INTRODUCTION

Rapid advances in the ability to produce nanoparticles of uniform size, shape and composition have started a revolution in the sciences. The development of lipid based drug carriers has attracted increased attention over the last years. Solid lipid nanoparticle is 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 the possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could be used for secondary and tertiary level of drug targeting. Hence, solid lipid nanoparticle hold great promise for reaching the goal of controlled and site specific drug delivery and hence has attracted wide attention for researchers.

History of nanoparticle:

During the last 20 years there was only one novel carrier system which can be considered a major innovative contribution in the dermal area, the liposomes first introduced to the cosmetic market by Dior in 1986. After some years, liposomes appeared on the market in pharmaceutical products. Apart from technological benefits, the liposome as a novel carrier found broad attention among the public. At the beginning of the 1990s, the solid polymeric nanoparticles comes which made from non-biodegradable and biodegradable polymers having size range from 10 to 1000 nm which are yet another innovative parenteral carrier system. In the middle of the 1990s, the attention of different research groups has focused on alternative nanoparticles made from solid lipids, the so-called solid lipid nanoparticles (SLN or lipospheres or nanospheres). The SLN combine the advantages of other innovative carrier systems (e.g. physical stability, protection of incorporated labile drugs from degradation, controlled release, excellent tolerability) while at the same time minimizing the associated problems. SLN formulations for various application routes (parenteral, oral, dermal, ocular, pulmonary, and rectal) have been developed and thoroughly characterized in vitro and in vivo.

At the turn of the millennium, modifications of SLN, the so-called nanostructured lipid carriers (NLC) and the lipid drug conjugate (LDC) nanoparticles have been introduced to the literature. These carrier systems overcome observed limitations of conventional. Lipid drug conjugate (LDC) nanoparticles were introduced to overcome the limitation of types of drugs incorporated in the solid lipid matrix. LDC enables the incorporation of both hydrophilic (e.g., doxorubicin and tobramycin) and lipophilic (e.g., progesterone and cycloporsine A) drugs.

LIPID DRUG CONJUGATE (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.

ABSTRACT:

Nanotechnology by manipulation of characteristics of materials such as polymers and fabrication of nanostructures is able to provide superior drug delivery systems for better management and treatment of diseases. The nanostructures employed as drug delivery systems have multiple advantages which make them superior to conventional delivery systems. Nanotechnology is one approach to overcome challenges of conventional drug delivery systems based on the development and fabrication of nanostructures. Some challenges associated with the technology as it relates to drug effectiveness, toxicity, stability and pharmacokinetics and drug regulatory control. Nanotechnology is a welcome development that is set to transform drug delivery and drug supply chain management, if optimally developed. 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.

Key words: Nanotechnology, Nanoparticle, LDC, SLN, Nanocarriers, Nanostructures, NLC
serious protozoal infections. Structure of LDC is shown in figure 1.

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 salts such 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. 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.9,10

SURFACANTS USED IN LDCs

There are different types of surfactants which are used in the preparation of Lipid Drug Conjugates. To achieve and maintain a lipid drug conjugate upon administration, the lipid nanoparticle’s melting point must exceed body temperature (37 °C). High melting point lipids investigated include tricaprylin glycerol (triglycerides), acylglycerols, fatty acids, steroids, waxes, and combinations thereof. Surfactants investigated include biological membrane lipids such as lecithin, bile salts such as sodium taurocholate, and biocompatible nonionic such as ethylene oxide/propylene oxide copolymers, sorbitan esters, fatty acid ethoxylates, and mixtures thereof.

Influence of the emulsifiers/surfactants

The concentration of the surfactant/surfactant mixture strongly affects the particle size of the lipid nanoparticles. In general, smaller particle sizes were observed when a higher surfactant/lipid ratio was chosen. The decrease in surfactant concentration resulted in increase of particle size during storage. Surfactants decrease the surface tension between the interface of the particles causing portioning of the particles and thereby increasing the surface area.

METHODS OF PREPARATION

Lipid Drug Conjugates are prepared from lipid, emulsifier, surfactant and water/solvent by using different methods and are discussed below.

- High pressure homogenization
- Hot homogenization
- Cold homogenization
- Ultra sonication/high speed homogenization
- 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

High pressure homogenization (HPH):

It is a reliable and powerful technique, which is used for the production of LDCs. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 Km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but up to 40% lipid content has also been investigated.

Two general approaches of HPH are hot homogenization and cold homogenization work on the same concept of mixing the drug in bulk of lipid melt. Hot homogenization: Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device. HPH of the pre-emulsion is carried out at temperatures above the melting point of the lipid. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles.

Cold homogenization: Cold homogenization has been developed to overcome various problems associated with hothomogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, Complexity of the crystallization step of the nanoemulsion leading to several modifications and super cooled melts. In this technique the drug containing lipid melt is cooled, the drug lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles.

Advantages
- Low capital cost.
- Demonstrated at lab scale.

