FORMULATION OF NANOSUSPENSION AND NANOEMULSION AS A NEW APPROACH FOR THE DELIVERY OF POORLY SOLUBLE DRUGS

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ABSTRACT
One of the major problems associated with poorly soluble drugs is very low bioavailability. The problem is even more complex for drugs poorly soluble in both aqueous and nonaqueous media, belonging to BCS class II as classified by biopharmaceutical classification system. Formulation as nanosuspension & nanoemulsion is an attractive and promising alternative to solve these problems. Nanosuspension consists of the pure poorly water-soluble drug without any matrix material suspended in dispersion. Preparation of nanosuspension is simple and applicable to all drugs which are water insoluble. A nanosuspension not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy. Nanoemulsions are clear, thermodynamically stable, isotropic liquid mixtures of oil, water, surfactant and co-surfactant. Reduction in droplet size to nanoscale leads to change in physical properties such as optical transparency & unusual elastic behavior. Nanoemulsions have many advantages; for instance, enhance drug solubility, perfect thermodynamic stability, ease of manufacturing and permeation over conventional formulations that convert them to important drug delivery systems, transparency at high droplet volume fraction, higher rate of bioavailability or diffusion and increased shelf life of the pharmaceuticals. The design and development of nanosuspensions and nanoemulsions aimed at controlling or improving required bioavailability levels of therapeutic agents. This review article describes the preparation methods, characterization, and applications of the nanosuspension and nanoemulsion.

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INTRODUCTION:

A range of parameters like solubility, stability at room temperature, compatibility with solvent, excipient, and photostability play a critical role in the successful formulation of drugs. Till date, more than 40% of the new chemical entities being generated through drug discovery programs are lipophilic or poorly watersoluble compounds[1,2]. Many formulation approaches are available to solve the problems of low solubility and low bioavailability of drugs. The conventional approaches include micronization, use of fatty solutions, use of penetration enhancer or cosolvents, surfactant dispersion method, salt formation, precipitation, etc., but still, these techniques having limited utility in solubility enhancement for poorly soluble drugs. Additional approaches are vesicular system like liposomes, dispersion of solids, emulsion and microemulsion methods, and inclusion complexes with cyclodextrins, which show beneficial effect as drug delivery system but major problems of these techniques are lack of universal applicability to all drugs [3]. Over the last decades, nanoparticle engineering has been developed and reported for pharmaceutical applications[4]. Nanotechnology can be used to solve the problems associated with various approaches described earlier. Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10−9 m. The drug microparticles/micronized drug powder is transferred to drug nanoparticles by techniques like Bottom-Up Technology and Top-Down Technology[5]. Nanosuspensions are submicron colloidal dispersions of nanosized drug particles stabilized by surfactants[6]. Nanosuspensions consist of the poorly water-soluble drug without any matrix material suspended in dispersion[7]. These can be used to enhance the solubility of drugs that are poorly soluble in water as well as lipid media. As a result of increased solubility, the rate of flooding of the active compound increases and the maximum plasma level is reached faster. This approach is useful for molecules with poor solubility, poor permeability, or both, which poses a significant challenge for the formulators. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without any blockade of the blood capillaries. The suspensions can also be lyophilized and into a solid matrix. Apart from these advantages, it also has the advantages of liquid formulations over others. Nanoemulsions are novel drug delivery systems consisting of emulsified oil and water systems with mean droplet diameters ranging from 50 to 1000 nm. The capacity of nanoemulsions to dissolve large quantities of low soluble drugs along with their mutual compatibility and ability to protect the drugs from hydrolysis and enzymatic degradation make them ideal drug delivery vectors [8]. The major advantages of nanoemulsions as drug delivery carriers include increased drug loading, enhanced drug solubility and bioavailability, reduced patient variability, controlled drug release, and protection from enzymatic degradation [9]. In the present review, we are mainly focusing on the different methods of preparation characterization of nanoemulsions & nanosuspension and its applications.

