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Review Article

Lipid Nanoparticles: Future of Oral Drug Delivery and their Current Trends and Regulatory Issues

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ABSTRACT
Lipid based nanoparticles have proved to be a boon to pharma research. It has offered a wide scope to fabricate drug delivery systems for hydrophilic as well as hydrophobic drug candidates with the advantage of being biocompatible, safe and nontoxic dosage forms with better drug loading and easy characterization parameters. Their scaling up being an easy task, has encouraged their industrial application. The article beautifully summarizes the different types of lipid nanoparticles, their methods of preparation, methods of characterization, regulatory aspects governing these nanoparticles, current trends and some developed lipid nanoparticles have also been listed so as to provide readers a deep insight into the vast scope of lipid based nanoparticles and their advantages.

Keywords: Lipid Nanoparticles, Oral Drug Delivery

INTRODUCTION

Nanotechnology is the most promising technology that is used today. It can be applied to almost all spheres of life, ranging from electronic storage systems, pharmaceutical, biotechnology[1], magnetic separation[2] magnetic separation and pre-concentration of target analytes, targeted drug delivery,3,4 and vehicles for gene and drug delivery[1,3-5] defense, transportations heat transfer to sports and aesthetics. Nanoparticles with their special characteristics small particle size, large surface area and the capability of changing their surface properties have numerous advantages compared with other delivery systems[6]. Nanoparticles are solid colloidal particles ranging from 10 to 1000 nm (1.0 μm), in which the active principles (drug or biologically active material) are dissolved, entrapped, and/or to which the active principle is adsorbed or attached[7]. In recent years, significant effort has been devoted to develop nanotechnology for drug delivery, since it offers a suitable means of delivering small molecular weight drugs, as well as macromolecules such as proteins, peptides or genes to cells and tissues and prevents them against enzymatic degradation[8]. The advantages of nanoparticles as drug delivery systems are that they are biodegradable, non-toxic, and capable of being stored for longer periods as they are more stable[7]

Nanoparticulate drug delivery systems (DDS) have attracted a lot of attention because of their size-dependent properties. Among all the nanoparticles which are currently investigated by pharmaceutical scientists, lipid nanoparticles have taken the lead due to its higher degree of biocompatibility and versatility. These systems are commercially viable to formulate pharmaceuticals for topical, oral, pulmonary or parenteral delivery. The proven safety and efficacy of lipid-based carriers make them attractive candidates for the formulation of pharmaceuticals, as well as vaccines, diagnostics and nutraceuticals[9,13]. Lipid nanoparticles as an oral drug delivery system, they are studied as components of various oily liquids and dispersions that are mainly designed to increase solubility and bioavailability of drugs belonging to the class II and IV of the biopharmaceutical drug classification system[10] . Lipid carriers are equally important for transdermal systems as they form a protective barrier as they make the skin water resistant and thereby reduce the trans-epidermal water loss and thus protect the skin against dehydration. They lead to a noticeable smoothening of the skin which simultaneously also reduces minor wrinkles[11]. It is also being proved that the unique properties of lipids due to their physiochemical diversity and biocompatibility help in reducing local irritancy and making them ideal carriers for topical usage[12]. The spectrum of applications for lipid-based formulations has widened. Lipid-based formulations may also protect active compounds from biological degradation or transformation that in turn can lead to an enhancement of drug potency. In addition, lipid-based particulate DDS have been shown to reduce the toxicity of various drugs by changing the biodistribution of the drug away from sensitive organs. This reduction in toxicity may allow for more drugs to be administered and forms the basis for the current success of several marketed lipid-based formulations of amphotericin B and doxorubicin[9,13]. Lipid nanoparticles (e.g. solid lipid nanoparticles, SLNs) are developing rapidly in the field of nanotechnology with several potential applications in drug delivery, clinical medicine and research, as well as in other varied sciences.

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Due to their size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics that could be used for secondary and tertiary level of drug targeting. Hence, lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and have attracted wide attention of researchers. Modifications of SLN, nanostructured lipid carriers (NLC) and lipid drug conjugate (LDC)-nanoparticles has been introduced14, 15 in addition to liquid crystal DDS. These carrier systems overcome observed limitations of conventional SLN and more fluid lipid DDS. Compared to liposomes and emulsions, solid particles possess some advantages, e.g. protection of incorporated active compounds against chemical degradation and more flexibility in modulating the release of the compound[13].

Increasing interest in lipid-based delivery systems is due to following reasons like[13,16]:

- Versatility of lipidic excipients
- Formulation versatility and the choice of different drug delivery systems
- Low risk profile
- Enhanced oral bioavailability and reduced plasma profile variability
- Enhanced permeation of these systems when used topically
- Formation of vesicular system which is passive, non-invasive and is available for immediate commercialization.
- Better characterization of lipidic excipients
- High market attractiveness for products with proprietary technology.
- Improved ability to address the key issues of technology transfer and manufacture scale-up.
- Ability to control and target drug release.
- Can improve stability of pharmaceuticals.
- The feasibility of carrying both lipophilic and hydrophilic drugs.
- Lipids used are biodegradable, and as such they have excellent biocompatibility, are non-toxic, non-allergenic and non-irritating.
- Can be formulated by water-based technologies and thus can avoid organic solvents.
- Easy to scale-up and sterilize.
- Lipids are less expensive than polymeric/surfactant based carriers.
- They are easy to validate.

CLASSIFICATION OF LIPID NANOPARTICLES

Solid Lipid Nanoparticles

Solid Lipid Nanoparticles (SLN), which were first mentioned in 1991, are colloidal lipid carriers, solid at room and body temperature[17]. SLN are obtained from GRAS (generally recognized as safe) lipids and surfactants, devoid of toxicity. SLN have a number of advantages over traditional colloidal systems, such as physical stability, protection of the active substance, controlled release of the active substance, biocompatibility, selective orientation, absence of organic solvents[18,19]. Solid lipid nanoparticles (SLN) spur high interest, particularly in the pharmaceutical industry20, 21, but also in cosmetics[22,23] and food[24] industries. Solid lipid nanoparticles (SLN) are used as an alternative drug delivery system to colloidal drug delivery systems such as lipid emulsions, liposomes and polymeric nanoparticles. Solid lipid nanoparticles (SLN) are aqueous colloidal dispersions, the matrix of which comprises of solid biodegradable lipids[25]. SLN formulations for various application routes (parenteral, oral, dermal, ocular, pulmonar, rectal) have been developed and thoroughly characterized in vitro and in vivo[26]. Increasing attention has also been paid to the coating of SLN to provide receptor mediated drug and gene delivery in recent years[28,29]. Coating of colloidal carriers has been demonstrated to improve stability of the particles and to enhance transmucosal transport of the associated compounds following either nasal[30], oral[31] or ocular administration[32].

Advantages of SLN[33-35]

- Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production methods
- Improved bioavailability of poorly water soluble molecules
- Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application
- Possibility of scaling up.
- Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment
- SLNs have better stability compared to liposomes
- Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated compound.
- High concentration of functional compound achieved.
- Lyophilization possible

Disadvantages of SLN[35,36]

- Poor drug loading capacity,
- Drug expulsion after polymeric transition during storage
- Relatively high water content of the dispersions (70-99.9%).

