was significant increase in flux and permeability coefficients with NE gel. The findings of in vitro antioxidant activity also proved the fact that the sufficient concentrations of drug in brain areas can be achieved with the nanoformulations as it can facilitate the drug transport to the brain areas through nose to brain delivery. Patel et al[79]have attempted to work on the development of the paliperidone NE for improvising the treatment for schizophrenic patients. Paliperidone is associated with the low aqueous solubility and extensive first pass metabolism leading to bioavailability of 28% only. Oleic acid (below 7%), labrasol-plurololeique CC 497 (47% to 51%) and water were used to prepare NE using aqueous titration method. The globule size and polydispersity indices of all the formulations were found to be below 150 nm and 0.270, respectively. The optimized formulation showed almost 85.00% of drug release after 4 h while it showed highest diffusion coefficient and flux after 4 h as compared to the other formulations and drug solutions. The developed formulation was stable for 6 months at room temperature and was nontoxic to nasal mucosa. Earlier findings suggested the potential of developed NE for efficient nose to brain delivery for the treatment of schizophrenic patients which need to be supported with the in vivo pharmacokinetics studies. Pandey et al.[80] have reported paroxetine NEs for intranasal delivery through olfactory region for better management of depression in patients. Paroxetine has poor oral bioavailability due to extensive first pass metabolism. This study aims to manufacture the paroxetine NE for direct nose to brain delivery to improve the therapeutic levels of drug in the target areas by improving the drug transport across biological membrane. Capmul MCM, solutol HS-15-propylene glycol and water were used as NE components. All the batches were having globules size below 70 nm with negative zeta potential of 33 mV suggesting stable formulation. In vitro permeation of drug loaded NE showed substantially higher permeation as compared to the permeation of drug suspension. Further, pharmacodynamic studies showed significant improvement in the behavioral activity of laboratory animals for drug NE as compared to drug suspension administered via intranasal route which supports the potential of the oily nanocarrier for nose to brain targeting as compared to the drug suspension. Biochemical estimation reveals that the GSH levels after administering drug loaded NE were significantly higher as compared to the suspension and control groups. Similar results were found with reactive oxygen species whose levels were considerably lowered with drug loaded NE as compared to the suspension and control groups. The study concludes that the NE-based system has potential to improvise the treatment of depression with compromised paroxetine using nose to brain delivery by enhancing its bioavailability in target brain areas. Prajapati et al. [81] have attempted to work on the development of the risperidone NE for improvising the treatment for schizophrenic patients. Risperidone is associated with the low aqueous solubility and extensive first pass metabolism leading to low oral bioavailability. Acrysol K 150 (12.00%), tween 80-caprol PGMC (45.00%) and water were used to prepare NE using aqueous titration method. The globule size of all formulations were found to be below 149 nm. The optimized formulation showed diffusion of more than 90.00% of drug after 4 h. The developed formulation was stable at room temperature and was nontoxic to nasal mucosa. Earlier findings suggested the potential of developed NE for efficient nose to brain delivery of risperidone for the treatment of schizophrenic patients which needs to be supported with the in vivo pharmacokinetic studies. Earlier studies highlight the significance of intranasal delivery of pharmaceutical agents for improvising the treatment of several CNS diseases. It showed that the nanocarrier through intranasal delivery has great potential for brain targeting for the various CNS diseases. It can have faster diffusion across nasal mucosa due to their nanosize and improved targeting potential in brain areas. There are ample of research papers to support these findings while only limited research papers could be explained taking care of limit of this chapter. However, there are various studies [58,82,84]that have obtained similar findings suggesting the significant applicability of NE-based drug delivery systems for intranasal delivery targeted to the brain.

Topical or transdermal or ophthalmic:

Topical and transdermal deliveries are associated with the drug diffusion across skin for local or systemic action respectively. Drug delivery through skin faces high resistance against diffusion into blood pool as upper layers of skin are the most intact layers with diffusion across stratum corneum forming rate limiting step. Simple formulations namely drug solution or suspensions are not sufficient for complete drug transport. In-fact novel deliveries can provide sound alternatives for effective delivery of drug across skin. While this is not the case, when local action is required for skin ailments. From various delivery methods such as iontophoresis, implantation, and carrier mediated novel delivery for systemic circulation through skin, carrier mediated delivery is most probably used due to its famous advantages including faster diffusion without injury to the tissue, self-medication, extended duration of transport, and open for all kind of population.