ADVANTAGES OF NANOEMULSION AND NANOSUSPENSION:

- Most cost effective.
- Useful for poorly soluble drugs.
- Physically more stable than liposomes.
- Provide ease of manufacture and scale up for large scale production.
- Rapid dissolution and tissue targeting.
- Reduction in tissue irritation.
- Higher bioavailability in ocular and inhalational drug delivery
- Its general applicability to most drugs & simplicity
- They can be applied for poorly water soluble drugs.\(^3\)
- They can be given by any route.
- Reduced tissue irritation in case of subcutaneous/intramuscular administration.
- Rapid dissolution & tissue targeting can be achieved by IV route of administration.
- Oral administration of nanosuspension provide rapid onset, reduced fed/fasted ratio & improved bioavailability.
- The absorption form absorption window can be increased, due to reduction in the particle size.
- Long term physical stability (due to absence of Ostwald ripening).
- Possibility of large-scale production, the prerequisite for the introduction of delivery system to the market.\(^3,4\)

DISADVANTAGES OF NANOSUSPENSION AND NANOEMULSION DRUG DELIVERY SYSTEM:

- Physical stability, sedimentation & compaction can cause problems.
- It is bulky sufficient care must be taken during handling & transport.
- Improper dose. Uniform & accurate dose cannot be achieved.\(^5\)

CHARACTERIZATION OF NANOEMULSION AND NANOEMULSION:

Different characterization parameters for NE include transmission electron microscopy, NE droplet size analysis, viscosity determination, refractive index, in vitro skin permeation studies, skin irritation test, in vivo efficacy study, thermodynamic stability studies, and surface characteristics. The surface charge of the nanoemulsion droplets has a marked effect on the stability of the emulsion system and the droplet in vivo disposition and clearance. The inset shows microscopy image at a higher magnification. Nanoemulsion droplets were in the size range of 25-40 nm with some particle aggregates in the size range of 100-150 nm.(Nanoemulsion). Nanosuspensions are evaluated as same as conventional suspensions such as appearance, colour, odour, assay, related impurities etc. Along with that particle size, zeta potential, morphology, dissolution study, in-vivo studies are also performed.
PHYSICOCHEMICAL CHARACTERIZATION OF NANOEMULSIONS

**Particle Size Analysis:** A Photon Correlation Spectrometer is used to monitor the particle size of nanoemulsions. Light scattering are monitor 90° angle and 25°C.

**Rheological measurements:** Rheological Measurements will perform at 25±0.1°C using a Bohlin rheometer equipped with a cone/plate apparatus 40 mm per 4°. For each sample, continuous variation of shear rate γ will applied and the resulting shear stress σ will measured. Viscosity of dispersions with Newtonian flow properties will be calculated according to the relation: η=σ/γ.

**Refractive Index:** Refractive index will be determined at 25°C using refractometer.

**Surface Tension:** Surface tension measurements will carry out at 20°C using a thermostatically controlled processor tensiometer K100.

**pH and Osmotic Pressure:** pH of the formulation will measured at 25°C using digital pH meter and the osmotic pressure will measured using Micro Osmometer.

**PHYSICOCHEMICAL CHARACTERIZATION OF NANOEMULSIONS**

The particle size, particle size distribution, and zeta potential affect the safety, efficacy, and stability of nanodrug delivery systems as well as dissolution performance is also altered by solid state of nanoparticles. Thus, characterization of nanoparticles plays a great role in forecasting *in vitro* and *in vivo* performance of nanodrug delivery systems. *In vivo* pharmacokinetic performance and biological function of nanosuspension strongly depends on its particle size and distribution, particle charge (zeta potential), crystalline state, and particle morphology.