METHOD OF PREPARATION OF SLN

SLNs are prepared from lipid, emulsifier and water/solvent by using different methods. These methods are discussed below:

1. High pressure homogenization
   - Hot homogenization
   - Cold homogenization
2. Ultrasonication/high speed homogenization
   - Probe ultrasonication
   - Bath ultrasonication
3. Solvent evaporation method
4. Solvent emulsification-diffusion method
5. Supercritical fluid method
6. Microemulsion based method
7. Spray drying method
8. Double emulsion method
9. Precipitation technique
10. Film-ultrasound dispersion

High Pressure Homogenization

Initially used for the production of solid lipid nanoemulsions, this method is reliable. It involves high

pressure homogenization which pushes the liquid with high pressure (100-2000 bar) through a narrow gap ranging a few microns. The fluid accelerates to a very short distance at very high viscosity of over 1000 km/h. Very high shear stress and cavitation forces disrupt the particles down to submicron range. As low as 5% to as high as of 40% lipid content has been investigated. Two general approaches to achieve HSH are hot homogenization and cold homogenization[35]. Hot homogenization is generally carried out at temperatures above the melting point of the lipid. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high shear mixing device. The resultant product is hot o/w emulsion and the cooling of this emulsion leads to crystallization of the lipid and the formation of SLNs. Smaller particle sizes are obtained at higher processing temperatures because of lowered viscosity of the lipid phase. However, high temperature leads to the degradation rate of the drug and the carrier. Increasing the homogenization temperature or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles. Generally, 3-5 homogenization cycles at a pressure of 500-1500 bar are used[35,37,38]. Cold homogenization has been developed to over-come the temperature related degradation problems, loss of drug into the aqueous phase and partitioning associated with hot homogenization method. Unpredictable polymeric transitions of the lipid due to complexity of the crystallization step of the nanoemulsion resulting in several modifications and/or super cooled melts. Here, drug is incorporated into melted lipid and the lipid melt is cooled rapidly using dry ice or liquid nitrogen. The solid material is ground by a mortar mill. The prepared lipid microparticles are then dispersed in a cold emulsifier solution at or below room temperature. The temperature should be regulated effectively to ensure the solid state of the lipid during homogenization. However, compared to hot homogenization, larger particle sizes and a broader size distribution are typical of cold homogenization samples[35,39].

Advantages[42]

- Low capital cost.
- Customary at lab scale.

Disadvantages[42]

- Energy intensive process.
- Polydisperse distributions.
- Unproven scalability.

Ultrasonication/high speed homogenization

Ultrasonication or high speed homogenization is another method for the production of SLNs. The advantage of this method is that the equipment used is commonly available at lab scale. However, this method suffers from problems such as broader size distribution ranging into micrometer range. Potential metal contaminations, physical instability like particle growth upon storage are other drawbacks associated with this technique[41]. There is reduced shear stress. But in this method there could be metal contamination and physical instability in the lipid nanoparticles thus produced[42].

Solvent evaporation

SLNs can be prepared by solvent evaporation method. The lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60 mbar)[42,43]. This method is scalable, a continuous process and uses mature technology. But it is an extremely energy intensive process, causes biomolecule damage[42].

Solvent emulsification-diffusion method

SLNs can also be produced by solvent emulsification-diffusion technique. The mean particle size depends upon lipid concentration in the organic phase and the emulsifier used. Particles with average diameters of 30-100 nm can be obtained by this technique. Avoidance of heat during the preparation is the most important advantage of this technique. Here, the lipid matrix is dissolved in water-immiscible organic solvent followed by emulsification in an aqueous phase. The solvent is evaporated under reduced pressure resulting in nanoparticles dispersion formed by precipitation of the lipid in aqueous medium[42,44,45].

Supercritical fluid method

This is a novel technique recently applied for the production of SLNs. A fluid is termed supercritical when its pressure and temperature exceed their respective critical value. The ability of the fluid to dissolve compounds increases. This technology comprises of several processes for nanoparticle production such as rapid expansion of supercritical solution (RESS), particles from gas saturated solution (PGSS), aerosol solvent extraction solvent (ASES), supercritical fluid extraction of emulsions (SFEE). The advantages of this technique includes avoidance of the use of solvents, particles obtained as a dry powder, instead of suspensions, requires mild pressure and temperature conditions. Carbon dioxide solution is the good choice as a solvent for this method[43,46,47]. This method has certain advantages such as it avoid the use of solvents, the particles are obtained as a dry powder, instead of suspensions, mild pressure and temperature conditions are needed[42].

Microemulsion technique

In order to obtain microemulsion with lipids in solid state at room temperature, the process temperature must be higher than lipid melting point. Lipids (e.g. fatty acids and/or triglycerides) are melted and the mixture of water, emulsifiers and co-emulsifiers is heated to the temperature of the lipids and blended under mild conditions. If the procedure runs correctly, we will obtain transparent, thermodynamically stable complex. The hot microemulsion is then dispergated in chilled water (2÷3°C) by smooth mechanical stirring, which ensures that the small particle size results from precipitation and not the mechanical stirring. The volume ratio of hot microemulsion to cold water should be from 1:25 to 1:50. The most popular emulsifiers are polysorbate 20, polysorbate 60 and soy lecithin. The most frequently used

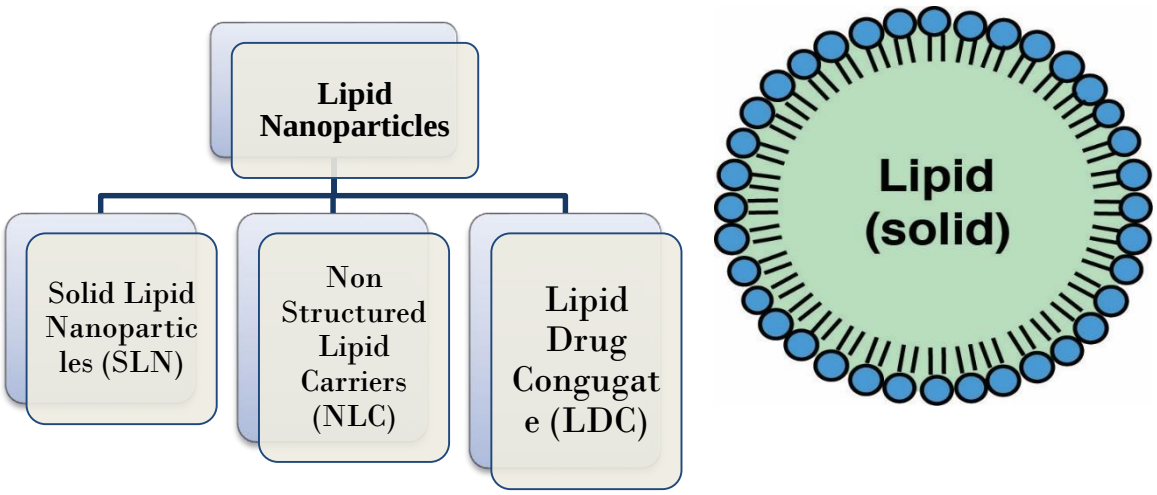

Figure 1. Structure of Solid Lipid Nanoparticle (SLN)27

co-emulsifiers are usually alcohols, e.g. butanol. Technically, the precipitation of lipid particles in water is equivalent to diluting the complex, which leads to decrease in solid substance content in SLN dispersion. Due to diluting stage the achievable lipid content is lower than in formulations obtained through HPH[37,44]

Spray Drying

It is an alternative technique to lyophilization in order to transform an aqueous SLN dispersion into a drug product. This is a cost-effective method than lyophilization and recommends the use of lipid with melting point >70°C. This method causes particle aggregation due to high temperature shear forces and partial melting of the particle. According to Freitas and Mullera (1998)[48] best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v)[35,48].

Double Emulsion

In this method, the drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion. Li et al. (2010)[49] prepared solid lipid nanoparticles loaded with bovine serum albumin (BSA) using double emulsion method[35,49].

Precipitation method

The glycerides are dissolved in an organic solvent (e.g. chloroform) and the solution will be emulsified in an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated forming nanoparticles[42,43].

Film-ultrasound dispersion

The lipid and the drug were put into suitable organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed[42,43].

