Lipids are a group of naturally occurring organic molecules, which comprises two different structural regions, one part consists of long hydrocarbon chain in its maximum reduced state (hydrophobic) and the other part consists of a polar head group (hydrophilic). Lipids are mostly non polar in nature but the presence of the hydrophilic and hydrophobic part in them give rise to the amphiphilic character. [1, 2] In aqueous medium the hydrophilic and the hydrophobic part interact differently. The polar head groups want to get exposed to the aqueous environment and the non polar tail wants to stay away from water. Presence of this contrasting character of the lipid molecules in the aqueous environment lead to the spontaneous formation of molecular aggregates. This special character of the lipid molecules are used in the development of lipid based drug delivery systems. Some common forms of lipids are waxes, fats, phospholipids, diglycerides, triglycerides, sterols, *etc*.[1, 2] They are also the essential components of cell membrane and other similar biological systems. Storage of energy, insulation of the cell, formation of the building blocks of steroid hormones for cell signaling, *etc.*, are some of the major functions of lipids in the biological systems. Higher melting point is observed for the lipids containing saturated hydrocarbon and increases with increasing the carbon number in the chain. Unsaturation lowers the melting temperature of lipids. There are several biosynthetic pathways by which lipids can be produced and break down inside a living being. Essential lipids like linoleic acid, α-linoieic acid cannot be obtained by those biosynthetic paths and must be consumed from external sources like foods.

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1. **Fatty acids:**

Fatty acids are organic molecules containing a long hydrocarbon chain and a carboxyl group at the end of the chain. Saturated as well as unsaturated hydrocarbon chain may be present in the fatty acid molecule. In the naturally occurring fatty acids, branching in the hydrocarbon chain is rare and the number of carbon atoms in the chain is even ranging from 4 to 28. Fatty acids containing unsaturated hydrocarbon chain are called unsaturated fatty acids and depending upon the number of unsaturation present they are known as mono and polyunsaturated fatty acids. Some common examples of unsaturated fatty acids are oleic acid, vaccenic acid, linoleic acid *etc*. Some common examples of saturated fatty acids are lauric acid, myristic acid, palmitic

acid, stearic acid, *etc*. Fatty acids are further classified on the basis of their chain length. They are short chain fatty acids (less than 6 carbon atoms), medium chain fatty acids (6 to 12 carbon atoms), long chain fatty acids (13 to 21 carbon atoms) and very long chain fatty acids (more than 22 carbons).

2. Classification of lipids:

Generally the lipids are classified into three major heads. They are simple lipids or homolipids, compound lipids or heterolipids and derived lipids. [1-4]

2.1. Simple lipids or homolipids:

They are the ester of different fatty acids and alcohols. Fats and oils are belonging to the simple lipid. They are tri-ester of different fatty acids and glycerol. Fats and oils are solid and liquid at room temperature respectively. [1, 2]

2.1.1. Glycerides:

They are the ester of glycerol and fatty acids. They are also known as acylglycerols. Glycerides are also classified as mono-, di- and triglycerides. [1, 2]

2.1.1.1. Monoglycerides:

In case of monoglycerides, only one hydroxyl group of glycerol is involved in the formation of ester linkage with a fatty acid molecule. Due to the presence of both primary and secondary hydroxyl group in glycerol, two different types of monoglyceride formation are possible. When the primary hydroxyl group is involved in the formation of ester linkage give rise to the 1, monoacylglycerols and involvement of secondary hydroxyl group in the formation of ester linkage give rise to 2, monoacylglycerols. Monolaurin, glyceryl hydroxysterate, *etc.*, are the common examples of monoglycerides. [1, 2]

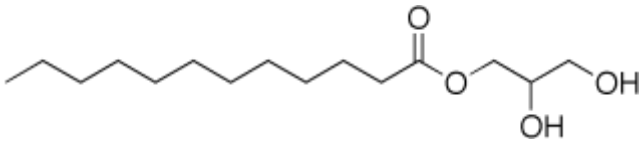

Figure 1. Molecular structure of monolaurin..

2.1.1.2. Diglycerides:

In case of diglycerides, two hydroxyl groups of the glycerol are involved in the formation of ester linkage with two fatty acid molecules. There is a possibility of formation of two different diglycerides, *viz.*, 1, 2-diacylglycerol and 1, 3-diacylglycerol. They act as surface active agents.

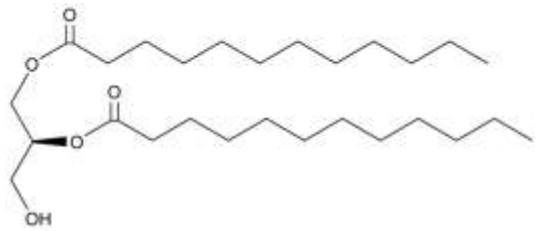

Figure 2. Molecular structure of 1,2-dilauroyl-*sn*-glycerol.

2.1.1.3. Triglycerides:

In case of triglycerides, three fatty acid molecules are involved in the formation of ester linkage with all three hydroxyl groups present in glycerol. Chain length of the fatty acids may be same or different. Triglycerides are also classified as saturated and unsaturated triglycerides depending upon the nature of fatty acid involve. Saturated triglycerids are generally solid at room temperature and unsaturated triglycerides are liquid at room temperature. Triglycerides are mostly found in body fats of animals and vegetable oils.

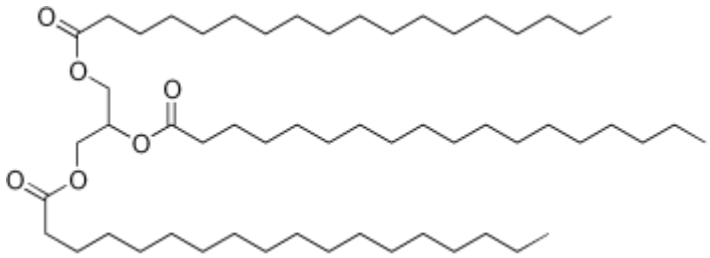

Figure 3. Molecular structure of tristearine.

2.1.2. Waxes:

Waxes are the ester of long chain fatty acids (saturated and unsaturated) and a monohydroxy alcohol of high molecular weight. They have melting point above 40°C. After melting they are found to produce low viscous liquid. Due to the nonpolar nature waxes are insoluble in aqueous medium but soluble in nonpolar organic solvents. Sorbitan tristearate, cetyl palmitate, *etc.*, are the common example of waxes.

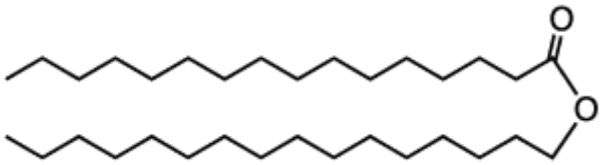

Figure 4. Molecular structure of cetyl palmitate.

2.2. Compound lipids or heterolipids:

Compound lipids or heterolipids are also ester of fatty acid and alcohols but they contain some other functional groups. [5]

2.2.1. Phospholipids:

They are also the compound of fatty acids and glycerol but they have two fatty acid chains attached to the two hydroxyl groups of glycerol and the third carbon of the glycerol contains a modified phosphate group. The modifiers play important role and regulate the biological role of the phospholipids in living organisms. Characteristics of the phospholipids depend upon the nature of modifier present in the phosphate group. They are amphiphilic in nature and hence can form bilayers. Phospholipids are the major constituents of the cell membranes. [1, 2, 4, 6]

Glycerophospholipids:

Glycerophospholipids are most available phospholipid in nature. They contain two esterifiedfatty acids with two adjacent hydroxyl groups of glycerol. The remaining hydroxyl group of glycerol involves in the formation of an ester linkage with phosphoric acid. [7]

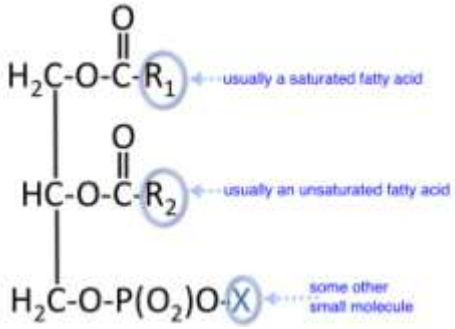

Figure 5. Molecular structure of glycerophospholipids.