**Particle size:**

Particle size and particle size distribution are two important parameters since it will affect the saturation solubility, dissolution rate, stability, and in vivo behavior of nanosuspensions. Any change in the particle size will leads to the change in the solubility and dissolution. Particle size determines the physiochemical behavior of the drug. Particle size can be determined by sem or tem analysis. Particle size distribution can be determined by photon correlation spectroscopy (pcs) or laser diffraction (ld). Particle size distribution will be expressed in polydispersity index (pi).pi value of 0.1-0.25 indicates fairly nanosize distribution where as its value greater than 0.5 indicates a very broad distribution.

**Surface charge (zeta potential):**

Zeta potential will determine the stability of nanosuspension. A minimum zeta potential of 30 mv is required where as in case of combined electrostatic or steric stabiliser, a zeta potential of 20 mv would be sufficient.

**Crystalline state and particle morphology:**

When the drug undergo nanosizing the crystalline nature and particle morphology will change. This can be detected by this method. X-ray diffraction analysis is mainly used for the determination of the solid state of the particle and is supplemented by scanning electron microscopy.

Saturation solubility and dissolution velocity: Nanosuspension will increase the solution solubility and dissolution velocity. It also helps for the in vitro behavior of the formulation. When the particle size reduced to nanometric range, dissolution velocity and dissolution pressure will increase which leads to the solution solubility due to the change in the surface tension.

**METHODS OF PREPARATION OF NANOEMULSIONS AND NANOSUSPENSION:**

**High -pressure homogenization:**

This technique makes use of high-pressure homogenizer/piston homogenizer to produce NEs of extremely low particle size (up to 1nm).

**Microfluidization:**

Microfluidization is a patented mixing technology, which makes use of a device called microfluidizer(Fig 1). This device uses a high-pressure positive displacement pump (500-20000 psi), which forces the product through the interaction chamber, which consists of small channels called "Microchannels." The product flows through the microchannels on to an impingement area resulting in very fine particles of submicron range. The two solutions (aqueous phase and oily phase) are combined together and processed in an inline homogenizer to yield a coarse emulsion. The coarse emulsion is into a microfluidizer where it is further processed to obtain a stable NE. The coarse emulsion is passed through the interaction chamber of the microfluidizer repeatedly until desired particle size is obtained. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets resulting in a uniform nanoemulsion.
Other method used for NE preparation is the phase inversion temperature technique. (Nanoemulsion)

There are different methods for the preparation of nanosuspensions,

- Homogenization in water (Disso Cubes).
- Media milling (Nanocrystal).
- Homogenization in non-aqueous media (Nano pure).
- Combined precipitation & homogenization (Nano edge).
- Nanojet technology.
- Emulsifying-solvent evaporation technique.
- Hydrosol method.
- Supercritical fluid method.
- Dry co-grinding.
- Emulsion as template.

**High pressure homogenization (Disso Cubes):**

Disso cubes are engineered using piston-gap-type high pressure homogenizers. High pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. The instrument can be operated at pressure varying from 100-1500 bars & up to 2000 bars with volume capacity of 40ml (Figure 2.)
The concern with this method is the need for small sample particles before loading & the fact that many cycles of homonization are required. Before subjecting the drug to the homogenization process, it is essential to form a pre-suspension of the microsized drug in a surfactant solution using high speed stirrer. During the homogenization process, the drug suspension is pressed through the homogenization gap in order to achieve nanosizing of the drug. In piston gap homogenizer, particle size reduction is based on the cavitation principle.

A piston-gap homogenizer like APV Gaulin type has been shown. Particles are also reduced due to high shear forces & the collision of the particles against each other. The dispersion contained in 3cm diameter cylinder, suddenly passes through a very narrow gap of 25μm. The reduction in diameter of 3cm to 25μm leads to increase in dynamic pressure & decrease of static pressure below the boiling point of water at room temperature. Due to this water starts boiling at room temperature & forms bubbles, which implode when the suspension leaves the gap & normal air pressure, are reached[14].