NANO- STRUCTURED LIPID CARRIERS (NLC)

NLC have been developed to overwhelm the drawbacks affiliated with SLN. They are advised to be the second lifetime of lipid nanoparticles. Contrasted to SLN, NLC show a higher loading capability for hard-working compounds by conceiving a less organized solid lipid matrix, i.e. by blending a fluid lipid with the solid lipid, a higher element drug stacking can be achieved. Thus, the NLC have an expanded drug stacking capacity in evaluation to SLN and the likelihood of drug expulsion during storage is less[14,37,50,51]. NLC have also a lower water content of the element suspension and a less inclination of unpredictable gelation[51-53]. NLC disclosed some benefits contrasted to the other colloidal carrier schemes. They supply a controlled pharmaceutical issue and an increase in chemical stability of the incorporated drugs. Furthermore, they are protected carriers which can be produced effortlessly on large scale[37,51,54-56,60]. It is well renowned from the study of suppositories that highly organized crystalline lipid matrices will lead topharmaceutical expulsion. Lipid nanoparticles and microparticles made from blends of solid lipids can experience this, especially when nanoparticles are arranged from highly purified lipids, for example, tristearin[57]. The formation of highly ordered βior β modifications, particularly during storage, departs little space for pharmaceutical molecules, and the expulsion of pharmaceuticals leads to drug crystals in suspensions and solid dosage forms. To avoid this difficulty, the particles should have a controlled nanostructure that boasts enough space to accommodate the pharmaceutical. Four distinct approaches were taken for an optimized nanostructure of NLCs. In kind I, solid lipids and fluid lipids (oils) are blended. The difference in the organizations of the lipids and exceptional requirements in the crystallization process lead to a highly disordered, imperfect lipid matrix structure proposing space for drug substances and amorphous clusters of pharmaceuticals (Figure 5, I)[60]. In general, drug solubility is higher in fluid lipids than in solid lipids. Founded on this, particles were produced with a high content of liquid lipids (oils). Throughout the production method, the liquid lipid particles (nanoemulsions) are chilled from the molten state to room warmth to crystallize and pattern solid particles. At high oil concentrations a miscibility gap of the two lipids (solid lipid plus oil)

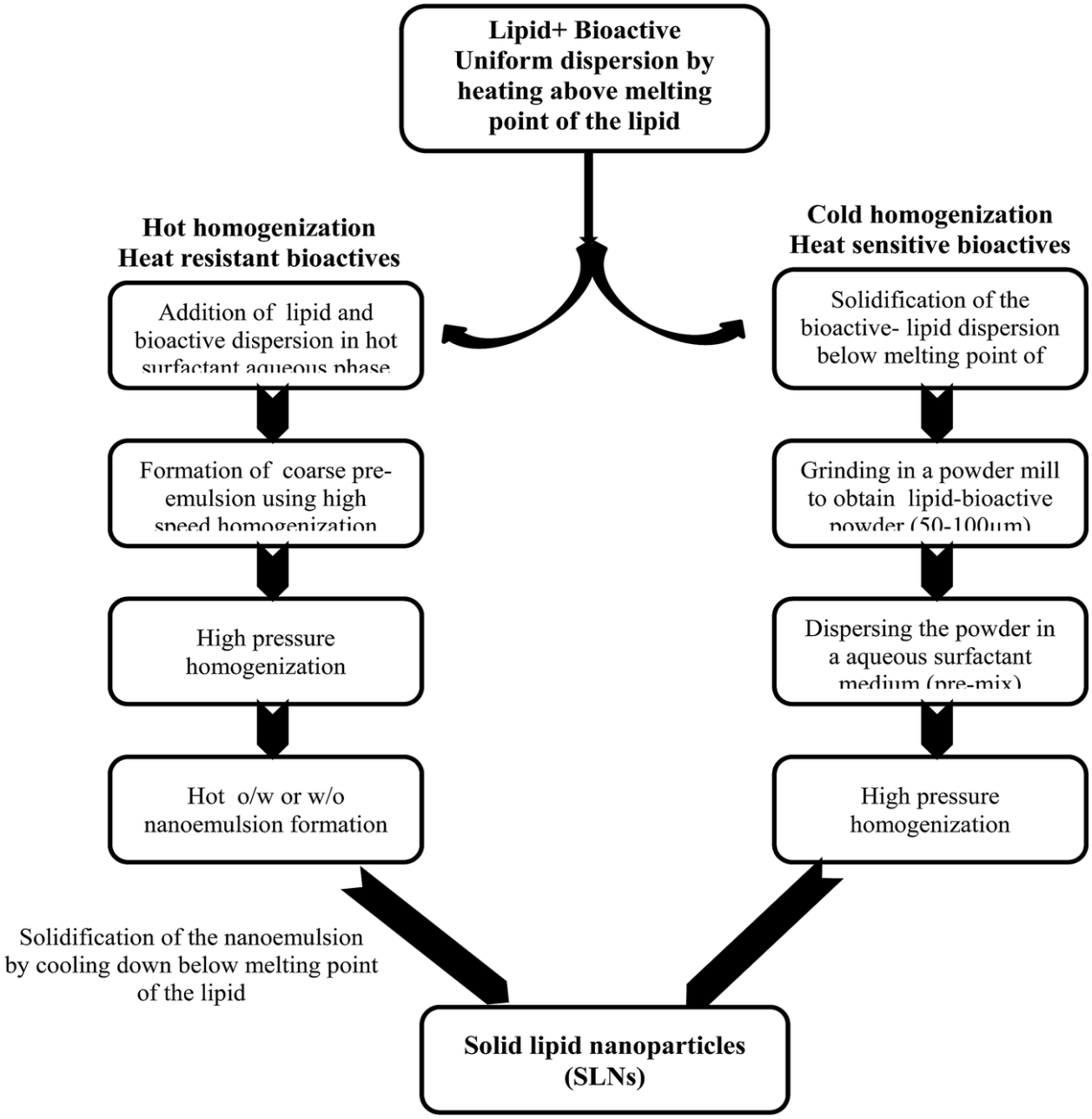

Figure 2. Schematic procedure of hot and cold homogenization techniques for SLN production40

happens throughout the chilling phase, leading to stage separation, that means precipitation of minute oily nanocompartments (Figure 5, II). In this multiple oil/fat/water, kind II drug can be accommodated in the solid, but at increased solubility in the oily components of the lipid matrix. In type III, lipids are blended in a way that stops them from crystallizing. The lipid matrix is solid, but in an amorphous state (Figure 5, III)[58]. The nonattendance of crystallization avoids pharmaceutical expulsion by crystallization. Lipid particles are preferentially matched to incorporate lipophilic pharmaceuticals; hydrophilic drugs can only be incorporated at a low percentage (however, this is still sufficient for highly powerful peptides and proteins). In a further variation of the lipid matrix, water-soluble pharmaceuticals were conjugated with a lipid, thus forming a water-insoluble lipidic conjugate. The lipid conjugate dust was dissolved and processed in the same way as the other types to yield a lipid drug conjugate (LDC) nanoparticle[59] counting on the conjugate, this lipidic conjugate has a pharmaceutical stacking of up to 30–50% for water-soluble pharmaceuticals. Conjugation is presented by salt formation or covalent linkage[60].