Phosphatidylcholine:

Phosphatidylcholine or lecithine is generally obtained in liver. In this type of phospholipid, collin is present as base. The collin unit helps to prevent the deposition of abnormal fat present in in liver. [7]

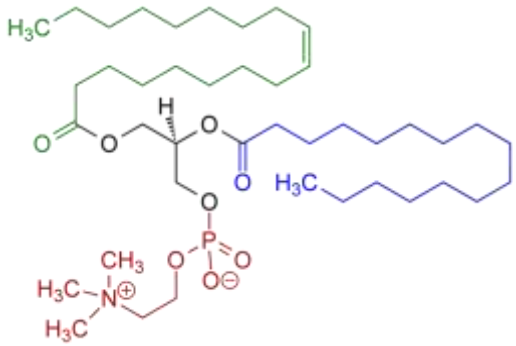

Figure 6. Molecular structure of phosphatidylcholine**.**

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Phosphatidylethanolamine

Phosphatidylethanolamine or cephalin are prepared by adding cytidine diphosphate ethanolamine and diglycerides. During this addition, cytidine monophosphate gets liberated. Ethanolamine unit is exist as base. This type of phospholipid is mostly present in brain and RBC

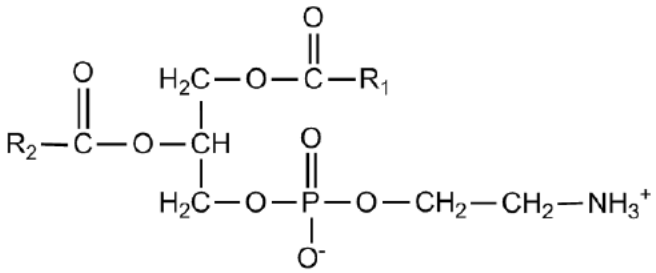

Figure 7. Molecular structure of phosphatidylethanolamine.

Phosphatidylserine:

Phosphatidylserine also consists of two fatty acids which are involved in the formation of ester linkage with the two successive carbon of glycerol. A phosphodiester linkage connects the serine unit and the third carbon of glycerol. Ir helps blood to get coagulated.

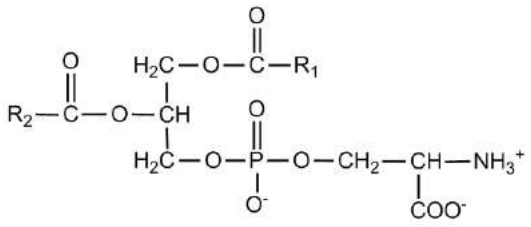

Figure 8. Molecular structure of phosphatidylserine.

Phosphatidylinositol:

Phosphatidylinositol has inositol as base. It does not contain nitrogen base. Nervous tissue and plants are the major source of this phospholipid.

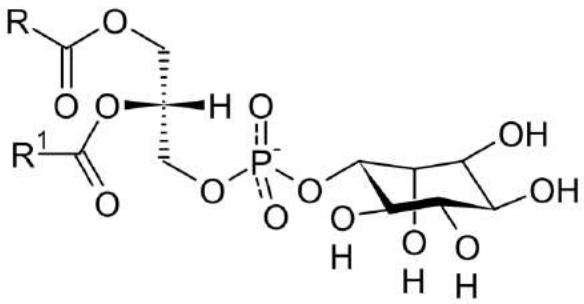

Figure 9. Molecular structure of phosphatidylinositol:

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Phosphatidylglycerol:

General structure of phosphatidylglycerol has a L-glycerol 3-phosphate backbone and saturated / unsaturated fatty acids are linked via ester bond with carbons 1 and 2. Glycerol (head group) is connected via a phosphomonoester. Inner membrane of mitochondria mostly contains this phospholipid.

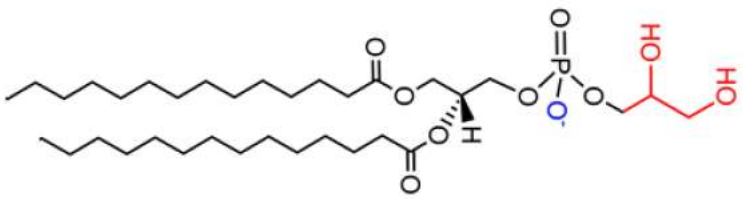

Figure 10. Molecular structure of phosphatidylglycerol.

Phosphatidylethanolamine (plasmalogens):

In case of phosphatidylethanolamine or plasmalogens unsaturated fatty acids are bonded through ester linkage with carbon and glycerol.

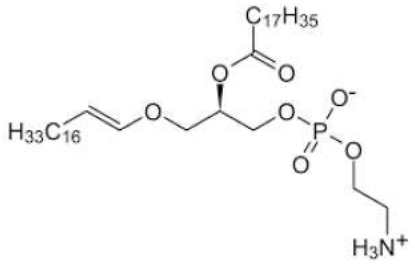

Figure 11. Molecular structure of phosphatidylethanolamine...

Sphingophospholipids:

Sphingophospholipids are produced by the addition of long chain amino alcohol sphingosine and long chain fatty acids. They are mostly observed in nervous tissue. Sphingolipids are classified into two different categories on the basis of composition. They are sphingomyelin and ceramides. [8]

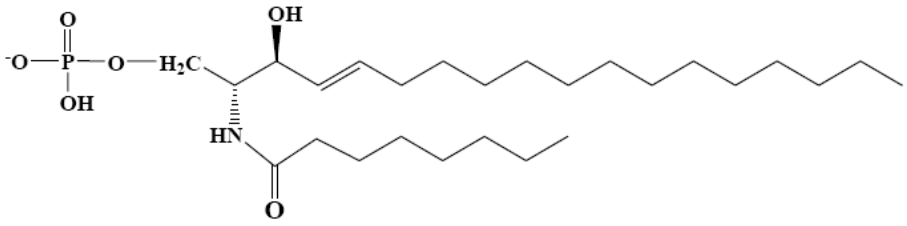

Figure 12. Molecular structure ofsphingophospholipids.

2.2.2. Glycolipids:

Lipids containing carbohydrates attached with the glycosidic linkage are called glycolipids. They do not have any phosphate group but they may have nitrogen containing groups. Glycolipids also include sulfolipids where sulfur containing functional group is present. The simplest form of the glycolipids is cerebrosides. In it glucose and galactose are present as carbohydrate unit. 2 to 20 units of carbohydrate chain is mostly observe in cerebtosides.

Gangliosides are the derivatives of cerebroside having N- acetyl neuraminic residue. Neutralized tetanus toxins, grey matter of brain, *etc*., mostly contain glycolipids. [9]

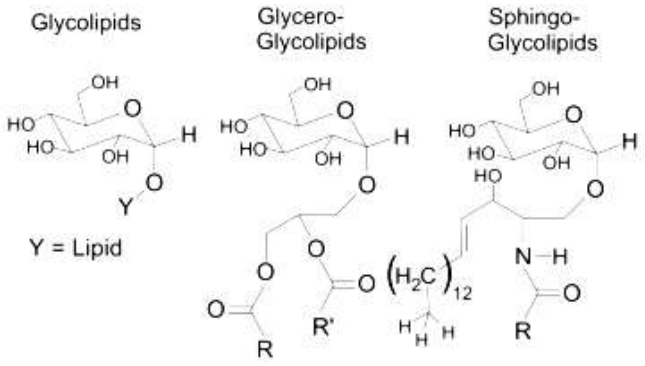

Figure 13. Molecular structure of glycolipids..

2.3. Derived lipids:

Derived lipids are obtained by the hydrolysis of simple lipids and compound lipids. Alcohols, fatty acids, diglycerides, monoglycerides, steroids, carotenoids, *etc*., are the common examples of derived lipids. [10]

2.3.1. Steroids:

Steroids are identified by their special structural feature. They have four fused ring. The structure of steroids is different from the lipids but they have incorporated in the lipid category due to the water insolubility and hydrophobicity. There are some steroids where hydroxyl group is present at a definite site. Such steroids are known as sterol. [10]

2.3.2. Cholesterol:

Cholesterol is a major constituent of the cell membrane and it also helps to produce important biological compounds like bile salts, steroid hormones *etc*. cholesterol belong to a large class of lipid, known as isoprenoids. They are prepared by the simple chemical condensation of isoprene. [10, 11]

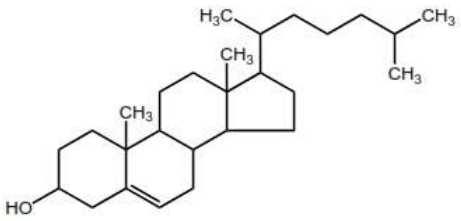

Figure 14. Molecular structure of cholesterol.

3. Drug:

A drug can be define as a chemical entity of known structure, different from the essential nutrient of food and produced different biological effect when it is present in leaving organisms. Generally, the drugs are collected from the medicinal plants present in the nature. In recent time drugs are also synthesized in the laboratory. Chemically drugs are classified according to their action on the human brain and body. Some common classes of drugs are stimulants, depressants, hallucinogens and opioids. In the present work some amphiphilic naturally occurring molecule having potent biological activity and water soluble tuberculosis drugs are used.