**Media milling (Nano Crystals):**

In this method, the nanosuspensions are produced using high-shear media mills or pearl mills (Figure 3). The media mill consists of a milling chamber, a milling shaft & a recirculation chamber. The milling chamber charged with polymeric media is the active component of the mill. The mill can be operated in a batch or recirculation mode. Crude slurry consist water & stabilizer is fed into the milling chamber & processed into nano-crystalline dispersion & the milling media or pearls are then rotated at a very high shear rate. The milling process is performed under controlled of drug, temperatures. The typical residence time generated for a nanometer-sized dispersion with a mean diameter of <200nm is 30-60min.

![Fig. 3. Schematic diagram of wet bead milling process. (www.intechopen.com).](image)

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**Homogenization in non-aqueous media (Nanopure):**

Nanopure is suspension homogenized in water free media or water mixtures i.e. the drug suspensions in the non-aqueous media were homogenized at 0°C or even below the freezing point & hence are called “deepfreeze” homogenization.

**Nanojet technology:**

This technique is also called as opposite stream uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure upto 4000 bar at high velocity of 1000m/s. The high shear force produces during the process result in particle size reduction.

**Emulsification-solvent evaporation techniques:**

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug.
Supercritical fluid method:

Supercritical fluid technology can be used to produce nanoparticles from drug solutions. The various methods attempted are rapid expansion of supercritical solution process (RESS), supercritical anti-solvent process & precipitation with compressed anti-solvent process (PCA). The RESS involves expansion of the drug solution in supercritical fluid through a nozzle, which leads to loss of solvent power of the supercritical fluid resulting in precipitation of the drug as fine particles [15].

![Diagram of emulsification-solvent evaporation](https://www.google.co.in)

**Figure 4: schematic representation of emulsification-solvent evaporation.**

In the PCA method, the drug solution is atomized into a chamber containing compressed CO2. As the solvent is removed, the solution gets super saturation & thus precipitates as fine crystals. The supercritical anti solvent process uses a supercritical fluid in which a drug is poorly soluble & a solvent for the drug that is also miscible with the supercritical fluid. The drug solution is injected into the supercritical fluid & the solvent gets extracted by the supercritical fluid & the drug solution gets supersaturated. The drug is then precipitated as fine crystals [16].

![Diagram of Supercritical fluid method](www.intechopen.com)

**Figure 5: Schematic diagram of Supercritical fluid method.**
**Emulsion as template:**

Apart from the use of emulsion as a drug delivery vehicle, they can also be used as template to produce nanosuspensions. The use of emulsion as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvents. Such solvents can be used as the dispersed phase of the emulsion. There are two ways of fabricating drugs nanosuspensions by emulsification method. An organic solvent or mixture of solvents loaded with drug is dispersed in the aqueous phase containing suitable surfactant to form an emulsion. The organic phase is then evaporated under reduced pressure so that the drug particle precipitates instantaneously to form a nanosuspension stabilized by surfactants. Since one particle is formed in each emulsion droplet, it is possible to control the particle size of the nanosuspension by controlling the size of the emulsion. Optimizing the surfactant composition increases intake of organic phase & ultimately the drug loading in the emulsion. Originally, organic solvents such as methylene chloride & chloroform were used. (Nanosuspension).

**APPLICATIONS OF NANOSUSPENSIONS:**

**Oral Drug Delivery:**

The oral route is the preferred route for drug delivery because of its numerous well-known advantages. Orally administered antibiotics such as atoquone & bupravaquone reflect this problem very well. Nanosizing of such drugs can lead to a dramatic increase in their oral absorption & subsequently bioavailability. The oral administration of naproxen nanoparticles leads to an area under the curve of 97.5 mg-h/l compared with just 44.7 mg-h/l for naprosyn suspensions & 32.7 mg-h/l for anapro tablets. Oral administration of gonadotrophin inhibitor Danazol as a nanosuspensions leads to an absolute bioavailability of 82.3 & the convectional dispersion only to 5.2%.