Method of Preparation Of NLC

Many methods are used for the preparation of lipid nanoparticles (NLC). These methods are high pressure homogenization, microemulsion technique, emulsification-solvent diffusion emulsification-solvent evaporation solvent injection (or solvent displacement), multiple emulsion technique, phase inversion, ultra-sonication and membrane contractor technique. However, high pressure homogenization is the most used method due

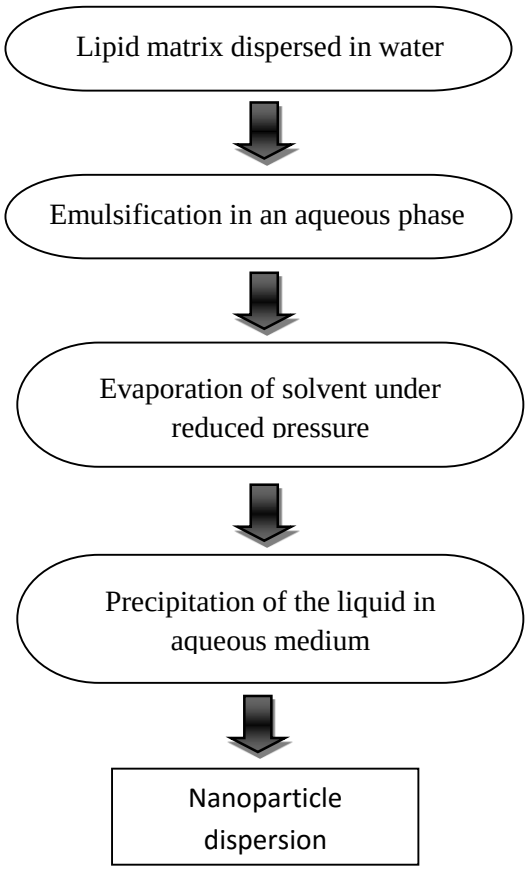

Figure 3. Schematic representation for emulsification- diffusion method

to the many advantages it has compared to the other methods, e.g. the avoidance of organic solvents, the short production time and the possibility of production on large scale. High pressure homogenizers are widely used in many industries including food industry (e.g. milk) and pharmaceutical industry e.g. emulsions for parenteral nutrition[65].

Lipid screening

Prior to the production of an NLC formulation a lipid screening should be performed to determine the most suitable lipid for the active ingredient to be incorporated in the NLC. This is performed by dissolving increasing amounts of the active ingredient in various melted solid lipids and determining the maximum amount of the active that could be dissolved in each lipid. After dissolution, the lipid/active mixtures are cooled down to room temperature for solidification. The solid mixtures are visually observed for the presence or absence of crystalline active (when this ingredient is a solid substance at room temperature). If the active ingredient is oil, the miscibility of the two materials (melted lipid and oil) is observed. After cooling down the mixture to room temperature the lipid will solidify again and the incorporation of the oil in the solid lipid matrix is investigated. This can be performed by smearing a piece of the solid mixture on a filter paper and observing if there are any oil spots on the filter paper. Calorimetric analysis can be performed on the solid solutions obtained using differential scanning calorimeter (DSC). These analyses will detect any presence of crystalline active (i.e. undissolved active) and also can show if there is an unincorporated part of active ingredient in the lipid matrix (i.e. oil)[37,65].

Production of the nanoparticles with high pressure homogenization

Homogenization is a fluid mechanical process that involves the subdivision of droplets or particles into micro- or nanosize to create a stable emulsion or dispersion. Homogenization is a very common processing step in the food and dairy industries. It improves product stability, shelf life, digestion and taste. Homogenization can also significantly reduce the amount of additives (e.g. stabilizer) needed in a product. In the cosmetic industry homogenization is essential for the quality and stability of the products and their texture (skin feeling). The bioavailability of the pharmaceutical products can be enhanced by homogenization; also the tolerance of some drugs can be improved. Moreover, high pressure homogenization has some advantages over other size-reducing processes (e.g. ball milling). It is considered to be a superior process from an economical and product quality prospects. The contamination of the products caused by the personnel or coming from the machine (machine parts wearing) is reduced. Also the exposure to thermal stress and microbiological contamination is clearly less due to the shorter production times. There are two types of high pressure homogenizers available on the market, the jet-stream homogenizers and the piston-gap homogenizers[61,65].

Preparation of nanoemulsions

Nanoemulsions are o/w emulsions which consist of a lipid phase (oil), a surfactant and an aqueous phase (water). These nanoemulsions can be prepared at Room temperature, but to maintain the same production conditions for all preparations (as for NLC) they were prepared at higher temperatures (80-90ºC). The lipid (oil) phase and the aqueous surfactant solution were heated up to about 80ºC, and the active substance (if any) was dissolved in the hot oil phase which is subsequently dispersed by a high speed stirrer at 8000 rpm for 20-30 sec in the hot aqueous surfactant solution. The obtained pre-emulsion is homogenized in a high pressure homogenizer applying a pressure of 800 bar and two homogenization cycles yielding a hot o/w nanoemulsion. The obtained product was filled in silanized glass vials, which were immediately sealed. A thermostated water bath adjusted to 15ºC has been used as cooling system to control the rate of cooling of the obtained product[65].

Preparation of aqueous NLC dispersion

Lipid nanoparticles with solid particle matrix are derived from o/w emulsions by replacing the liquid lipid (oil) by a solid lipid at room temperature.The first generation of solid lipid nanoparticles (SLN) was developed at the beginning of the nineties.They were produced from a solid lipid only. In the second generation technology the nanostructured lipid carriers (NLC) are produced by using a blend of solid and liquid lipids, this blend is solid at room temperature. The production process is identical for both particles SLN and NLC. The solid lipid or lipid blend is melted at 5-10ºC above the melting point of the solid lipid,

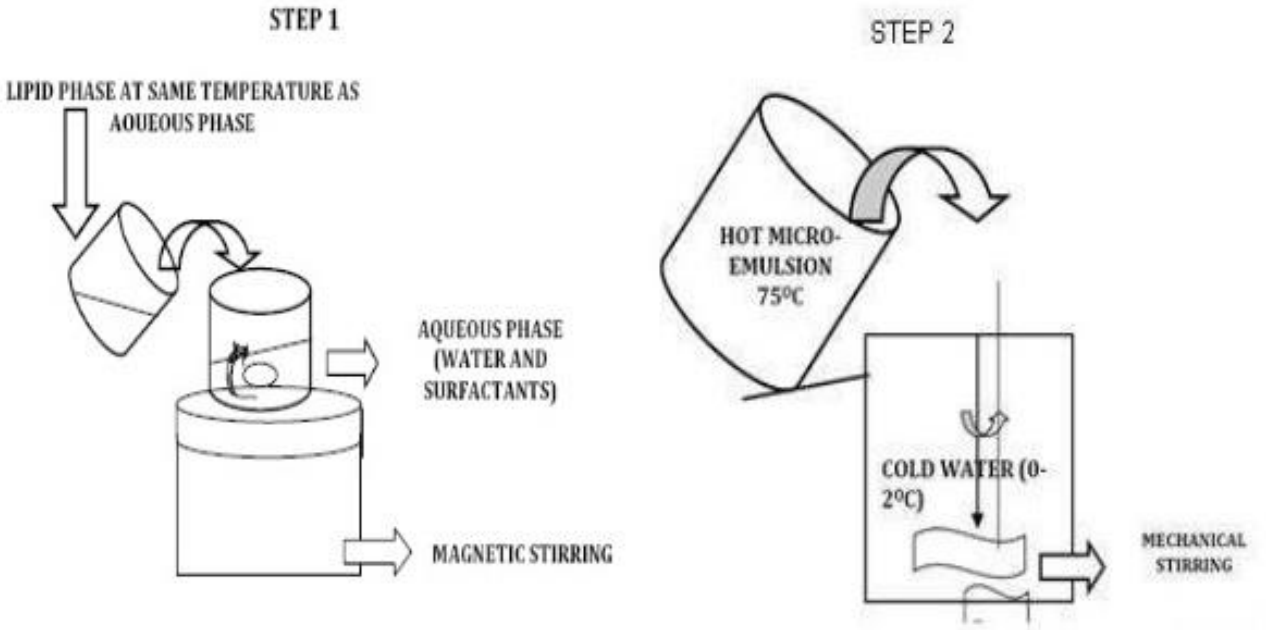

Figure 4. Schematic diagram showing the structures formed during the production of SLN by microemulsion technique42

the active substance is dissolved in the melted lipid phase,which is subsequently dispersed by a high speed stirrer at 8000 rpm for 20-30 sec in the aqueous surfactant solution previously heated up to the same temperature. The obtained pre-emulsion is homogenized in a high pressure homogenizer applying a pressure of 800 bar and two homogenization cycles (unless otherwise mentioned) yielding a hot o/w nanoemulsion. The obtained product was filled immediately in silanized glass vials and the vials were sealed properly. The obtained samples were cooled down to room temperature in a thermostated water bath adjusted to 15ºC. After cooling down the emulsion droplets crystallize forming lipid nanoparticles with solid particle matrix, depending on the lipids used either SLN or NLC are obtained[62-65].