Drugs used in the present work:

Curcumin (CUR):

Curcumin is a polyphenolic natural compound having low molecular weight. Commonly it is known as turmeric, it is an excellent antioxidant agent with various biological activity. It can be used in the treatment of inflammatory disorder, cancer, HIV infections, cystic fibrosis and alzheimer, *etc.* But poor aqueous solubility and low bioavailability are the major difficulty in its use as a potential drug. Hence, a suitable drug delivery system is required for its wide application as drug. Curcumin always exists in equilibrium between its keto and enol form in the solution. This tautomerism is found to be dependent on the pH of the medium.X-ray analysis of the cyrcymin crystal has proved that, it undergoes keto-enol tautomerism even in the solid state. [12, 13]

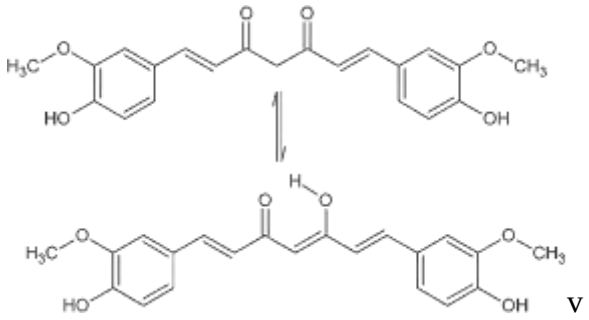

Figure 15. Keto-enol tautomerism in curcumin.

Chrysin (CHR):

Chrysin is a naturally occurring flavonoid. It is obtained from several wild and edible plants, honey and propoles. It has wide biological activities like anti-inflammation, anti-oxidant and anticancer activity. Recent studies have showed that it can reduce the malondialdehyde level and elevate antioxidant enzyme activity. But lower bioavailability of chrysin is a major drawback of it. A suitable drug delivery system is required for the improvement of its biological activity. [14, 15]

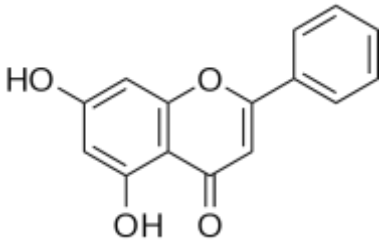

Figure 16. Molecular structure of chrysin..

Oleanolic acid (OLA):

Oleanolic acid is a naturally occurring pentacyclic triterpenoid. It is collected from thr leaves and roots of *Olea europaea*, *Viscum album L.*, *Aralia chinensis L.*, *etc.*, 120 different plant species. It has hepatoprotective, anti-hyperlipidemic effects, anti cancer activity, *etc*. Use of it in the liver disorders has also found in traditional Chinese medicine. However poor aqueous solubility and low bioavailability are the limitations for its pharmaceutical applications. So lipid base drug delivery systems are required to solve the mentioned drawbacks. [16, 17]

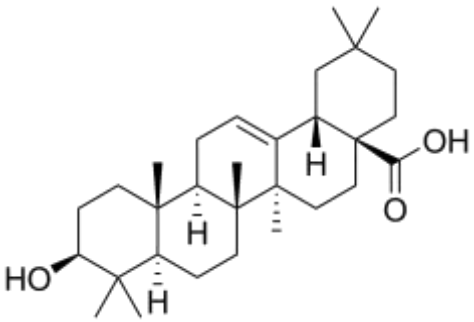

Figure 17. Molecular structure of oleanolic acid..

Pyrazinamide (PYZ):

Pyrazinamide is a \first line drug in the treatment of the active tuberculosis. It is used in combination with isoniazid, rifampicin and ethambutol in the treatment of active tuberculosis. It is also used as a potent drug for ueicosuric disuses. In addition to this, it also helps in the diagnosis of hypouricemia and hyperuricosuria. High water solubility, high rate of execration and high dose frequency are restricting its pharmaceutical applications. So a suitable delivery system is needed for it to improve its performance. [18, 19]

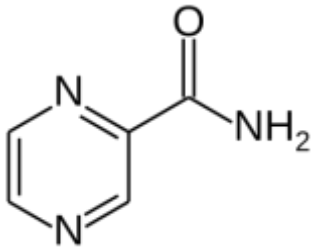

Figure 18. Molecular structure of pyrazinamide.

4. Different drug delivery systems:

In early days, various pharmaceutical dosage forms are used as the delivery agent for different drug in different route of administration. The different pharmaceutical dosages like tablets, liquids, capsules, creams, suppositories, ointments, *etc*. But those conventional drug deliveries suffer from serious limitations like side effects and complications due to their wide distribution through the body fluids and their dependency on the drug characteristics.[20-25] In addition to this low drug solubility, poor gastrointestinal absorption and rapid metabolism of the drug also limit the use of the conventional drug deliveries.[20, 21, 26-28] In modern time, with increasing need in the improvement of human health care vigorous research in developing

efficient drug delivery systems are warranted. The problems associated with the conventional drug delivery systems can be overcome by developing a suitable drug delivery agent having the capacity of sustain and control release of the loaded active drug component in the specific area of interest during treatment. It clearly implies that the activity of drug should be governed by the drug delivery agent not by the property of drug itself inside human body. [20, 21, 26-28] In this regard the size of the drug delivery systems is the area of main concern depending upon the different rout of administration. In this aspect the lipid based drug deliveries like colloidal carriers (few nanometer), microparticles (micrometer range) and implants (several millimeters) catch attention of the modern researchers having tremendous possibility and applicability in various routs of administration.[23-29] Among those lipid based delivery systems micro particles and implants having larger size are not suitable for intravenous application. But lipid based colloidal carries having size in the nanometer rang cover all the possible rout of administration and therefore regarded as superior among the other known lipid base drug delivery. [20-24, 26-28]

5. Colloidal drug delivery systems:

Colloidal system or colloidal dispersion is a heterogeneous system which is made up of dispersed phase and dispersion medium. In colloidal systems the substance present in lesser amount called dispersed phase and the substance present in larger quantity called the dispersion medium. In case of dust, solid particles are dispersed phase and air is dispersion medium. The word colloid is derived from Greek word "*KOLLA*" for glue prepared from gelatinous polymers and represents microscopic particles having size almost equal to 50μm. Hence, the microscopic particles of one phase dispersed in another are called as colloidal solution / dispersions. Colloidal carrier systems, basically nanocolloidal dispersions, have received growing interest in the field of drug delivery because they can offer several advantages like the following:

- The possibility to formulate poor water soluble drug substances in aqueous systems.
- Protection of drugs against degradation.
- Alteration of their biodistribution after intravenous administration.
- High drug loading capability.
- Target specific drug delivery leading to reduction in dosage and toxicity.

- Ability to improve the pharmacokinetics and increase biodistribution of therapeutic agents.

6. Overview of different colloidal drug delivery systems:

Colloidal drug delivery systems include several delivery systems among them O/W emulsions, liposomes, micelles, microemulsions and solid lipid based nanoparticles lightened a new way in effective targeting of the incorporated pharmaceuticals.

6.1. O/W emulsion:

In the beginning of 1960 O/W emulsion based drug delivery systems were introduced containing various drugs. This type of systems have excellent tolerance limit. But they suffer from the limitations related to its stability problem in presence of drug that include agglomeration and drug expulsion which restrict its wide uses. In addition, common oils used for the preparation of O/W emulsion show insufficient solubility of drug. Thus the need of new oils with improved drug solubility are warranted which also warrant expensive toxicity studies. [23, 30-33]

6.2. Microemulsion and nanoemulsion:

Microemulsions are thermodynamically stable systems that consist water, oil, surfactant and co surfactant. They are optically transparent and low viscous liquid.[23, 30-33] They can incorporate both hydrophobic and hydrophilic drugs. However, need of high surfactant concentration in this type of system is the major limitation. Its uses are restricted to dermal and parenteral applications only.

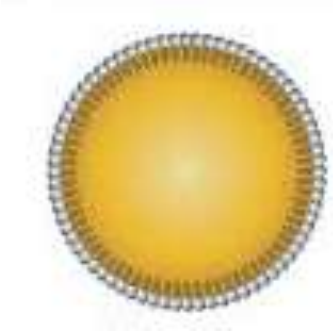

Figure 19. A schematic diagram of O/W nanoemulsion.