**Parenteral Drug Delivery:**

One of the important applications of nanosuspension technology is the formulation of intravenously administered products. IV administration results in several advantages, such as administration of poorly soluble drugs without using a higher concentration of toxic co-solvent, improving the therapeutic effect of the drug available as convectional oral formulations & targeting the drug to macrophages & the pathogenic micro-organism residing in the microphages. Injectable nanosuspensions of poorly soluble drug tarazepide have been prepared to overcome the limited success achieved using convectional solubilising techniques, such as use of surfactants, cyclodextrins etc. To improve bioavailability[17,18]

**Pulmonary Drug Delivery:**

Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizer for lung delivery. Basically the nanosuspensions can be used in all nebulizers. The dispersions can be relatively high concentrated. Due to presence of many small particles instead of a few large microparticles, all aerosol droplets are likely to contain drug nanoparticles. Budesonide, a poorly water-soluble corticosteroid, has been successfully prepared as a nanosuspension for pulmonary delivery. A good relationship was obtained between increasing the drug concentration in the formulation & the number of micrograms of drug delivered per actuation. In addition, buparvaquone nanosuspensions were formulated for treatment of lung infections by using nebulizers.

**Topical Formulations:**

Drug nanoparticles can be incorporated into creams & water free ointments. The nanocrystalline forms leads to an increased saturation solubility of drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin.

**Ocular Drug Delivery:**

Nanosuspension can be boon for drug that exhibit poor solubility in lachrymal fluids. By their inherent ability to improve the saturation solubility of drug, represented an ideal approach for ocular delivery of hydrophobic drugs & nanoparticulate nature of the drug allows its prolonged residence in the cul-de-sac, giving sustained release of the drug.
MAJOR CHALLENGES:

- Although nanoemulsion and nanosuspension provide great advantages as a delivery system, however they suffer for some major challenges and limitations which include.
- Although nanoemulsion and nanosuspension provide great advantages as a delivery system, however they suffer for some major challenges and limitations which include.
- The formulation of nanoemulsion is an expensive process due to size reduction of droplets is very difficult as it required a special kind of instruments and process methods.
- For example, homogenizer (instrument required for the nanoemulsions formulation) arrangement is an expensive process. More ever micro-fluidization and ultrasonicication (manufacturing process) require large amount of financial support.
- One problem associated with nanoemulsion is their stability. Although it is generally accepted that these systems could remain stable even by years, however, due to the small droplet size, it has been reported that the Oswald ripening could damage nanoemulsions and nanosuspensions, causing their application to be limited. Therefore, in most cases, nanoemulsions and nanosuspensions are required to be prepared shortly before their use.
- Use of a large concentration of surfactant and cosurfactant necessary for stabilizing the nano droplets.
- Limited solubility capacity for high melting substances.
- Nanoemulsion stability is influenced by environmental parameters such as temperature and pH.
- Lack of understanding of the mechanism of production of submicron droplets and the role of surfactants and cosurfactants.
- Lack of demonstration of the benefits that can be obtained from using nanoemulsions when compared with the classical macroemulsion and macrosuspension systems.
- Lack of understanding of the interfacial chemistry that is involved in production of nanoemulsions and nanosuspension[19,20]

APPLICATIONS OF NANOEMULSIONS:

Use of nanoemulsion in cosmetics

Nanoemulsions are oil-in-water droplets that range from 200 to 600 nm. They are composed of oil and water and are stabilized by surfactants and alcohol. The NE has a broad-spectrum activity against bacteria (e.g. E. coil, Salmonella , S. aureus), enveloped viruses (e.g. HIV, Herpes simplex), fungi (e.g. Candida, Dermatophytes), and spores (e.g. anthrax). The NE particles are thermodynamically driven to fuse with lipid-containing organisms.77

This fusion is enhanced by the electrostatic attraction between the cationic charge of the emulsion and the anionic charge on the pathogen. When enough nanoparticles fuse with the pathogens, they release part of the energy trapped within the emulsion. Both the active ingredient and the energy released destabilize the pathogen lipid membrane, resulting in cell lysis and death. In the case of spores, additional germination enhancers are incorporated into the emulsion.