Disadvantages
- Energy intensive process.
- Demonstrated at lab scale Biomolecule damage.
- Polydisperse distributions.
- Unproven scalability.

Ultra sonication/high speed homogenization

LDCs are also prepared by ultra sonication or high speed homogenization techniques. For smaller particle size combination of both ultra sonication and high speed homogenization is required.

Advantages
- Reduced shear stress.

Disadvantages
- Potential metal contamination.
- Physical instability like particle growth upon storage.

Solvent evaporation

LDCs can also 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).
**Advantages**
- Scalable
- Mature technology
- Continuous process
- Commercially demonstrated

**Disadvantages**
- Extremely energy intensive process.
- Polydisperse distributions.
- Biomolecule damage.

**Solvent emulsification-diffusion method**
The particles with average diameters of 30-100 nm can be obtained by this technique. Voidance of heat during the preparation is the most important advantage of this technique.

**Supercritical fluid method**
This is an alternative method of preparing LDCs by particles from gas saturated solutions (PGSS).

**Advantages**
- Avoid the use of solvents.
- Particles are obtained as a dry powder, instead of suspensions.
- Mild pressure and temperature conditions.
- Carbon dioxide solution is the good choice as a solvent for this method.

**Microemulsion based method**
This method is based on the dilution of microemulsions. As micro-emulsions are two-phase systems composed of an inner and outer phase (e.g. o/w microemulsions). They are made by stirring an optically transparent mixture at 65-70°C, which typically composed of a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. LDC dispersion can be used as granulation fluid for transferring in to solid product (tablets, pellets) by granulation process, but in case of low particle content too much of water needs to be removed.

**Advantages**
- Low mechanical energy input.
- Theoretical stability.

**Disadvantages**
- Extremely sensitive to change.
- Labor intensive formulation work.
- Low nanoparticle concentrations.

**Spray drying method**
It is an alternative technique to the lyophilization process. This recommends the use of lipid with melting point more than 70oC. The best results were obtained with LDC concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture.

**Double emulsion method**
Here the drug is encapsulated with a stabilizer to prevent the partitioning of drug in to external waterphase during solvent evaporation in the external water phase of w/o/w double emulsion.

**Precipitation method**
The glycerides are dissolved in an organic solvent (e.g. chloroform) and the solution will beamulsified in an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated forming nanoparticles.

**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 LDC with the little and uniform particle size is formed.

**Characterization of quality and structure 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.

**Measurement of particle size and zeta potential**
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). Smaller particles cause more intense scattering at high angles compared to the larger ones. The development of polarization intensity differential scattering (PIDS) technology greatly enhanced the sensitivity of LD to smaller particles. LD and PCS detect light scattering effects which are used to calculate particle size. Further, difficulties may arise both in PCS and LD measurements for samples which contain several populations of different size. Therefore, additional techniques might be useful. For example, light microscopy is recommended, although it is not sensitive to the nanometer size range. It gives a fast indication of the presence and character of microparticles. Electron microscopy provides, in contrast to PCS and LD, direct information on the particle shape. Zeta potential is an important product characteristic of LDCs since its high value is expected to lead to deaggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. It is usually measured by zetameter.

**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. This function is fit to an exponential, or some combination or modification thereof, with the corresponding decay constant(s) being related to the diffusion coefficient(s). The advantages of the method are the speed of analysis, lack of required calibration, and sensitivity to submicrometer particles.

**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.
Acoustic methods
Another ensemble approach, acoustic spectroscopy, measures the attenuation of sound waves as a means of determining size through the fitting of physically relevant equations. In addition, the oscillating electric field generated by the movement of charged particles under the influence of acoustic energy can be detected to provide information on surface charge.

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.

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. 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.

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.

STERILIZATION OF LDCs
Sterilization of LDCs is an issue in the case of pulmonary or parenteral administration. Intravenous and ocular administration LDC must be sterile. The high temperature reach during sterilization by autoclaving causes a hot o/w micro emulsion to form in the autoclave, modifies the size of the hot nano droplets. On subsequent slow cooling, the LDC reformed, but some nano droplets may coalesce, producing larger LDC than the initial ones. Amounts of surfactant and co surfactant present in the hot system are smaller. There for the nanoparticles are not stabilized. Autoclaving at 121°C cannot be performed when using sterically stabilizing polymers, e.g. poloxamer series. The autoclaving temperature seems to be too close to the critical flocculation temperature (CFT) of the polymers, at least the polymer adsorption layer seems partially to collapse leading to insufficient stabilization and particle aggregation. This can be avoided by reducing the autoclaving temperature (e.g. 121°C to 110°C, but simultaneously prolonging the autoclaving time).

To sum up, SLN dispersions can be sterilized or prepared aseptically using already established techniques in the pharmaceutical industry.

ROUTE OF ADMINISTRATION
LDCs are given by following route of administration
1. Oral administration.
2. Parenteral administration.
3. Transdermal application.