The term nanoemulsion was coined in the year 1950. In contrast to microemulsion, in the preparation of nanoemulsion an energy input is necessary. The nanoemulsion is thermodynamically unstable. But lower side effects make them superior over microemulsion based drug delivery. However, stability problem is one of the major drawbacks of nanoemulsion. In addition, sustained and controlled release of the incorporated drug is not possible. Higher mobility of the incorporated drug is mainly responsible for this. [23, 30-33]

6.3. Polymeric nanoparticles:

Polymeric nanoparticles are prepared form biodegradable and nonbiodegradable polymers. The control release and side specific targeting of drug makes it advantages over previously mentioned drug delivery systems. [30, 33-35] But cytotoxicity of the used polymer after *in vivo* degradation is its major limitation. In addition, problem in large scale production and hydrolysis of constituting polymers during storage restrict it use as potential drug delivery agents. [30, 33-35]

6.4. Liposomes:

Liposomes were introduced in the year 1965 by Bangham. They are a special type of vesicular drug delivery system. Liposomes are spherical vesicle composed of one or more monolayer of phospholipid. Initially they were used in the production of cosmetic products and latter on they were used in pharmaceutical industries. [34-36] Lipophilic and hydrophilic, both type of drug can be successfully incorporated in it. The lipophilic drug gets located in the phospholipid bilayers and the hydrophilic drug gets incorporated in the aqueous core. These

systems are effective in enhancing the efficacy of the incorporated drug and minimize the side effect. But instability during storage and unwanted drug leakage, low biological activity of the incorporated drug, non specific targeting are the major limitations of liposomal drug delivery systems. [34-36]

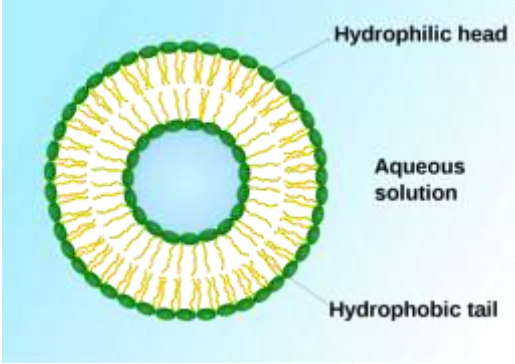

Figure 20. A schematic diagram of liposome

6.5. Solid lipid nanoparticles (SLN):

In the middle of the year 1990, investigation in the field of drug delivery finds a new way by the introduction of solid lipid nanoparticles as drug carrier system. The lipid employed for the production of this type of delivery systems are solid at room and body temperature so the systems are known as solid lipid nanoparticles. [20, 23, 24, 30-33, 37-39] The lipids are non toxic and biodegradable. They are capable to overcome all the limitations and shortcomings associated with the previously mentioned delivery systems. Higher physical stability and low aggregation rate, low drug leakage, low toxicity and low production cost make them advantageous over all known drug delivery systems. [20, 23, 24, 30-33, 37-39] In general, they are the dispersion of solid lipid particle in aqueous surfactant solution. The size of the lipid particles are found in the range of 50 - 1000 nm. Although all type of surfactants like cationic, anionic, zwitterionic and nonionic an be used in preparing SLN, however, nonionic surfactants are preferentially used as the emulsifying agent in SLN. The solid lipid core in contrast to other lipid based drug delivery provides many advantages like low drug expulsion and physical stability.

Although SLN shows valid advantages, but it also suffers from several drawbacks.[20, 23-25, 30-33, 37-42] To mention a few:

- Insufficient drug loading due to the presence of highly ordered lipid matrix.
- A polymorphic transition during storage causes expulsion of the incorporated drug.
- High water content of the dispersion.

6.6. Nanostructured lipid carriers (NLC):

To overcome the drawbacks associated with SLN, NLCs are introduced. They are also called second generation solid lipid nanoparticles. In general, two or more structurally different lipids are used in the preparation of NLC. The used structurally different lipid systems effectively reduced the crystallinity of the lipid matrix. In some cases solid lipid in combination with the liquid lipid is used to enhance the multicrystallinity. [20, 23-25, 30-33, 37-42] Higher amount of imperfections reduce the drug expulsion and enhance the drug incorporation efficiency.

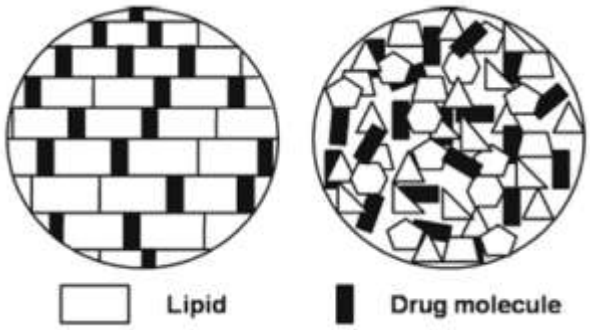

Figure 21. Schematic diagram of the drug loaded SLN (left) and NLC (right). [31]

7. Different types of NLC:

Depending on the different production procedures and the lipid compositions, different types of NLC can be obtained. The basic idea is to provide a certain internal morphology to the lipid matrix so as to enhance the drug incorporation and reduce the drug expulsion during storage. There are three different classes of NLC. [21-23, 31, 43, 44]

- Imperfect type
- Amorphous type
- Multiple type

7.1. Imperfect type:

Structurally different lipids are mixed, and thus imperfections are created in the lipid matrix of the nanoparticles. Distances between fatty acid chains in the lipid matrix of the lipid nanoparticles can be increased by using glycerides composed of significantly different fatty acids. Therefore, the matrix contains imperfections and the created imperfections help to accommodate drug. Introduction of small amounts of structurally different liquid lipids (oils) with solid lipids increases the structural disorder and increases the drug payload. [26, 31, 39, 42-45]

7.2. Amorphous type:

This kind of NLC can be prepared by mixing solid lipids with medium chain triglycerides. Therefore, drug expulsion caused by the process of crystallization to β-forms during storage is prevented by the special structure of the medium chain triglycerides present in the lipid matrix. [31, 43, 44, 46] Since, this type of NLC exist in solids amorphous state but not in crystalline state.

7.3. Multiple types:

The solubility of the drug in the lipid matrix diminishes during the cooling process after homogenization and then the crystallization process during storage. Continues reduction in the drug solubility leads to drug expulsion from the lipid nanoparticles. This phenomenon is prominent when the concentration of the drug is too high in the prepared formulations. Generally, solubility of drugs is higher in liquid lipid in comparison to the solid lipid. When liquid lipids having appreciable drug solubility are introduced in combination with the solid lipid, multiple type NLCs are formed. The solid lipidic phase displays the advantages of the solid matrix which prevented drug leakage and the liquid lipophilic regions (oily nanocompartments) show comparatively high drug solubility. [31, 43, 44, 46]

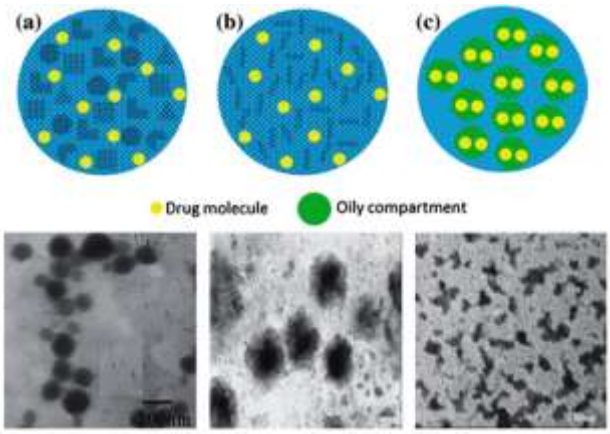

Figure 22. Schematic representations and TEM images of different types of NLC formulation (a), imperfect type; (b), amorphous type and (c), multiple type. [40]

8. Drug incorporation models of NLC:

8.1. Solid solution model:

In this model the incorporated drug is uniformly distributed inside the lipid matrix. This type of NLC can be prepared by cold homogenization without using any surfactant or drug solublising agent. In this type of NLC, the incorporated drug releases by simple diffusion technique. [25, 31, 41, 43]

8.2. Drug enriched shell model:

In this type of NLC, the drug generally accumulates in the shell of the nanoparticles. This type of NLC can be prepared by high pressure homogenization. At the time of homogenization the drug get distributed between lipid phase and aqueous surfactant solution. The drug solubility of aqueous surfactant enhances at elevated temperature. During cooling the drug again starts to get distributed between aqueous phase and lipid phase. Lower temperature diminished the aqueous solubility of the drug. Hence, at reduce temperature redistribution of the drug at the lipid phase increases. At the same time cooling causes recrystallization of the lipid core so the lipid core cannot accommodate any more drugs. Hence, the added drug gets accumulated only on the shell of the lipid nanoparticle. This type of NLC shows burst release of the surface accumulated drug. [25, 31, 41, 43]