Antimicrobial nanoemulsion

Antimicrobial NEs are oil-in-water droplets that range from 200 to 600 nm. They are composed of oil and water and are stabilized by surfactants and alcohol. The NE has a broad-spectrum activity against bacteria (e.g. E. coil, Salmonella , S. aureus), enveloped viruses (e.g. HIV, Herpes simplex), fungi (e.g. Candida, Dermatophytes), and spores (e.g. anthrax). The NE particles are thermodynamically driven to fuse with lipid-containing organisms.77

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Nanoemulsion as a mucosal Vaccine

NEs are being used to deliver either recombinant proteins or inactivated organisms to a mucosal surface to produce an immune response. The first applications, an influenza vaccine and an HIV vaccine, can proceed to clinical trials. The NE causes proteins applied to the mucosal surface to be adjuvanted and it facilitates uptake by antigen-presenting cells. This results in a significant systemic and mucosal immune response that involves the production of specific IgG and IgA antibody as well as cellular immunity. Initial work in influenza has demonstrated that animals can be protected against influenza after just a single mucosal exposure to the virus mixed with the emulsion. Research has also demonstrated that animals exposed to recombinant gp120 in NE on their nasal mucosa develop significant responses to HIV, thus providing a basis to examine the use of this material as an HIV vaccine. The analysis of gp120-specific CTL proliferation, INF-γ induction, and prevalence of anti-gp120 IgG2 subclass antibodies indicated that nasal vaccination in NE also induced systemic, Th1-polarized cellular immune responses. This study suggests that NE should be evaluated as a mucosal adjuvant for multivalent HIV vaccines. Hepatitis B virus infection remains an important global health concern despite the availability of safe and effective prophylactic vaccines. Limitations to these vaccines include requirement for refrigeration and three immunizations thereby restricting use in the developing world. A new nasal hepatitis B vaccine composed of recombinant hepatitis B surface antigen (HBsAg) in a novel NE adjuvant (HBsAg-NE) could be effective with fewer administrations. Comprehensive pre-clinical toxicology evaluation demonstrated that HBsAg-NE vaccine is safe and well tolerated in multiple animal models. Our results suggest that needle-free nasal immunization with HBsAg-NE could be a safe and effective hepatitis B vaccine, or provide an alternative booster administration for the parental hepatitis B vaccines [21-23]

Nanoemulsion as a Non-toxic disinfectant cleaner

A breakthrough nontoxic disinfectant cleaner for use in commercial markets that include healthcare, hospitality, travel, food processing, and military applications has been developed by EnviroSystems, Inc. that kills tuberculosis and a wide spectrum of viruses, bacteria and fungi in 5-10 min without any of the hazards posed by other categories of disinfectants. The product needs no warning labels. It does not irritate eyes and can be absorbed through the skin, inhaled, or swallowed without harmful effects. The disinfectant formulation is made up of nanospheres of oil droplets 106 mm that are suspended in water to create a NE requiring only miniscule amounts of the active ingredient, PCMX (parachlorometaxylenol). The nanospheres carry surface charges that efficiently penetrate the surface charges on microorganisms' membranes-much like breaking through an electric fence. Rather than "drowning" cells, the formulation allows PCMX to target and penetrate cell walls [24].

Nanoemulsion in cell culture technology:

Cell cultures are used for in vitro assays or to produce biological compounds, such as antibodies or recombinant proteins. To optimize cell growth, the culture medium can be supplemented with a number of defined molecules or with blood serum. It has been very difficult to supplement the media with oil-soluble substances that are available to the cells, and only small amounts of these lipophilic compounds could be absorbed by the cells. NEs are a new method for the delivery of oil-soluble substances to mammalian cell cultures[25-27]

Nanoemulsion formulations for improved oral delivery of poorly soluble drugs:

NE formulations were developed to enhance oral bioavailability of hydrophobic drugs. Paclitaxel was selected as a model hydrophobic drug. The oil-in-water (o/w) NEs were made with pine nut oil as the internal oil phase, egg lecithin as the primary emulsifier, and water as the external phase. Stearylamine and deoxycholic acid were used to impart positive and negative charge to the emulsions, respectively. The formulated NEs had a particle size range of 90-120 nm and zeta potential ranging from +34 mV to 245 mV. Following oral administration, a significantly higher concentration of paclitaxel was observed in the systemic circulation when administered in the NE relative to control aqueous solution. The results of this study suggest that NEs are promising novel formulations that can enhance the oral bioavailability of hydrophobic drugs[28].

Nanoemulsion as a vehicle for transdermal delivery:

From in vitro and in vivo data, it was concluded that the developed NEs have great potential for transdermal drug delivery of Aceclofenac. The NEs of the system containing ketoprofen evidenced a high degree of stability. Ketoprofen-loaded NEs enhanced the in vitro permeation rate through mouse skins as compared to the control. The study was developed to evaluate the potential of NEs for increasing the solubility and the in vitro transdermal delivery of carvedilol. The prepared NEs were subjected to physical stability tests. Transdermal permeation of carvedilol through rat abdominal skin was determined with the Keshary-Chien diffusion cell. Significant increase (P < 0.05) in the steady state flux (Jss) and permeability coefficient (Kp) was observed in NE formulations as compared to control or drug-loaded neat components. The irritation studies suggested that the optimized NE was a non-irritant transdermal delivery system [29].
CONCLUSION
Nanosuspensions & Nanoemulsions are distinctive and commercially feasible approach to solve the problems of hydrophobic drug such as poor solubility and poor bioavailability. For large-scale production of Nanosuspensions & Nanoemulsions, media milling and high-pressure homogenization technology have been successfully used. Striking characteristics, like improvement of dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification, and ease of postproduction processing, have widened the applications of nanosuspensions & Nanoemulsions for various routes of administration. The applications of Nanosuspensions & Nanoemulsions in oral and parenteral routes have been very well established, although applications in pulmonary and ocular delivery have to be evaluated. However, their delivery through buccal, nasal, and topical delivery is yet to be done. Nanosuspensions & Nanoemulsions formulations offer several advantages for the delivery of drugs, biological, or diagnostic agents. Traditionally, NEs have been used in clinics for more than four decades as total parentral nutrition fluids. Several other products for drug delivery applications such as Diprivan®, Liple®, and Ropion® have also reached the marketplace. Although NEs are chiefly seen as vehicles for administering aqueous insoluble drugs, they have more recently received increasing attention as colloidal carriers for targeted delivery of various anticancer drugs, photosensitizers, neutron capture therapy agents, or diagnostic agents. Because of their submicron size, they can be easily targeted to the tumor area. Moreover, the possibility of surface functionalization with a targeting moiety has opened new avenues for targeted delivery of drugs, genes, photosensitizes, and other molecules to the tumor area.

FUTURE DIRECTION
Nanosuspensions & Nanoemulsions appear to be unique & yet commercially viable approach to combating problems such as poor bioavailability that are associated with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. The dissolution problems of poorly water soluble drugs have been largely solved to improve drug absorption & bioavailability. Nanosuspension technology can be combined with traditional dosage forms: tablets, capsules, pellets, & can be used for parenteral products. To take advantage of nanosuspension drug delivery, simple formulation technologies & variety applications, nanosuspensions will continue to be interest as oral formulations & non-oral administration develop in the future.

CONFLICT OF INTEREST
The authors confirm that this article content has no conflict of interest.

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ABRIVATIONS
- BCS: biopharmaceutical classification system
- %: Percentages
- nm: Nanometer
- NE: Nanoemulsion
- pi: Polydispersity index
- pcs: Photon Correlation Spectroscopy
- Id: laser diffraction
- mv: Millivolt
- psi: per square inch
- ml: Mililiter
- μm: Micrometer
- m/s: Miter per second

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