Oral administration:
Forms of LDCs preparation which are given by oral route are aqueous dispersions. LDCs loaded dosage form such as tablets, pellets and capsule. The microclimate of the stomach favors particle aggregation due to the acidity and high ionic strength. It is to be expected that food will have a large impact on LDC performance.

Parenteral administration:
LDCs generally administered intravenously to animals. Distribution of LDC was found to have higher drug concentrations in lung, spleen and brain, while the solution led to more distribution into liver and kidneys. LDC showed higher blood levels in comparison to a commercial drug solution after intravenous.

Transdermal application:
The smallest particle sizes are observed for LDC dispersions with low lipid content (up to 5%). Disadvantages of dermal administration are low concentration of the dispersed lipid and the low viscosity. The incorporation of the LDC dispersion in an ointment or gel is necessary in order to achieve a formulation which can be administered to the skin.

ADVANTAGES OF LIPID DRUG CONJUGATE
The lipid drug conjugate nanoparticles are having lots of advantages in nanoparticulate drug delivery system which are outlined below:

- Incorporation of both lipophilic and hydrophilic drugs.
- Feasibilities of carrying both lipophilic and hydrophilic drugs.
- Control and/or target drug release.
- No bio-toxicity of the carrier.
- Excellent biocompatibility.
- Improve stability of pharmaceuticals.
- High and enhanced drug content.
- Easy to scale up and sterilize.
- Better control over release kinetics of encapsulated compounds.
- Enhanced bioavailability of entrapped bioactive compounds.
- Easier to validate and gain regulatory approval.
- Chemical protection of labile incorporated compounds.
- Much easier to manufacture than biopolymeric nanoparticles.
- No special solvent required.
- Conventional emulsion manufacturing methods applicable.
- Very high long-term stability.
- Application versatility.
- Can be subjected to commercial sterilization procedures.

DISADVANTAGES OF LIPID DRUG CONJUGATE
Although the lipid drug conjugate has various advantages, it has also some common disadvantages which are as follows:

- Particle growth.
- Unpredictable gelation tendency.
- Unexpected dynamics of polymeric transitions.
Lipid Drug Conjugates (LDCs) form the basis of colloidal drug delivery systems, which are biodegradable and capable of being stored for at least one year. There are several pharmaceutical applications of LDCs, some of which are given below:

**LDC nanoparticles as novel carrier system for the hydrophilic antitrypanosomal drug diminazenediaceturate**

The hydrophilic drug diminazenediaceturate at a high loading is incorporated into lipid nanoparticles by creating nanoparticles from lipid-drug conjugates (LDC). Due to the composition of the LDC bulk materials, nanoparticles with a high drug load of 33% (w/w) were obtained even for this highly water-soluble drug diminazenediaceturate. Transforming water-soluble hydrophilic drugs into LDC and formation of nanoparticles allows prolonged drug release and targeting to specific sites by IV injection. These results provide a first basis of using LDC-polyborate 80 nanoparticles for brain delivery of dimazene to treat second stage human African trypanosomiasis (HAT).

**LDC nanoparticles as cosmeceuticals**

The LDCs have been applied in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers. The in vivo study showed that skin hydration will be increased by 31% after 4 weeks by addition of 4% LDC to a conventional cream. Better localization has been achieved for vitamin A in upper layers of skin with glyceryl behenate LDCs compared to conventional formulations.

**LDCs in breast cancer and lymph node metastases**

Mitoxantrone-loaded LDC local injections were formulated to reduce the toxicity and improve the safety and bioavailability of drug. Efficacy of doxorubicin (Dox) has been reported to be enhanced by incorporation in LDCs. In the methodology the Dox was complexed with soybean-oil-based anionic polymer and dispersed together with a lipid in water to form Dox-loaded solid lipid nanoparticles. The system is enhanced its efficacy and reduced breast cancer cells.

**LDCs as a targeted carrier for anticancer drug to solid tumors**

LDCs have been reported to be useful as drug carriers to treat neoplasms. Tamoxifen, an anticancer drug incorporated in LDC to prolong release of drug after IV administration in breast cancer and to enhance the permeability and retention effect. Tumour targeting has been achieved with LDCs loaded with drugs like methotrexate and camptothecin.

**LDC as potential new adjuvant for vaccines**

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 LDCs will be degraded more slowly providing a longer lasting exposure to the immune system.

**CONCLUSION**

Lipid based nanocarriers have the greater importance in the developing field of nanotechnology with several advantages apart from various carriers. Lipid based carriers are a promising nanoscaler delivery system for the pharmaceutical industry. In the early days of the 20th century, Paul Ehrlich envisioned his magic bullet concept; the idea that drugs reach the right site in the body, at the right time, at right concentration. It should not exert side effects, neither on its way to the therapeutic target, nor at the target site, nor during the clearance process. The LDCs have the potential to achieve, at least partially, these broad objectives. Apart from these, the regular objective of controlled drug delivery is aptly achieved with LDCs. We can expect many patented dosage forms in the form of LDCs in the future.

**REFERENCES**

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**Fig 1:** structure of Lipid drug Conjugate

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