8.3. Drug enriched core model:

Drug enriched core model of NLC is formed when precipitation of the incorporated drug is faster than the lipid recrystallization during cooling process. When the lipid melt is saturated with drug gives rise to drug enriched core NLC. [25, 31, 41, 43]

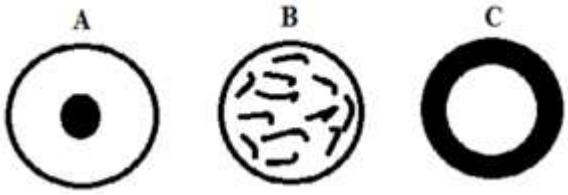

Figure 23. Schematic diagram of different type of drug incorporation models for NLC formulations. A, drug enriched core model ; B, solid solution model and C, drug enriched shell model**.** [31]

9. Advantages of NLCs over SLNs:

In SLNs, the drug is mainly dispersed in molecular form, for example, located in between the fatty acid chains of the glycerides whereas in NLCs, blend of structurally different solid lipids or solid and liquid lipids are used and due to the differences in structure they cannot fit together very well to form a perfect crystalline system. This arrangement creates a lot of imperfections in matrix leading to the enhanced accommodation of drug in molecular form. Some major advantages of NLCs are as follows:[20-25, 31, 42, 43, 45, 47]

- Superior physical stability.
- Easy preparation.
- Good dispensability in an aqueous medium.
- High incorporation efficiency of lipophilic and hydrophilic drugs.
- Controlled particle size.
- Advanced and efficient drug delivery system in particular for lipophilic substances.
- Enhanced skin occlusion.
- Sustained drug release.

- ❖ Advantageous for topically applied drugs as their lipid components have an approved status in commercially available topical cosmetic or pharmaceutical products.
- ❖ Small size of the lipid particles ensures close contact to the stratum corneum thus enhancing drug penetration into the mucosa or skin.
- ❖ Improve benefit/risk ratio.
- ❖ Increase of skin hydration and elasticity.
- ❖ These carriers are highly efficient systems due to their solid lipid matrices, which are also generally recognized as safe or have a regulatory accepted status.

10. Limitations of NLCs:

Despite of several potential advantages, NLCs are found to face several limitations like: [20-25, 31, 42, 43, 45, 47]

- ❖ Limited storage time.
- ❖ Instability of the lipid core due to the ongoing lipid modifications.
- ❖ Lesser application and efficiency towards protein and peptide based drugs.
- ❖ Applicability is very less as gene delivery system.
- ❖ Insufficient preclinical and clinical studies with these nanoparticles.

11. Materials used for the NLC production:

The nano lipid carriers used for topical applications are mainly formulated with variety of lipids such as glycerol behenate, glycerol palmitostearate, cetylpalmitate (wax). In case of NLCs, liquid lipids such as medium chain triglycerides are also used. Oleic acid, one of the frequently used fatty acid usually used to enhance the skin penetration of NLC. [23, 24, 32, 37-39, 43, 47-49] Hence the drug uptake depends on the type and concentration of the lipids, 0.5 – 5% surfactant is also added for physical stability of NLCs. Nonionic surfactants are preferentially used instead of ionic surfactants. Various lipids and surfactants used for preparation of lipid nanocarriers are illustrated in the Table 1.

The nature and concentrations of surfactant also affect the quality and efficacy of NLCs. Surfactants is preferentially located in interfacial regions where they reduced the interfacial tension between lipid and aqueous phases. This is due to their amphiphilic nature and stabilizing

effect over the NLC systems. Ionic surfactant, sodium deoxycholate having low emulsification property can be employed to increase the charge of NLC. [23, 24, 32, 37-39, 43, 47-49] Thus the ionic surfactants provide the electrostatic stabilization which is related to the enhancement in electrostatic repulsion. Nonionic surfactants provide additional steric stability which avoid aggregation among NLC.

Table 1. Common lipids and surfactants used for the preparation of NLC formulations. [22-25]

Lipids		
Sl. No.	**Type of lipids**	**Examples**
1.	Triacylglycerols	Tricaprin, trilaurin, trimyristin, tripalmitin and tristearin
2.	Acylglycerols	Glycerol monostearate, glycerol behenate and glycerol palmitostearate
3.	Fatty acids	Stearic acid, palmitic acid, decanoic acid and behenic acid
4.	Waxes	Cetyl palmitate
5.	Cyclic complexes	Cyclodextrin and *para* acyl calixarenes
Surfactants		
Sl. No.	**Type of surfactant**	**Examples**
1.	Phospholipids	Soy lecithin, egg lecithin and phosphatidylcholine
2.	Ethyleneoxide / propylene oxide copolymers	Poloxamer 188, poloxamer 182, poloxamer 407 and poloxamine 908
3.	Sorbitan ethylene oxide / propylene oxide copolymers	Polysorbate 20, polysorbate 60 and polysorbate 80
4.	Alkylaryl polyether alcohol polymers	Tyloxapol
5.	Bile salts	Sodium cholate, sodium glycolcholate, sodium taurocholate and sodium taurodeoxycholate
6.	Alcohols	Ethanol and butanol

12. Different preparative procedures of NLCs:

Production method for solid lipid nanoparticles and the nanostructure lipid carriers are almost similar. There are so many well known methods in the literature. However the most important methods are[20, 22-25, 32, 37-41, 43, 44, 47-50]

- Hot/ cold High pressure homogenization
- Microemulsion technique
- Solvent emulsification and evaporation technique
- Hot homogenization followed by ultrasonication technique

12.1. High pressure homogenization:

This is the most common method for the preparation of NLC. It includes two different basic production method, these are hot and cold high pressure homogenization. In both the technique the lipid mixture is melted above the melting temperature (5-10 ºC). In case of hot homogenization, aqueous surfactant solution maintained at the same temperature should be added to the melted lipid mixture. Then the mixture is stirred to produce a pre emulsion. After that the pre emulsion is subjected for high pressure homogenization. Maximum three cycles of homogenization at 500 bar is needed. The homogenized nanoemulsion is then subjected for cooling at or below room temperature to get NLC. [31, 41, 43, 45, 47, 51]

In cold homogenization, the melted lipid mixture is rapidly cooled under liquid nitrogen temperature and grinded to prepare lipid microparticles. The pre suspension is prepared by adding cold aqueous surfactant solution in the micro lipid particles. Then the pre suspension is subjected for high pressure homogenization at or below room temperature to produce NLC. The cold high pressure homogenization technique is very much helpful for the system having thermo labile drug components. [31, 41, 43, 45, 47, 51]

12.2. Microemulsion technique:

In this method, a hot pre emulsion is prepared by stirring the melted lipid mixture with hot aqueous surfactant solution maintained at same temperature like hot homogenization technique. But in this method a cosurfactant solution is used in high concentration. The hot emulsion is then dispersed in cold water under mild mechanical mixing to get NLC formulation. This method is mainly applicable for the large scale production of NLC. [41, 43, 45, 47]

12.3. Solvent emulsification and evaporation method:

In this method the lipid mixture is dissolved in a water immiscible organic solvent. Then the lipid solution is dispersed in aqueous phase. After that the organic solvent is evaporated and precipitation of the lipid phase in the form of NLC is obtained. This is also a useful technique for the preparation of NLC loaded with thermolabile drug. But this method suffers a serious limitation. Organic solvent may present in the final dispersion as the complete separation of the organic solvent is impossible. [41, 43, 45, 47]

12.4. Solvent diffusion technique:

In the solvent diffusion method water miscible solvents like benzyl alcohol, ethy formate *etc*., are used. The solvents are mutually saturated with water until the equilibrium is reached. The lipid mixture then mixed with water saturated solvent and emulsified with solvent saturated aqueous surfactant solution at higher temperature. Then excess water is added to get the precipitation of the lipid phase as NLC. [41, 43, 47]

12.5. Hot homogenization followed by ultrasonication technique:

It is the most applicable and accepted method for the preparation NLC in laboratory scale. The simplicity and low cost of preparation is the major advantage of this preparative technique. In this technique the lipid mixture is melted at higher temperature than the melting temperature of the lipid components. Hot surfactant solution maintained at the same temperature is then added to the melted lipid mixture and subjected for high speed stirring for the preparation of pre emulsion. Then the pre emulsion is subjected for ultrasonication using a probe sonicator maintaining the same temperature. The obtained nanoemulsion is then cooled at room temperature to get the NLC. Narrow size distribution and high stability of the suspension can be

achived by this method of preparation. But metal contamination and low lipid concentration are the major drawbacks of this method. [43, 47, 52]

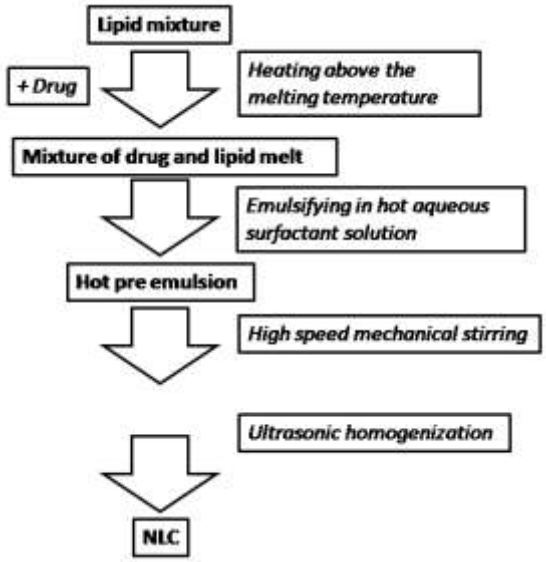

Figure 24. Flow diagram for the preparation of NLC using hot homogenization followed by ultrasonication technique.

