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A Review Article on Characterization of Solid Lipid Nanoparticles

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ABSTRACT:
Nanoparticles has got an increasing attention in various therapeutics and diagnosis purposes. Different types of nanoparticles like lipid-based nanoparticles, polymeric nanoparticles, metal nanoparticles, ceramic nanoparticles etc has been used as drug carriers to improve the efficacy of various drugs. In Nanopartciles, Solid Lipid Nanoparticles (SLN) has got increasing attention for promoting the advantages and excluding the disadvantages of the colloidal carriers. SLNs consists of solid lipid core made up of phospholipid shell with single layer. The core contains the dispersion of drug in high melting fat matrix. The chains of the phospholipids are enclosed in the fat matrix. One of the main production technique for preparing SLNs are High pressure homogenization and ultrasound method. The Present study outlines about the characterization of the Solid-lipid nanoparticles like particle size, surface morphology, Polymorphism, Degree of crystallinity, In-vitro drug release studies, Storage stability and Drug incorporation.
Keywords : solid lipid nanoparticles, polymorphism, high pressure homogenization

INTRODUCTION :

In Recent years, Therapeutic failure had become the common problem. One of the main reasons for the therapy failure includes:

1) Higher plasma level fluctuations are seen due to interaction of food inside the body upon oral administration
2) Lower Drug Solubility
3) Poor Oral absorption, more rapid metabolism etc leading to insufficient drug concentration

Development of drug carrier systems excludes these kind of problems.The invivo behaviour of the drug is not determined by the actual drug which is administered, but it is determined by the carrier system, which promotes the controlled, localized release of active ingredient. The carrier size depends on the mode of administration and also size ranging from nanometers to micrometer range. A best example for localized drug release is implants which are biodegradable used for the treatment of various diseases and also targeted to the specific tissue as desired. Other systems like nanoparticles, liposomes, nano suspensions, nano emulsions etc is used as colloidal carriers.

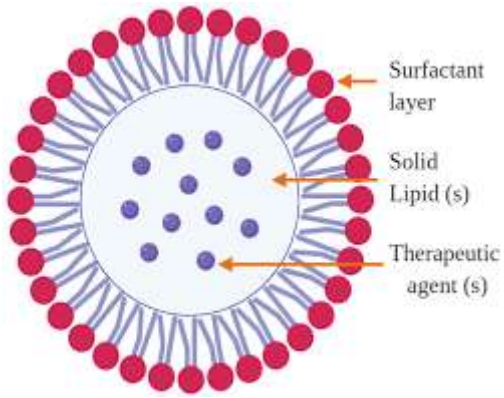

Fig 1 ; Structure of Solid lipid nanoparticle

In Nanopartciles, Solid Lipid Nanoparticles (SLN) has got increasing attention for promoting the advantages and excluding the disadvantages of the colloidal carriers. SLNs consists of solid lipid core made up of phospholipid shell with single layer. The core contains the dispersion of drug in high melting fat matrix. The chains of the phospholipids are enclosed in the fat matrix {1}. One of the main production technique for preparing SLNs are High pressure homogenization method. Another method for producing SLNs are ultrasound method.

ADVANTAGES:
1) Enhanced drug content
2) Higher Biocompatibility

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3) Enhanced stability of pharmaceuticals
4) Easy Manufacturing Process
5) Organic Solvents are avoided{1}
6) Less Toxic Lipids are used compared to other polymeric nanoparticles
7) Drug targeting is possible
8) Toxicity of the carrier can be avoided

DRAWBACKS :

1) Unwanted particle growth is observed
2) Drug Loading Capacity is very low
3) Drug degradation is possible due to high pressure
4) Gelation tendency is unpredictable
5) Higher water content is observed in dispersions
6) Possibility of drug expulsion during crystallization process.
7) Intial burst release
8) Unexpected polymeric transitions

CHARACTERIZATION OF SLNs :

Characterization is mandatory for the quality control of SLNs. Complexity, Colloidal size of the particles and nature of the delivery system is a promising challenge for the characterization of the SLNs. Various Important Parameters influence the stability and the release pattern of the solid lipid nanoparticles. They are Particle Size, Zeta potential, Polymorphism, Drug content, In-vitro drug release, Surface morphology etc

1) Particle Size:

Photo Correlation Spectroscopy and Laser Diffraction are mostly commonly used tools for the measurements of particle size. Photon Correlation Spectroscopy measures fluctuations in the intensity of the scattered light caused by the movement of the particle. This method covers the size from nanometers to 0.3 microns. The disadvantage about photon correlation spectroscopy is, it is unable to detect the larger microparticles. This problem can be overcome by visualizing the LD measurements.The laser diffraction technique is basically dependence of the angle diffracted on the particle radius. LD measures the size range of 40nm to 2000 micrometers. One major disadvantage of this technique is it's difficulty to measure the size of the non-spherical molecules. Another developed method to enhance the sensitivity of Laser Diffraction towards smaller particles is polarization intensity differential scattering (PIDS) .{1}