Nanocarrier mediated delivery of therapeutic agents is most efficient alternative for safe and faster delivery.[13,28,53]. It is most successful in overcoming the biological barrier confronted by drug molecules during diffusion across skin. Oil-based NE can facilitate the permeation of drug across skin due to excellent properties of surfactants while oil part can serve as penetration enhancer due to its lipophilicity which is not possible with other nanoformulations[85]. Moreover, in the case of topical delivery, oil-based NE can serve as suitable alternative for local action due to its property of enhanced retention on skin layers with oily nature and pleasant feel. The main advantage of using NE for topical delivery is that the drug cannot be washed away due to its sufficient viscosity and its enhanced local distribution can be achieved.[55,53,85]. Ophthalmic delivery is generally less profound with ophthalmic solution due to nasolacrimal drainage and lacrimal secretion of potential drugs from precorneal area. It can lead to sub-optimal treatment due to the minimum amount of drug available to the ophthalmic areas. For effective ophthalmic treatment, drug retention or contact in target areas is prime requirement which is possible with the oil-based NE. It helps in retention of the drug for sufficient period of time in target areas and facilitates the drug diffusion into ocular areas due to oily compositions.[55]. Moreover, such oil-based NE can further reduce systemic exposure and dosing frequency thereby improving the patient compliance. Some of the research reports, using NE-based system for either of mentioned routes, are explained here suggesting the potential of the NE-based system in enhancing the treatment efficiency via these routes of delivery. Rachmawati et al.[86]. attempted the use of curcumin NE in transdermal application for improving its biological efficiency in treatment of multiple disorders. Curcumin is highly hydrophobic agent which is unstable in an alkaline medium. It also has rapid first pass metabolism when administered orally. NE-based system of curcumin was manufactured using glyceryl monooleate (16%), cremophore RH 40 (4%)-polyethylene glycol, and water as NE components using spontaneous emulsification method. Further, these were converted to gel form using viscolam AT 100P as gel forming matrix. The optimized formulation was found to be having globule size below 100 nm with polydispersity index of 0.18. The formulations (gels and NE gel) were exposed for stability for the period of 1 month at room temperature and 40C which confirmed the fact that gel containing curcumin NE was more stable than conventional curcumin gel as seen by high zeta potential. The ex vivo permeation study revealed that the NE gel of curcumin has improved permeation after 24 h as compared to conventional gel of curcumin. The results of this study confirmed the fact that the encapsulation of curcumin in NE gel will facilitate the penetration of curcumin across stratum corneum and improved the stability of the drug by providing the impermeable gel barrier against unfavorable environment. One more study by Jeengaret al.[87].Based on transdermal delivery of curcumin using therapeutic oil for manufacturing NE provided the similar outcomes as by the previous study. Both the earlier studies, can strongly be supported with pharmacokinetic study to provide evidence-based hypothesis of improved curcumin efficiency through transdermal route. El-leithyet al.[88]. have worked on the development of indomethacin NE for transdermal delivery. Medium chain triglycerides, tween 80, and pluronic and transcutol-propylene glycol were used as NE components. All the formulations were having globule size below 150 nm with good polydispersity indices. The results of stability studies indicated that the formulations were stable for the period of 6 months. From the various formulations, the formula with highest oil to surfactant ratio was found to be the one with improved drug permeation across animal skin. This study claims that it has highest drug permeation rates as compared to other transdermal formulations which clearly indicated the significance of NEbased system for efficient transdermal delivery. Potential formulations were further evaluated for in vivo studies in albino rats which stated that the indomethacin plasma concentration was within range (ideal range 0.53 µg/mL) for the period of 32 h indicating that the prolonged indomethacin treatment was possible using NEbased system for transdermal delivery. working on similar lines realized improved treatment efficiency for the vaccine delivery across skin. Mostafa et al. [88].and Arora et al.[89].have obtained similar results with NEbased drug delivery for therapeutic molecules with enhanced permeation and improved treatment efficiency in variety of disorders. Hussainet al.[90]. had worked on the development of NE-based gel for topical delivery of antifungal drug, amphotericin B. NE-based gels were prepared using sefsol-218, tween 80, and transcutol P using spontaneous titration method and simultaneous embedding in carbopol for gel formation. The globule size of various NEs was found to be below 200 nm. The final formulation was having low polydispersity index and high zeta potential which indicated the improved stability of developed NE-based gel. In vitro release and ex vivo permeation showed improved drug profile for NE gel over period of 24 h as compared to drug solution. In vivo histopathological examination suggested that the developed formulations were safe for their application. The earlier findings revealed that the NE-based gel for topical delivery of antifungal drug has potential of effective treatment for local fungal infection and also has faster permeation rates as compared to the drug solution. Various research teams have also successfully developed topical drug delivery of NE-based systems which clearly supported the potential of NE systems for improvising the local treatment of skin disorders.[91,92]. Another application of NE-based system is ophthalmic delivery of ocular agents which can increase the retention time of formulation in ocular cavity and helps in faster drug diffusion to reach ocular areas. Akhter et al.[93]. have worked on the improvement of ocular delivery of immunosuppressant drug with mucoadhesive NE-based system. Cyclosporin A is a strong immunosuppressive agent with poor aqueous solubility which inhibits its usage in the form of solution in ocular delivery. NE-based systems can improve the solubility of drug with aqueous dispersion of hydrophobic agent, suitable for improving the therapeutic efficiency of compromised pharmaceutical agents by virtue of their physicochemical properties. Mucoadhesion in this system can improve the retention time of the formulations in corneal surface leading to improvement of therapeutic efficiency in ocular disorders. Oleic acid, tween 20-transcutol P and water were used to manufacture NE components using aqueous titration method. The optimized formulation was having acceptable parameters with small globule size (below 20 nm) and narrow size distribution (polydispersity below 0.2). The mucoadhesive NE was prepared using 1% w/v chitosan solution with high positive zeta potential indicating its good stability. The drug permeation studies revealed that the NE and mucoadhesive NE permeated drug till 12 h. Further, gamma scintigraphy study revealed that the mucoadhesive NE had highest retention in corneal area as compared to other NE.