13. Stability of the NLC formulations:

NLCs are advantageous and have higher stability in comparison to other colloidal drug delivery like micelles, mixed micelles, liposomes and nanoemulsions. Still NLC suffers from major stability issues during storage, such as particle size enhancement, gelation of the dispersion and drug expulsion from the lipid matrix. [25, 38, 40-43] Gelation takes place due to formation of the network and lipid bridges between the particles. The physical stability of these dispersions is generally investigated by the measurement of particle size, zeta potential (ZP) and ploydispersity using dynamic light scattering. Thermal analysis is performed using differential scanning calorimetry (DSC). The long term storage of lipid dispersions leads to aggregation and shell formation as reported in case of nanocolloidal dispersions having multicrystallinity. [25, 38, 40-

[43] In case of highly concentrated NLC dispersions the particles form a pearl like network, thus undergoing collision and subsequent flocculation. After the administration of NLCs and their dilution with gastrointestinal fluid, the network is destroyed releasing single non-aggregated particles. Lipid particle dispersions were produced at identical surfactant concentration, but with low lipid content. The low particle dispersion aggregated during storage time, the gel-like NLC dispersion remained stable during storage and after dilution single particles were obtained showing no size enhancement. Freely diffusible nanoparticles in low concentration dispersion can collide and aggregate, while in highly concentrated dispersions the particles are fixed in a network, where further dilution with water releases non-aggregated definite nanoparticles. [25, 38, 40-43] There are several well known technique for giving stability to the NLC systems, among them two well known methods are spray drying and lyophilisation. [31, 39-41]

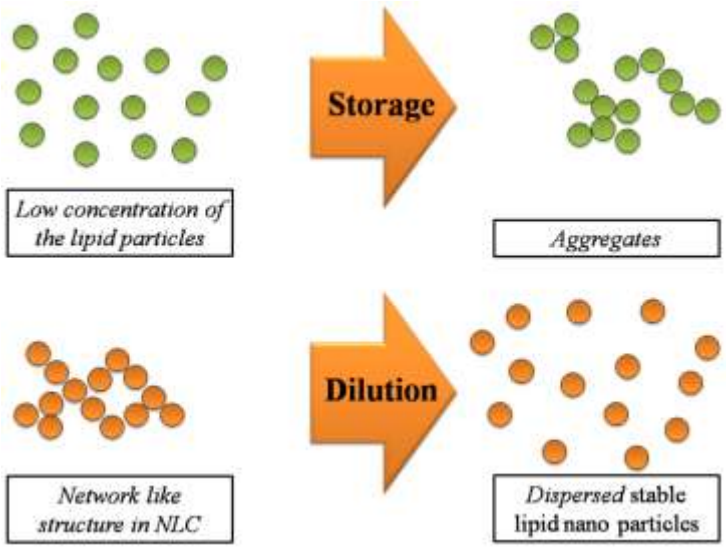

Figure 25 Aggregation method in reducing intensified dispersions and pearl like network in the NLC dispersion with stabilizing effect. [42]

14. Physicochemical characterization of NLCs:

Detail characterization of NLC formulations are very important to get detail over view regarding the quality and the application potential of the prepared formulations. But detailed characterization of NLC is a challenging task due to the complex structure and the dynamic lipidic core. Different physicochemical properties like hydrodynamic diameter, polydispersity index, zeta potential, phase transition temperature, phase transition enthalpy, heat capacity,

crystallinity index, drug loading capacity and the release mechanism etc., decide the physicochemical character of NLC. The mentioned physicochemical parameters are also helpful in understanding the interaction of NLC and the incorporated drug molecules. Hence, major characteristics like particle size, polydispersity index, zeta potential, thermal properties, drug incorporation, drug loading, drug release mechanism and the biological performance are needed to be discussed for the detailed evaluation of the NLC formulation. Some brief description of the mentioned properties is discussed below

14.1. Particle size, morphology, polydispersity index and zeta potential:

Dynamic light scattering is efficient analytical tool for the determination of particle size. It determines the variation in the scattered light intensity resulted by the random movement of the dispersed particles. In general He- Ne leaser having emission wavelength 628 nm is used in dynamic light scattering studies. The leaser with an angle 90º interacts with the diffused colloidal particles. The instrument collects the scattered light to measure the translational diffusion coefficient (D). The hydrodynamic diameter (d_h) is obtained using Stokes-Einstein's equation [53-55]

$$d_h = \frac{kT}{3\pi\eta D}$$

where, k, T and η are Boltzmann constant, temperature and viscosity of water respectively.

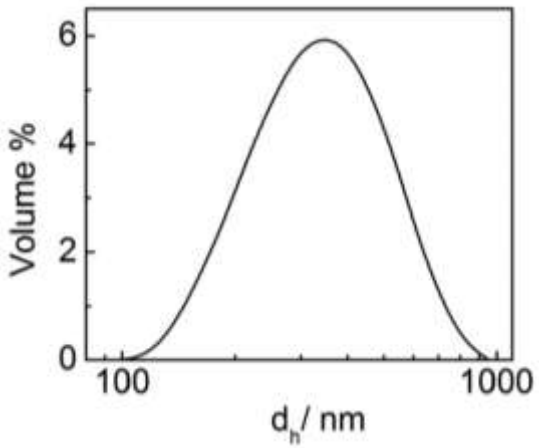

Figure 26. Size distribution curve of NLC (SLC + TS + PA, 2:2:1, M/M/M) formulation obtained from the DLS studies.[37]

This technique is applicable for the determination of size of particles having size in the ranges 10 to 1000 nm. On the other hand, laser diffraction (LD) is able to determine the size of the larger particle having size higher than 1000 nm. Laser diffraction mainly based on the principle related to the variation in the diffraction angle with the radius of the dispersed particles. Particles with smaller radios resulted strong and instance scatterings in the higher angles range in comparison to the large particles. [22, 25, 52-54, 56] All the discussed methodology and technique are not able to give direct determination of particles size but size of the particle can be determined from the scattered light. Among the discussed technique PCS is the most effective and sophisticated technique for the determination of particle size. [40, 41, 43] But there are so many associated problems in the PCS and LD in the determination of the size of the lipid dispersions. Due to the presence of the particle populations having different size range, size distribution is mainly generated in the determination of size. [22, 25, 52-54, 56] In some cases having particle size above the nanometer rang light microscopy is also used for the size measurement. But this method is not applicable for the particles having size in the nanometer range. Electron microscopy like scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) are very trusted method in the evaluation of the particle size and morphology of the dispersed particles. These methods are also very important in the evaluation of the size and the corresponding distribution. [22, 25, 52-54, 56] SEM utilizes the transmitted electrons from the surface of the sample under investigation. On the other hand TEM uses the transmitted electron from the sample under study.

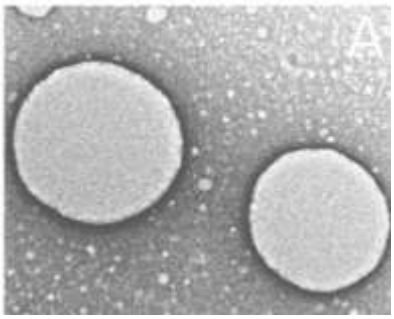

Figure 27. TEM image of NLC (CP+TO+PA, 2:2:1, M/M/M) formulation. [57]

In case of SEM and TEM direct idea regarding the morphology, shape and size are obtained. But SEM is not that good in the determination of the size of the NLCs and SLNs in the nanometer range. [24, 25, 56] Field emission SEM (FESEM) is a modification over the conventional SEM is found to be very effective in the determination of size in the nanometer range. However, solvent removal and drying processes during the SEM analysis significantly alter the particle size and morphology. FESEM involving the cryo system is very promising in this case. In this process the liquid dispersion get frozen in the liquid nitrogen temperature and images are obtained in the solid frozen state. [24, 25, 53, 54, 56] AFM is also very applicable in the evaluation of the size and the surface topology of the lipid nanoparticles. AFM is also important in generating three-dimensional image of the surface which is not possible in the electron microscopy.