LIPID CONJUGATES (LDC)

Lipid Drug Conjugates (LDCs) are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery and research. Due to their unique size dependent properties, lipid nanoparticles offer possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could use for drug targeting. Hence lipid drug conjugates hold great promise for reaching the goal of controlled and site specific drug delivery and hence attracted wide attention of researchers. Solid lipid nanoparticle technology represents a promising new approach to lipophilic drug delivery. A major problem of SLNs is the low capacity to load hydrophilic drugs due to partitioning effects during the production process. Only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix[66]. In order to overcome this limitation, the so called LDC nanoparticles with drug loading capacities of up to 33% have been developed[14]. An insoluble drug- lipid conjugate bulk is first prepared either by salt formation (e.g. with a fatty acid) or by covalent linking (e.g. to ester or ethers). The obtained LDC is then processed with an aqueous surfactant solution (such as Tweens) to a nanoparticle formulation using high pressure homogenization (HPH). Such matrices may have potential application in brain targeting of hydrophilic drugs in serious protozoal infections[67]. Lipid drug conjugate nanoparticles generally are spherical in shape and are comprised of a lipid drug core stabilized by a surfactant interfacial region. The core lipids can be fatty acids, acylglycerols, waxes,and mixtures of the same. Biological membrane lipids such as phospholipids, sphingomyelins, bile saltssuch as sodium taurocholate, sterols such as cholesterol, and mixtures of the same are utilized as surfactant stabilizers. Polyethylene glycol incorporation can provide steric stabilization and inhibit immune clearance[70]. Ligands can be conjugated to nanoparticles to promote tissue targeting. The physical properties of LDC's during prolonged storage can be determined by monitoring changes in zeta potential, particle size, drug content, appearance and viscosity as the function of time. External parameters such as temperature and light appear to be of primary importance for long term stability. The zeta potential should be in general, remain higher than -60mV for a dispersion to remain physically stable[68,69].

Method of Preparation of LDC

Lipid Drug Conjugates are prepared from lipid, emulsifier, surfactant and water/solvent by using different methods same as the SLN.

High pressure homogenization

- Hot homogenization
- Cold homogenization

Ultra sonication/high speed homogenization

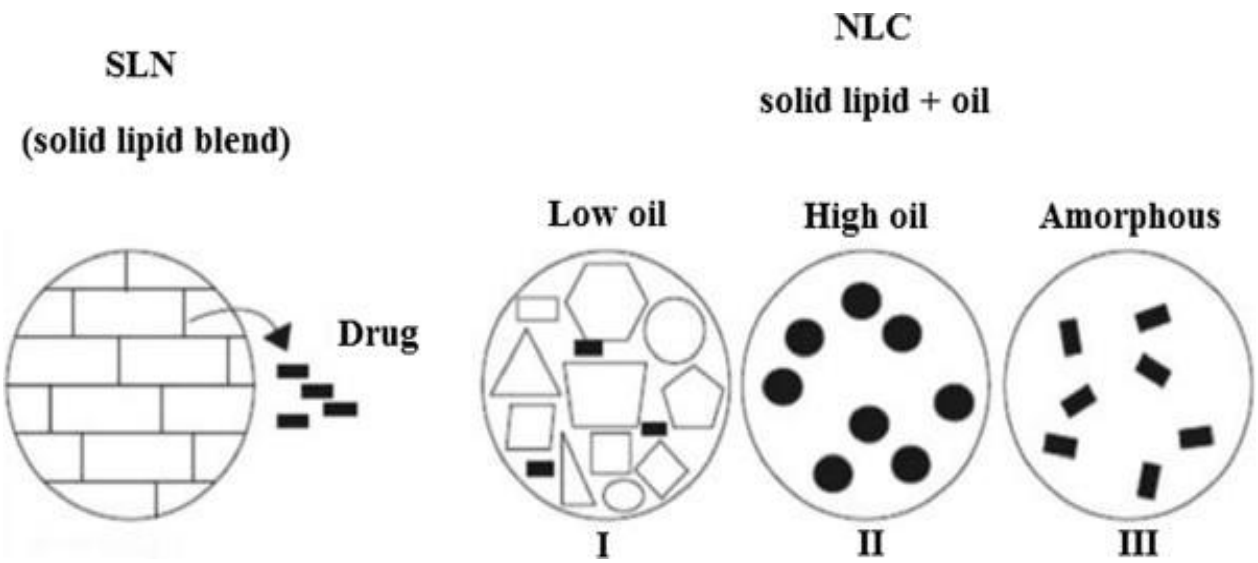

Figure 5. SLN with high crystallinity and Different types of NLC60

- Probe ultrasonication
- Bath ultrasonication

Solvent evaporation method
Solvent emulsification-diffusion method
Supercritical fluid method
Microemulsion based method
Spray drying method
Double emulsion method
Precipitation technique
Film-ultrasound dispersion
Characterisation of Lipid Nanoparticles
Characterisation of SLN

Adequate and proper characterization of the SLNs is necessary for its quality control. However, characterization of SLN is a serious challenge due to the colloidal size of the particles and the complexity and dynamic nature of the delivery system. The important parameters evaluated for the SLNs include particle size, size distribution kinetics (zeta potential), degree of crystallintity and lipid modification (polymorphism), coexistence of additional colloidal structures (miscelles, liposome, super cooled melts, drug nanoparticles), time scale of distribution processes, drug content, in-vitro drug release and surface morphology[35].

Particle size and Zeta potential

The physical stability of SLNs depends on their particle size. Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for determination of particle size. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light, which is caused by particle movement. The particle size determination by photon correlation spectroscopy (PCS) detects size range of 3nm to 3µm and by laser diffraction in size range of 100 nm to 180 µm. Although PCS is a good tool to characterize nano-particles, but is capable for the detection of larger microparticles (Pandey et al., 2005)[71]. The LD method is based on the dependence of the diffraction angle on the particle size (Fraunhofer spectra). Smaller particles cause more intense scattering at high angles compared to the larger ones[35]. Zeta potential measurement can be carried out using zeta potential analyzer or zetameter. Before measurement, SLN dispersions are diluted 50-fold with the original dispersion preparation medium for size determination and zeta potential measurement (Luo et al., 2006)[72]. Higher value of zeta potential may lead to deaggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. Zeta potential measurements allow predictions about the storage stability of colloidal dispersions[35].

Electron microscopy

Scanning electron microscopy and transmission electron microscopy offer a way to directly observe nanoparticles and physical characterization of nanoparticles. Transmission electron microscopy has a smaller size limit of detection, is a good validation for other methods and one must be cognizant of the statistically small sample size and the effect that vacuum can have on the particles. Currently, the fastest and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. Photon-correlation spectroscopy requires the viscosity of the medium to be known and determines the diameter of the particle by Brownian motion and light scattering properties. Lipidic nanoparticles containing cyclosporine were prepared by the emulsification-diffusion method and their physicochemical stability was characterized by evaluating particle size. It was observed that SLNs, variations in size were greater and particle size also increased over time in all batches; this effect may have been caused by a probable expulsion of the drug due to the lipid's partial rearrangement[42,73,74].