Biodistribution study confirmed that the maximum concentration of drug was found from mucoadhesive NE in corneal area after 24 h as compared to drug suspension and NE. As a measure of the toxic effects of drug due to nanolacrimal drainage, plasma concentration of drug was obtained and was found to be minimal with mucoadhesive NE as compared to other formulations. Ocular safety evaluation also showed that the developed formulations were safe for efficient treatment of ocular disease. Earlier findings clearly support the fact that NE-based systems can improve the drug behavior in vivo by improving its permeation and bioavailability in target areas for ocular delivery. Ammaret al.[94].Have also developed NE-based system for ophthalmic delivery of dorzolamide hydrochloride and presents similar findings of improvement of drug delivery across ocular cavity with utmost safety as compared to conventional eye drops.

CHALLENGES FACED BYNANOEMULSIONS:

Due to their various versatile properties, nanoemulsions have been the subject of greater interest for formulation scientists. However, there are some limitations and challenges faced by nanoemulsions. The process of preparing nanoemulsions becomes expensive due to the droplets size reduction as it either requires energy or modern sophisticated equipments. This is clearly evident from the arrangement of a homogenizer for the formulation of a nanoemulsion. Similarly, micro fluidization and ultrasonication also require a huge budget for the equipments involved in the manufacturing of nanoemulsions. Formulation stability concern is another concern for nanoemulsions. Though, nanoemulsions are considered to remain stable for some time, the process of Ostwald ripening leads to damage their stability by virtue of small size of droplets.

Thus there stability issues are major hurdles in making their applicability limited. The problem is effectively addressed by pre- paring nanoemulsions just shortly before their use. Similarly, the use of surfactants and co-surfactants in the nanoemulsions formulations is also a matter of great concern. Nanoemulsions are also prone to the issue of limited solubility capacity of drugs having high melting points. The influence of environmental parameters like temperature and pH on the nanoemulsions stability is also a matter of great concern. The lack of understanding the role of surfactants and cosurfactants in reducing the size of nanoemulsions droplet size is also a major challenge for formulation scientists.

CONCLUSION

This chapter portraits the NE-based systems as the most suitable alternative for delivery of therapeutics across major routes of administration as compared to their conventional counterparts. The physicochemical properties of NE are so exciting that lured the formulators to utilize the expertise of NE for delivering compromised or problematic drug molecules. Their precise advantages for some specific applications including nanosize and extraordinary large surface areas facilitated the faster, efficient, and safe delivery of therapeutic molecules thereby improvising the old therapy using conventional techniques and formulations. Over and above, the fabricating methods of NE as described are not so complicated which add to their selectivity. The significance of NE in delivery of compromised therapeutic molecules is further depicted by prominent publications in that area which conclude the above fact with their research findings. Also, patents (published or granted) in related area, confirm the fact that among many liquid carrier systems, NEs can prove beneficial in improvising the drug delivery in variety of disease conditions across major routes of drug delivery.

FUTURE ASPECTS:

Nano emulsions are proposed for numerous applications in pharmacy as drug delivery systems because of their capacity to solubilize non-polar active compounds. Future perspectives of Nano emulsion are very promising in different fields of therapeutics or application in development of cosmetics for hair or skin. One of the versatile applications of Nano emulsions is in the area of drug delivery where they act as efficient carriers for bio actives, facilitating administration by various routes. The advantages and applications of Nano emulsions for oral drug delivery are numerous, where the droplet size is related to their absorption in the gastrointestinal tract. Due to the renewed interest in herbal drug formulation, Nano emulsion may be the ideal delivery platform for these difficult-to-formulate phytopharmaceuticals.

List of abbreviations:

ADME - Absorption distribution metabolism and excretion
AUC - Area under the curve
EIP - Emulsion inversion point
GIT - Gastrointestinal tract
HLB - Hydrophilic lipophilic balance
NE - Nano emulsions
MTT - Dimethylthiazol
PIC - Phase inversion composition

Conflict of Interests:

The authors declare that there is no conflict of interests regarding the publication of this paper.

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