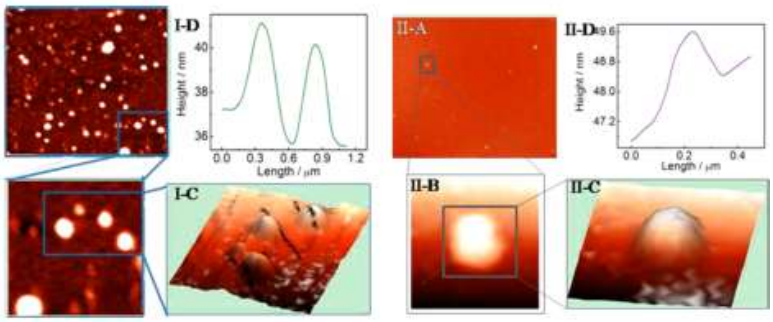

Figure 28. Representative AFM images of the NLC formulations comprising TB + HSPC + BA, 2:2:1, M/M/M (I) and TE + HSPC + OA, 2:2:1, M/M/M (2). [54]

AFM is also very applicable in the determination of size in the angstrom range. In this technique, the force generating between the sample surface and the tip provides a resolution up to 0.01 nm in the image formation. [54]

It is well known that the colloidal particles are polydispersed in nature and the determination of size requires simultaneous evaluation of the polydispersity index (PDI). The PDI value in the range 0.1 to 0.5 is regarded for the stable dispersion system. [32, 36, 38, 44, 47, 49, 53, 54] Higher PDI value than the mentioned range indicated the non-homogeneous and unstable systems. In most of the cases for the NLCs and SLNs the reported PDIs are found in the range of 0.3 to 0.5. [24, 25, 35, 47]

The determination of the zeta potential is also very important as it is directly related to the stability of the SLN and NLCs. Zeta (ξ) potential can be calculated using Smoluchowski equation based on electrophoretic mobility of the colloidal particles: [53-55]

$$v = \binom{\varepsilon\, E}{\eta} \xi$$

where, v, ε, η and E indicted electrophoretic velocity, electrical permittivity, viscosity and electric field respectively. The value of zeta potential in the range of ±30 mV found to show reasonable repulsive interaction between the charged colloidal particles which significantly reduces the aggregation and flocculation rate of NLCs. [39, 51, 52, 58] However, in presence of the high concentration of the surfactants the above assertion is not totally applicable. The presence of surfactants provides the steric stability to the NLCs and SLNs. [39, 51, 52, 58] As a result of this, surfactants get adsorbed on the surface of the SLN and NLC. Due to the shift in the shear plane of the dispersed particles in the presence of surfactants, decreased the magnitude of zeta potential.

14.2. Degree of crystallinity and lipid modification:

The determination of the extent of crystallinity commonly known as crystallinity index and the lipidic modification are also vital aspects in characterizing NLC. The mentioned parameters are very important in controlling the drug incorporation and release phenomenon. [31, 43, 47, 59]

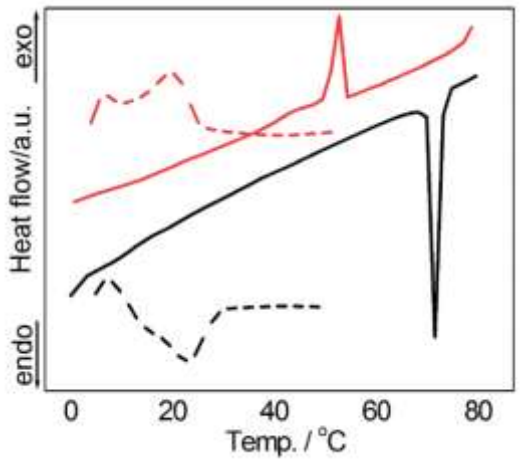

Figure 29. DSC thermograms of the physical mixture of lipids (solid line) and NLC (SLC + TS + PA, 2:2:1, M/M/M) formulations (dotted line). [56]

The thermodynamic stability of the NLC are said to enhance and drug loading capacity reduces when it moves from supercooled melt to crystalline state through different crystalline modification. [31, 43, 47, 59] Particles with smaller size are found to show lesser recrystallization and the lipid modifications. Differential scanning calorimetry (DSC) and X-ray scattering are two extensively used tool in the investigation of the crystallinity of NLC. DSC is based on the principal that different lipid modifications have various melting temperature and enthalpies. X-ray scattering is very useful in estimating the length of the long and short gaping present in the lipid lattice in NLC. [47, 59] But X-ray diffraction also suffers from limitations like the high sensitivity and time consuming measurement process. Such problems are overcome by the introduction of synchrotron to the conventional X-Ray diffractometer. Infrared (IR) and Raman spectroscopy is also very useful tool in determining the state of crystallinity and the extent of lipid modification of NLC formulations. But the application of IR and Raman spectroscopy is not very common for the characterization of NLC systems.

14.3. Drug loading capacity and drug incorporation efficiency:

An improved and efficient drug carrier should allow incorporating a large amount of drugs. In addition to this, it should resist the drug for significantly long time. The incorporated drug mainly reside in between fatty acid chains or in the imperfections created by the structural mismatches among the lipid molecules. [27, 52-54, 56] The locations of the drug in the NLC entirely

govern by the ratio of drug to lipid and the solubility of the incorporated drug in the lipid physical mixture. The incorporated drug can reside in the shell of the NLC or it may reside in the core of the formulations. The following equations are used for the calculation of the drug incorporation efficiency and drug loading capacity: [53-55]

$$\text{Drug incorporation efficiency} = \frac{W_{TD} - W_{FD}}{W_{DC}} \times 100\%$$

$$\text{Drug loading capacity} = \frac{W_{TD} - W_{FD}}{W_{TD} - W_{FD} + W_{TL}} \times 100\%$$

where, W_{TD}, W_{FD} and W_{TL} are weight of total drug, weight of free drug and weight of total lipid respectively. There are many reports on the formation of the molecularly dispersed drug loaded NLC formulations. [20-24] The incorporated drug also affects the size of the NLC formulation and the physical stability. By optimizing the drug to lipid ratio the physicochemical stability of the NLC formulation can be increased. The lipid core of NLC also protects the incorporated drug from chemical degradation and provides stability to the labile drugs. [20, 23, 24] Thus NLC systems ensure the high entrapment efficiency and high retention ability of the incorporated drug. The nature of the phospholipid present in the NLC formulation also governs the drug incorporation and the drug loading capacity. The generation of phospholipid bilayers also helps in the incorporation of the amphiphilic drugs. The amphiphilic drugs are mainly incorporated inside the generated bilayers. [29, 34, 55, 60]

The determination of the entrapment efficiency and the drug loading capacity, the separation of the incorporated and the free drug are necessary. Method of centrifugation is mainly used for the separation of the incorporated drug and the free dispersed drug molecules. [34, 52-56, 60] Cooling centrifuge is mostly preferred for this process. It prevents the generation of heat during centrifugation. The quantitative determination of the drug present in the sedimentation and in continues medium is analyzed by UV spectroscopy. [34, 52-56, 60] More accurate estimation can be done by HPLC. The size exclusion chromatography is also very promising tool in the estimation of the drug present in continues medium and loaded in NLC.

14.4. Release of the incorporated drug:

The release of the incorporated drug from the NLC formulation is an important parameter as it is directly related with the therapeutic efficacy and the application potential of the NLC formulation. The detailed drug release mechanism from NLC is still unknown and a good area of investigation. Due to the complex nature of the lipid matrix in NLC make the release complicated in contrast to the release mechanism of SLN where simple diffusion governs the release mechanism. [31, 34, 43, 49, 52-54, 56, 61, 62]

The main problem regarding the determination of release kinetics of the incorporated drug is the burst release. The extent of burst release of the incorporated entirely dependent on the production procedure like hot and cold homogenization. Dialysis bag method is the most applicable method for the release study.[34, 52-56, 60] The released drug can be estimated quantitatively by UV spectrophotometer or by HPLC technique. The release mechanism of the NLC formulations can also studied by analyzing the different release models. DD solver an add-in program is used for the determination of the release formalisms. [34, 52-56, 60]

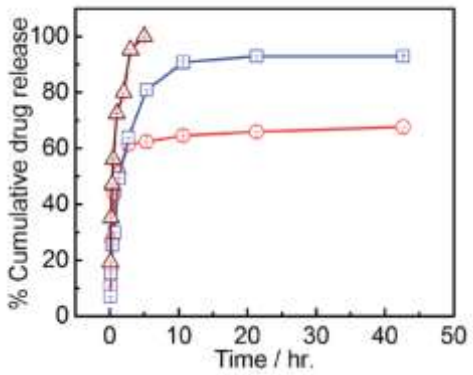

Figure 30. Representative release profiles of incorporated procaine hydrochloride from NLC (Span 65 + SLC + SA, 2:2:1, M/M/M) formulations. [53]

A prolonged drug release is only possible for the NLC system with higher stability and lesser lipidic modification. The release mechanism is also directly related to the nature of the lipid matrix, concentration of surfactant. [31, 34, 43, 49, 52-54, 56, 61, 62] The production parameters are also indirectly govern the release of the drug from NLC system. In case of the NLC formulations, *in vitro* drug release is successfully sustained for five to seven weeks.