Dynamic Light Scattering (DLS)

DLS or quasi-elastic light scattering records the variation in the intensity of scattered light on the microsecond time scale. This variation results from interference of light scattered by individual particles under the influence of brownian motion and is quantified by compilation of an autocorrelation function. This function is fit to an exponential, or some combination or modification thereof,

Table 1. Examples of drugs incorporated into lipid nanoparticles

Drug	Lipid	Advantage	System	reference
Apomorphine	Glyceryl monostearate, polyethylene glycol monostearate	Enhanced the bioavailability in rats	SLN	125
Baclofen	Stearic acid	Significantly higher drug concentrations in plasma	SLN	124
Calcitonin	Trimyristin	Improvement of the efficiency of such carriers for oral delivery of proteins	SLN	126
Camptothecin	Monostearin and Soybean Oil 788	Stable and high performance delivery system	NLC	127, 128
Clozapine	Trimyristin, tripalmitin, and tristearin	Improvement of bioavailability	SLN	129
Cyclosporin A	glyceryl monostearate, and glyceryl palmitostearate	Controlled release	SLN	130, 131
Dexamethasone	Compritol 888 ATO	Drug delivery topical use	SLN	132
Diazepam	Compritol ATO 888 and Imwitor 900 K	Prolonged release	SLN	133
Doxorubicin	Glyceryl caprate	Enhanced apoptotic death	SLN	134
Ibuprofen	stearic acid, triluarin, tripalmitin	Stable formulation and negligible cell cytotoxicity	SLN	135
Ketoprofen	mixture of beeswax and carnauba wax	SLN with beeswax content exhibited faster drug release as compared carnauba wax	SLN	136
Lopinavir	Compritol 888 ATO	Bioavailability enhanced	SLN	137
Nimesulide	Glyceryl behenate, palmitostearate, glyceryl tristearate	Sustained drug release	SLN	138

with the corresponding decay constant(s) being related to the diffusion coefficient. The advantages of the process are the speed of analysis, lack of requisite calibration, and sensitivity to submicrometer particles.73, 75, 76. Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for routine measurements of particle size. The Coulter method is rarely used to measure SLN particle size because of difficulties in the assessment of small nanoparticle and the need of electrolytes which may destabilize colloidal dispersions. PCS (also known dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by the particle movement. This method covers a size range from a few nanometers to about 3 microns. This means that PCS is a good tool to characterize nanoparticles, but it is not able to detect larger microparticles. They can be visualized by means of LD measurements. This method is based on the dependence of the diffraction angle on the particle radius (Fraunhofer spectra). Smaller particles cause more intense scattering at high angles compared to the larger ones. A clear advantage of LD is the coverage of a broad size range from the nanometer to the lower millimeter range[73,75,76].

Atomic force microscopy (AFM)

In this technique, a probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on the forces at play between the tip and the surface. The probe can be dragged across the sample (contact mode), or allowed to hover just above (non-contact mode), with the exact nature of the particular force employed serving to distinguish among the sub techniques. That ultra-high resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size, e.g., colloidal attraction or resistance to deformation, makes AFM a valuable tool (Mukherjee et al., 2009)[77].

Static light scattering (SLS)/Fraunhofer diffraction

This method studies the pattern of light scattered from a solution of particles is collected and fit to fundamental electromagnetic equations in which size is the primary variable. It is fast and rugged method, but requires more cleanliness than DLS, and advance knowledge of the particles' optical qualities[35].

Differential scanning calorimetry (DSC)

DSC and powder X-ray diffractometry (PXRD) is performed for the determination of the degree of crystallinity of the particle dispersion. The rate of crystallinity using DSC is estimated by comparison of the melting enthalpy/g of the bulk material with the melting enthalpy/g of the dispersion (Siekmann and Westesen, 1994)[78].

Characterisation of NLC[79-83]

Imaging analysis

The major advantage that microscopic techniques have over most of the other methods used for size analysis is that the particle size itself is measured, rather than some property which is dependent on particle size. In other words, microscopic technique is a direct measurement and do not depend on any other factors that might influence the measurements (e.g. temperature, refractive index, etc.). In this work both light and electron microscopy have been used.

Light microscopy

The size of a particle which can be detected by microscopy is limited by the diffraction of the light used to form the image. The resolution of a microscope is calculated approximately as the wavelength of the light divided by the numerical aperture of the microscope objective. All substances, which are transparent when they are examined by microscope that has crossed polarizing filters, are either isotropic or anisotropic. Amorphous substances, such as supercooled melts and non-crystalline solid organic compounds, or substances with cubic crystal lattices, are isotropic materials, having one refractive index. On the other hand, anisotropic materials have more than one refractive index and appear bright with brilliant colors (birefringence) against a black polarized background. The interference colors depend upon the thickness of the crystal and the differences are either uniaxial, having two refractive indices or biaxial, having three principal refractive indices. Most materials are biaxial corresponding to either, an orthorhombic, a monoclinic or a triclinic crystal system. Light microscopy is an important procedure to know if the relatively larger particles detected by laser diffractometry (LD) technique is really particles or agglomerates of nano sized particles.

Scanning electron microscopy (SEM)

This technique can be used to investigate the shape of the particles prepared and to assess the particle size of these particles. Aqueous NLC dispersions can be applied and spread on a sample holder (thin carbon film). The samples will be placed inside of the vacuum column of the microscope and the air was pumped out of the chamber. An electron gun placed at the top of the column emits a beam of high energy primary electrons. The beam of the electrons passes through the lenses which concentrates the electrons to a fine spot and scan across the specimen row by row. As the focused electron beam hits a spot on the sample, secondary electrons are emitted by the specimen through ionization. A detector counts these secondary electrons. The electrons are collected by a laterally placed collector and these signals are sent to an amplifier.

Energy dispersive X-ray spectroscopy (EDX)

EDX is an analytical technique used predominantly for the elemental analysis or chemical characterization of a sample. Being a type of spectroscopy, it relies on the investigation of a sample through interactions between the electromagnetic radiation and the matter, analyzing X-rays emitted by the matter in this particular case.

Zeta potential (ZP)

Zeta potential is the electric potential of a particle in a suspension. It is a parameter which is very useful for the assessment of the physical stability of colloidal dispersions. In suspensions the surfaces of particles develop a charge due to ionization of surface groups or adsorption of ions. This charge depends on both the surface chemistry of the particles and the media around these particles. The surface charge generates a potential around the particle, which is at the highest near the surface and decays with distance into the medium. The zeta potential can be measured by determining the velocity of the particles in an electrical field (electrophoresis measurement).

Differential scanning calorimetry (DSC) analysis

DSC is usually used to get information about both the physical and the energetic properties of a compound or formulation. DSC measures the heat loss or gain as a result of physical or chemical changes within a sample as a function of the temperature. Qualitative measurements of processes have many applications, such as materials identification, study of purity, polymorphism, solvation, degradation quantitative and qualitative analysis, aging, glass transition temperature and compatibility of substances.

Characterisation of LDC

Characterization of LDC is a serious challenge due to the colloidal size of the particles and the complexity and dynamic nature of the delivery system. The important parameters which need to be evaluated for the LDCs are, particle size, size distribution kinetics (zeta potential), degree of crystallinity and lipid modification (polymorphism), coexistence of additional colloidal structures (micelles, liposome, super cooled, melts, drug nanoparticles), time scale of distribution processes, drug content, in vitro drug release and surface morphology[86].

Measurement of particle size and zeta potential[84]

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for routine measurements of particle size. The Coulter method is rarely used to measure LDC particle size because of difficulties in the assessment of small nanoparticle and the need of electrolytes which may destabilize colloidal dispersions. PCS (also known dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by the particle movement. This method covers a size range from a few nanometers to about 3 microns. This method is based on the dependence of the diffraction angle on the particle radius (Fraunhofer spectra).

Dynamic light scattering (DLS)

DLS, also known as PCS or quasi-elastic light scattering (QELS) records the variation in the intensity of scattered light on the microsecond time scale. This variation results from interference of light scattered by individual particles under the influence of Brownian motion, and is quantified by compilation of an autocorrelation function[85].

Static light scattering/Fraunhofer diffraction

Static light scattering (SLS) is an ensemble method in which the pattern of light scattered from a solution of particles is collected and fit to fundamental electromagnetic equations in which size is the primary variable. The method is fast and rugged, but requires more cleanliness than DLS, and advance knowledge of the particles' optical qualities[86].

Nuclear magnetic resonance (NMR)

NMR can be used to determine both the size and the qualitative nature of nanoparticles. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle.

Electron microscopy

SEM and TEM provide a way to directly observe nanoparticles, physical characterization of nanoparticles with the former method being better for morphological examination. TEM has a smaller size limit of detection, is a good validation for other methods, and affords structural required, and one must be cognizant of the statistically small sample size and the effect that vacuum can have on the particles[85].

Atomic force microscopy (AFM)

In this technique, a probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on the forces at play between the tip and the surface. The probe can be dragged across the sample (contact mode), or allowed to hover just above (noncontact mode), with the exact nature of the particular force employed serving to distinguish among the sub-techniques[85]. That ultrahigh resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size, e.g., colloidal attraction or resistance to deformation, makes AFM a valuable tool[86].

X-ray diffraction (powder X-ray diffraction) and differential scanning colorimetry (DSC)

The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus permitting the degree of crystallinity to be assessed. Another method that is a little different from its implementation with bulk materials, DSC can be used to determine the nature and speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperatures and their associated enthalpies[86].

REGULATION OF LIPID NANOPARTICLES

Nanotechnology development in India has led to an overwhelming focus on the range of applications in which nanotechnology could enable enormous amount of business opportunities[87]. The government has itself been a major contributor and has also enthusiastically responded to this by unveiling an ambitious programme – "Nano Mission" based on the three prongs; first, investment in basic science research; second, education and human resource training and third, offering incubation support facilities[88]. Almost concomitantly but much more silently (and with less fanfare), the last few years have witnessed the launch of a range of consumer products, including medical applications (diagnostics, new drug delivery systems, etc), cosmetics and textiles using nano-materials[89]. There is a need of regulation of the nanotechnology as the Global R & D funding in Nano S & T is increasing and has reached US $20 billion/yr. The Nanotechnology has been found to have potential applications in almost all spheres of human activity including household, medical, industrial and military. Every year Nanotechnology based consumer products are growing (54 in 2005 to 1317 in 2010) and the market for nanotechnology products & services are expected to reach 1.5 trillion by 2015.90 Institutionally, Ministry of health and family welfare (MoHFW) is in charge of prevention and control of health related hazards although it has been included under Indian Council of Medical Research (ICMR). Another level, at which the ministry plays an instrumental role, is that of regulating drugs and pharmaceuticals through the Central Drugs Standards Control Organization. There are many challenges faced by the government Institutes that are responsible for the regulation of the nanoparticles. One of the solution focuses on technology development as part of the state development agenda has been the setting up of individual departments at the level of central government with a view of promotion of specific technologies, thus we have the Department of Biotechnology, Department of Atomic Energy and the Department of Information Technology. The setting up individual departments is to provide strategic leadership and guidance for technology development in the specific sectors like ICT and Biotechnology as well as the primary objective of the department is to promote and facilitate the development of that technology. The Ministry of Science and Technology administers its functions through three departments – department of science and technology (DST), department of biotechnology (DBT) and department of scientific and industrial research (DSIR). Of these DST is the most important one with the objective of objective of promoting new areas of science and technology and to play the role of a nodal department for organizing, coordinating and promoting S&T activities in India. Currently, DST is the most instrumental wing of government for providing a thrust to nanotechnology development. The Department, engaged with the agenda of promoting nanotech as a thrust area, has declared large investments for basic and applied research promotion, infrastructure support, education and international collaboration under the Nano Mission started in 2007.Speaking at the 93rd Indian Science Congress, Prof CNR Rao, chairman of the Nano Mission Councel said, "If we don't join the (nano) race, we will be left behind". It is this fear of being left behind by other countries in the nano revolution that has triggered a single point agenda for giving a thrust to nanotechnology R&D and application[91]. Nano Mission is an umbrella programme implemented by DST for capacity building towards overall development of the field of nanotechnology research in India. Of the total proposed outlay of Rs. 19,300 crores for Department of Science and Technology under the XI five-year plan, Rs. 1000 crores have been assigned for the nano mission. There are certain public private initiatives in the form of industry-linked projects under the Mission, half of which are with companies dealing with drugs and pharmaceuticals[91,92]. In order that nanotechnology and nanomaterials can be developed responsibly, with optimization of benefits and minimization of risks, international cooperation on identifying and resolving gaps in knowledge is required. It is recognized that a major barrier to progress in this area is the confidential nature of much of the research on nanoparticles. Means of facilitating co-operation with industry to fill some of the critical knowledge gaps for risk assessment purposes need to be found to avoid the experience of the biotechnology industry of public perception of the risks[93]. A transparent

framework for risk benefit analysis should also be developed that is able to achieve wide acceptability[93].

CURRENT TRENDS OF LIPID NANOPARTICLES

Since a decade, trials are being made to utilize solid lipid nanoparticles (SLN) as alternative drug delivery system to colloidal drug delivery systems such as lipid emulsions, liposomes and polymeric nanoparticles due to their nanotoxicity and cost/effectiveness relationship. SLN combines the advantages of different colloidal carriers and also avoids some of their disadvantages. Several local or systemic therapeutic applications may be foreseen, such as immunisation with protein antigens, infectious disease treatment, chronic diseases and cancer therapy[94]. Insulin, commonly administered parenterally in the treatment of diabetes mellitus. Injections are often painful and must be administered daily, which result in low patient compliance. Unfortunately, oral administration of insulin, produced by solvent emulsification-evaporation method based on a w/o/w double emulsion, has limitations such as low bioavailability due to degradation in the stomach, inactivation and degradation by proteolytic enzymes, and low permeability across the intestinal epithelium because of lack of lipophilicity and high molecular weight[95]. The main advantages of incorporate insulin into SLN would be the enhancement of transmucosal transport and protection from the degradation in the GIT. SLN can be used to improve the bioavailability of drugs e.g. cyclosporine A and to obtain sustained release of lipophilic drugs like camptothecin. Lipid-based formulations may also protect active compounds from biological degradation or transformation that in turn can lead to an enhancement of drug potency. In addition, lipid-based particulate DDS have been shown to reduce the toxicity of various drugs by changing the biodistribution of the drug away from sensitive organs. This reduction in toxicity may allow for more drug to be administered and forms the basis for the current success of several marketed lipid-based formulations of amphotericin B (Ambisome®, Abelcet®) and doxorubicin (Doxil®, Myocet®)[96]. Nasal administration was a promising alternative noninvasive route of drug administration due to fast absorption and rapid onset of drug action, avoiding degradation of labile drugs (such as peptides and proteins) in the GI tract and insufficient transport across epithelial cell layers (Lee et al., 1994)[97] In order to improve drug absorption through the nasal mucosa, approaches such as formulation development and prodrug derivatization have been employed. SLN has been proposed as alternative transmucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups (Muller and Keck 2004; Prego et al., 2005)[98,99].In a recent report, coating polymeric nanoparticles with PEG gave promising results as vaccine carriers (Vila et al., 2004)[30,100]. Assessment of inhaled radio-labeled SLN bio distribution has been described and the data showed an important and significant uptake of the radio-labeled SLN into the lymphatic after inhalation (Videira et al., 2002)[101]. In a recent study, antitubercular drugs (rifampicin, isoniazid and pyrazinamide) were incorporated into various formulations of solid lipid particles ranged from 1.1–2.1 μm and formulations were nebulized to guinea pigs by mouth for direct pulmonary delivery (Pandey et al., 2005a and 2005b)[71,102]. Nebulization of solid lipid particles carrying antitubercular drugs was observed to be successful in improving drug bioavailability and reducing the dosing frequency for better management of pulmonary tuberculosis.SLN signifi-cantly enhanced the drug bioavailability in the aqueous humor. Cavalli et al., (1995)[103] also studied pilocarpine delivery via SLN, which is commonly used in glaucoma treatment, earlier. They reported very similar results in order to enhance the ocular bioavailability of drug.PEG coating seems to be a promising approach on rectal delivery and consequently, enhancement of bioavailability[104]. Researchers have reported intensively on the topical application of SLN. During the last few years, SLN and NLC have been studied with active compounds such as Vitamin E (Dingler et al., 1999)[105], tocopherol acetate (Wissing and Muller 2001)[106], retinol (Jenning et al., 2000)[52] , ascorbyl palmitate (Uner et al., 2005a and 2005b)[107,108], clotrimazole (Souto et al., 2004)[109], triptolide (Mei et al., 2003)[110], phodphyllotoxin (Chen et al., 2006)[111] and a nonsteroidal antiandrogen RU 58841 (Munster et al., 2005)[112] for topical application. A completely new, recently discovered area of application is the use of SLN in sun-protective creams[113]. Tamoxifen, an anticancer drug have been incorporated in SLN to prolong the release of drug following i.v. administration in breast cancer (Murthy, 2005)[114] Tumor targeting has been achieved with SLN loaded with drugs like methotrexate and camptothecin. Metoxantrone SLN local injections were formulated to reduce the toxicity and improve the safety and bioefficacy of the drug in treating breast cancer and lymph node metastases (Wong et al., 2006)[115]. Adjuvants are used in vaccination to enhance the immune response. The safer new subunit vaccines are less effective in immunization and therefore effective adjuvants are required. New developments in the adjuvant area are the emulsion systems. These are oil-in-water emulsions that degrade rapidly in the body. Being in the solid state, the lipid components of SLNs will be degraded more slowly providing a longer lasting exposure to the immune system. Mitoxantrone SLN local injections were formulated to reduce the toxicity and improve the safety and bioavailability of the drug[116]. Drug delivery research employing micelles and nanoparticles has wide application in ultrasonic drug and gene delivery in recent years. Of particular interest is the use of these nanovehicles that deliver high concentrations of cytotoxic drugs to diseased tissues selectively, thus reducing the agent's side effects on the rest of the body. Ultrasound, traditionally used in diagnostic medicine, is finding a place in drug delivery in connection with these nanoparticles. In addition to their non-invasive nature and the fact that they can be focused on targeted tissues, acoustic waves have been credited with releasing pharmacological agents from nanocarriers, as well as rendering cell membranes more permeable. Ultrasonic drug and gene delivery from nanocarriers has tremendous potential because of the wide variety of drugs and genes that could be delivered to targeted tissues by