The NLC formulations can also show sustained release without having any burst release of the incorporated drug. But the percentage of the burst release and the sustained release can be manipulated according to the application need by modifying the lipid matrix of the NLC formulations. The burst release is important when a higher initial dose of the incorporated drug is warranted. The release profile of the NLC formulations are not directly related with the size of the particle but directly dependent on the shape and morphology of the NLC. The distribution of the incorporated drug between the lipid phase and the aqueous surfactant solution during the production of NLC also regulate the release of the incorporate drug. During production of NLC using hot homogenization, drug molecules get partitioned from the melted lipid phase to the aqueous surfactant solution. The partitioning behavior of the incorporated drug to the aqueous phase is mainly governed by the aqueous solubility of the drug. Higher temperature and high surfactant concentration enhanced the saturation solubility of the incorporated drug in the aqueous surfactant solution medium. However, during cooling after the homogenization process, solubility of the incorporated drug in the aqueous surfactant solution reduces progressively. The reduction in temperature causes the re-partitioning of the drug over the lipid phase of the NLC formulation. After achieving the recrystallization temperature of the lipid matrix, a solid lipid matrix starts forming containing the incorporated drug. After the formation of the crystallized lipid core is unable to incorporate further amount of drug,

The incorporated drug present in the outer shell of the NLC formulation get released in the form of a burst release and the drug incorporated into the core of NLC is released in a prolonged manner. However, the extent of burst release is mainly determined by the solubility of the drug in the aqueous surfactant medium. Higher temperatures and higher amount of surfactant enhanced the burst release. During the production of NLC at room temperature stop the partitioning phenomenon of the incorporated drug into the aqueous medium and subsequent reappearance of the drug in the lipid phase. The productions of NLC at room temperature effectively eliminate the burst release of the incorporated drug. The use of the surfactant having negligible solubility of the incorporated drug is also very effective in effectively eliminating the unwanted burst release of the incorporated drug.

15. Popular routes of administration used for NLC formulations:

The flexibility of the NLC formulations towards all kind of drug and applicability of it in various routes of administration makes it very much advantageous over all popular drug delivery formulations. Protection of the incorporated drug from chemical degradation and prevention of unwanted loss of drug in different routes of administration is admirable for the NLC formulations. Protein type of drugs are generally used for parenteral administration. The traditional oral administration is difficult due to reaction of the drug with enzyme present in the GI path. Due to the degradation of the drug frequent parenteral administration is required since the drug half-lives are also very short. The problems are solved by the development of a efficient parenteral drug carrier system with controlled and prolonged release property. NLC are very useful for parental administration because they are prepared using physiologically tolerated lipids. [44] The NLC formulations are also very important in preventing the drug degradation in the parental route of administration. [20-23, 31, 43]

The use of NLC formulation for the oral drug in case of peptide drugs has concerned considered recent interest among the pharmacists. Controlled release of the incorporated drug from the NLC formulations enables the drug in bypassing the gastric and intestinal degradation of the drug. The stability of the NLC formulation in contact with GI fluid, smaller size and use of the biodegradable material make them very efficient as oral delivery agent. [63] In the oral route, the preferential absorption of the lipid nanoparticles occurs by mucosa present in the intestine.[31, 40, 41, 43]

The use of the NLC formulations as the topical delivery agent is well explored in recent time. The NLC formulations are found to be very effective in the treatment of the infectious skin and found to show the desirable effect of the treated region. Due to the used of the biodegradable and non toxic lipid, they are also non irritant towards the skin.[20, 21, 24, 25, 49, 64]

Lungs are very efficient in adsorbing drugs as they offer high surface area for drug absorption and avoid first-pass problems. Aerosolization of the drugs is a very efficient method for the effective adsorption on the walls of alveoli present in the lung. The preparation of the nebulished NLC is a new and developing area of investigation. NLCs are used as the carrier for anticancer drugs in lung cancer. They also enhanced the bioavailability of the peptide drugs. Nebulized NLC formulations are found to be very successful in improving the performance of

drug in the treatment of pulmonary tuberculosis. They are also very efficient in reducing the dose frequency of the drug. [31, 38, 43, 44, 54]

The NLC formulations are found to be very promising in enhancing the bioavailability of drugs in the ocular rout of administration. The NLC formulations are found to be more efficient than the polymeric nanoparticle used for the ocular delivery of different drugs. Biocompatibility and muco-adhesive characteristics of the NLC formulations improve their efficiency in the ocular path of drug delivery. Prolong release time of the incorporated drug also make the NLC formulation a advantageous delivery agent in the ocular route of administration. [23, 31, 43]

Nasal administration route is a very advantageous route for the delivery of the chemically labile drug having risk of degradation in the other route of administration. NLC formulations with hydrophilic coating are found to be particularly very advantageous for this route of drug administration. Recently PEG coated NLC formulations are studied for the vaccine carrier also. [23, 31, 43]

Rectal administration rout is preferred when rapid pharmacological results are warranted. The efficacies of some drugs are found to be higher in the rectal route of administration in comparison to the orally or intramuscularly administered drug. Diazepam is an successful drug in the rectal administration using NLC.[20-25, 31, 43]

16. Applications of NLCs:

16.1. NLCs as the delivery system for anticancer agent:

There are several available reports on NLC as an anticancer drug delivery agent. It was observed that tamoxifen was successfully incorporated in the NLC systems. Intervenes application of it was found to be advantageous for the breast cancer treatment due to its more permeability and retention effects. Drugs like methotrexate and camtothecin were also successfully incorporated in NLC and used as a targeted delivery for tumors cells. The efficacy of the anticancer drug also found to be enhanced in combination with NLC formulations. The efficacy of doxorubicin was found to enhance by many fold over the cancerous cell lines. [20-25, 31, 43, 53, 65, 66]

16.2. NLCs as anti-tubercular drug delivery agent:

NLC systems were also employed as a successful drug delivery agent for a large number of anti tubercular drugs. It was observed that the dose frequency of some important tubercular drugs was found to reduce in combination with NLC. Drugs like refampicin, isoneazide and pyrazinamide were found to incorporate successfully in NLC and the dose frequency of them were found to decrease to a considerable extent. The NLC formulations were also prevented the drug-drug interaction which is very common for the anti tubercular drugs. The drugs like isoneazide and refampicin was found to show the adverse drug-drug interaction. But in the presence of NLC, considerable reduction in the drug-drug interaction has been reported. Srefampicin was successfully targeted with minimum cytotoxicity and reported safe for *in vivo* applications. [38, 44, 67]

16.3. Some other applications of NLC:

In recent time NLC has come out as a successful drug delivery system for brain targeting. They are very much capable and efficient to carry the drug molecules to the particular portion of human brain without effecting the chemical reactivity and therapeutic efficacy of the drug. It has been proved that chitosen coated NLC systems were very promising in delivering drug in the human brain through the nasal administration route. [31, 43, 44, 66, 67] High penetrating capacity of the NLC through the blood brain barrier and compatibility with all kind of drug makes NLC formulation advantageous in this route of administration. So it is doubt less that in future NLC will become a promising drug delivery agent for brain due to its high penetration capacity and compatibility with wide verity of drugs. [31, 43, 44, 66, 67] NLC systems are also very useful for the topical application. There are a large number of drugs which are successfully used for the topical applications in combination with NLC. The names of some drugs are ketoconazole, tropolide, imidazole, isotretine, etc. not only drugs vitamin A and DNA was also delivered using NLC as delivery for topical formulations.[20-25, 66] NLC has been widely used by many pharmaceuticals company for the preparation of the sunscream containing UV radiation protector. It was proved that, the presence of NLC in the conventional creams was found to enhance the skin hydration to a considerable extent.[20-25, 66]

R**eferences**

References are given in BIBLIOGRAPHY under references for INTRODUCTION (pp. 147-150).