fairly non-invasive means[117]. Excellent properties of SLN make them attractive drug carrier systems even for pharmaceutical companies. SLN products of several pharmaceutical companies can be given as follows: cationic solid lipid nanoparticles (SLN) for gene transfer namely TransoPlexR was produced by PharmaSol DDS (Germany) (Olbrich et al 2001)[118]. AlphaRx (USA) is developing vancomycin and gentamicin products with VansolinTM and ZysolinTM trade names. They are very effective in treatment of life-threatening infectious disease such as pneumonia. The intention of incorporating them into SLN has been to increase their efficacy while reducing their side effects. SkyePharma (UK) also have formulations of nanoparticulate technology which includes nanosuspensions and solid lipid nanoparticles under preclinical development[119] Nano-enabled DDS have already hit the market with a number of FDA approved compounds. Initially these have primarily been with the polymer Polyethylene glycol (PEG) in which PEG is conjugated with peptides and proteins but this will soon change and novel nanostructures and nanoparticles will begin to take a larger share of the new nanoenabled DDS. As an example Nucryst is in Phase 2 clinical trials with silver nanoparticles for drug delivery to treat atopic dermatitis, and Accusphere is in Phase 1 clinical trials with a nanoparticle that treats solid tumors while the US FDA approved the first inhalable version of insulin in 2006. The novel alternative to injectable insulin for the treatment of type-1 and type-2 diabetes was developed by Pfizer with Sanofi-Aventis and Nektar Therapeutics, and is marketed as "Exubera". Unlike other markets in which nanotechnology is merely projected to have an impact, nano-enabled DDS already represents a $3.39 billion market. But we are just seeing the tip of the iceberg as the technology shifts from polymer therapeutics through to truly innovative approaches enabled by our control of materials on the same scale at which nature works. The value of these nano-enabled compounds will sky rocket, reaching $220 billion by 2015[120]. Nanotechnology-enabled drug delivery systems (DDS) over the next five years are forecast to dramatically reshape the way existing drugs are delivered. The growing range of nanotechnology enabled drug delivery methods is poised to change the way new compounds are formulated, and to extend the life cycle of existing compounds. After 2015, nano-enabled technologies will take the lion's share of the market, making up nearly 90% of the drug delivery market--a complete transformation of the way DDS are formulated[17]. Successful in vivo studies also include rifampicin, isoniazid, and pyrazinamide that are used in tuberculosis treatment. These drugs achieved higher bioavailability when incorporated into SLN compared to the free solutions. Rifampicin has poor cellular penetration which requires high doses to reach effective concentrations. Rifamsolin is a rifampicin-loaded SLN under preclinical phase by AlphaRx. The methodology employed for production is acceptable by the regulatory agencies and has been addressed by various papers and patents[121]. Poor water-soluble drugs, as camptothecin, vinpocetine, and fenofibrate, can have their solubilization improved if incorporated into SLN[122,123]. Various companies are interested in solid lipid nanotechnology for oral drug delivery. Pharmatec (Italy) developed a cyclosporine SLN formulation for oral administration. Avoidance of high plasma peak and low variability in plasma profi le were provided in this case. AlphaRx have also rifampicin-loaded SLN under preclinical phase (RifamsolinTM). Rifampicin is mainly used to treat tuberculosis, which requires long-term treatment due to poor cellular antibiotic penetration. AlphaRx aims to deliver this drug inside the human cell, to increase its efficacy and as a result to increase patient compliance. An interesting example that could be cited is the case of NanoLipid Restore CLR® developed by Chemisches Laboratorium Dr. Kurt Richter, Germany and distributed by Pharmacos India. NanoLipid Restore CLR® consists of a white to light yellow liquid NLC dispersion containing black current seed oil, as a liquid lipid. This oil is rich in ω-3 and ω-6 fatty acids, being this product designed for regenerative care of dry, scaly, rough and aged skin, restoring the skin barrier and reducing transepidermal water loss (TEWL). Additionally, the NLC technology is able to protect the fatty acids against oxidation and permits a controlled release of the incorporated black current seed oil. Other components of this dispersion include carnauba wax as a solid lipid, decyl glucoside as a surfactant and water. NanoLipid Restore CLR® is a semi-finished product used in the cosmetic product line IOPE® from Amore Pacific, South Korea. Additionally, other products containing NLC are in the market such as Nanorepair Q10® (cream and serum) and Nanovital Q10® (cream) from Cutanova® (Dr.Rimpler, Germany) and Surmer® from Isabelle Lancray (France)[124]. The development of lipid-based drug carriers has attracted increased attention over the last decade. Lipid nanoparticles (e.g. solid lipid nanoparticles, SLNs) are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicine and research, as well as in other varied sciences. Due to their size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics that could be used for secondary and tertiary level of drug targeting. Hence, lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and has attracted wide attention of researchers[94].

CONCLUSION

Thus, it can be concluded that lipid based nanoparticles are surely a reliable and cost effective means of drug delivery attributed to its vast scope and numerous advantages. It has already achieved milestones and yet there is a huge scope for its applicability to various classes of drugs. It can serve as a boon to anticancer drugs whose oral dosage forms are still limited because of various stability issues. According to the authors, the article has aptly and justly tried to cover all the aspects of these novel nanoparticle forms. The regulatory guidelines and current scenario governing these lipid based formulations gives a deeper insight into the advancements attained in the field of lipid nanoparticles**.**

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