By another method, cryo-FESEM the microstructural pattern of the dispersion can be easily determined. In this method, liquid dispersion is frozen and seen in the frozen state. This method determines the spherical droplets in nanometer range. The cryo-FESEM shows the results similar to that LD and PCS.{1}

Almost every particle in interaction with liquid must attain electric charge on their surface. The electric charge at the shear plane is known as zeta potential. Zeta potential is a useful tool to predict and control the stability of colloidal systems. As the zeta potential increases, the suspension becomes stable because the charged molecules repel each other and eliminate the natural tendency to aggregate. The storage stability of the colloidal system can be determined by the zeta potential measurements. Currently, it is accepted that zeta potentials under 30 mV, Optimum 60 mV are required for electrostatic stabilization.

Coulter Counter Method (CC Method) is also the mostly used technique for determining the particle size.. It works based on the principle of measuring the change in the electro resistance with in the sensing zone when a solution of electrolyte is moved through. The CC Method is used because of the tiny particle size of SLN and Need for electrolytes which usually destabilizes the system .

Recently developed technique, field flow fractionation (FFF) is worked on the separation principle in which the particles are placed on perpendicularly applied field in a laminar flow. Different type of FFF like sedimentation FFF, charge FFF or cross flow FFF and even the combination of all these, can give better results.

2) Polymorphism and Degree of lipid Crystallinity :

Polymorphism is defined as the ability of crystal or an object to exist in different forms. It is the one of the degradation pathway which the effects the stability of the dosage units, because as their chemical properties are same, but they differs in thermodynamic factors like MP, Solubility etc{2}

The modification and the degree of Crystallinity of the lipid are highly important for characterization because they are correlated with the drug incorporation and rate of release. The lipid modification can be determined by X-ray

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diffraction patterns, They are identified by plotting the intensity vs scattering vectors such as modification of glycerol lipid side chain with single scattering reflex at Bragg distance of 0.415 nm is known as alpha-modification, modification with more than one reflex i.e; two reflex of 0.389 nm and 0.420 nm bragg distances is known as beta' – modification and lastly, modification which doesn't meet the above criteria is known as beta-modification. {2}

3) In-vitro drug release studies :

Release profile of drug active substance can be led in dialysis tubing. In dialysis, the solid lipid nanoparticles are taken into pre washed dialysis tubing, which is hermetically sealed and then dialyzed against disintegration media at constant temperature with steady mixing. Tests were taken at different circumstances, mixed or centrifuged and measured for the medication.{2} This method is not enough to determine the rapid discharge rate of medication from the colloidal carriers.

Methods used to study the invivo release of drug are:

- Dialysis bag diffusion technique.
- Reverse dialysis bag technique.

4) Storage Stability :

The Solidness of the SLNs can be controlled by checking changes in the particle size, viscosity and appearance. These parameters can be determined by Thin layer chromatography. Other parameters like light and temperature is important for longterm steadiness.{1}

At 50°C – Faster particle size development was observed.

At 20°C – Upon long term storage, loss of medication was observed.

4°C- Positive Stockpiling Temperature.

The Zeta potential greater than 60mV for scattering to remain steady physically.

5) Drug Incorporation and Entrapment Efficiency :

It is very important to determine the amount of drug incorporated in solid lipid nanoparticles, since it affects the release characteristics. The amount of drug encapsulated is determined, when free drug and solid lipids are separated from the aqueous medium. This kind of separation can be done by filtration, gel permeation chromatography and centrifugation. Various filters like Ultra free-MC, Ultrasart-10 are used for centrifugation filtration. The degree of encapsulation is measured by determining the supernatant after filtration of solid lipid nanoparticle suspension or by dissolving the sediment in a suitable solvent and subsequent analysis. Different analytical methods such as HPLC, Liquid Scintillation counting can be used to assay the drug.

The lipid Crystalline structure is a key parameter to determine that a drug is expelled or incorporated into carrier. In the structure of nanoparticle, lipid forming crystals with regularly arranged lattice will cause drug expulsion. On the other side, the defects of lattice in lipid structure could help in drugs accommodation. As a result, the beneficial factor to drug loading capacity will be the less ordered lattice arrangement in structure of nanoparticles.

Higher drug entrapment efficiency is one of the major advantage of solid lipid nanoparticles. The Entrapment efficiency (EE) is usually determined by spectroscopic method after the centrifugation of aqueous dispersion. The EE can be calculated by the equation :

$$EE\ (\%) = \frac{W_{\text{initial drug}} - W_{\text{free drug}}}{W_{\text{initial drug}}} \times 100$$

Where, the W initial drug is mass of initial drug used for assay and W free drug is the mass of free drug detected in supernatant after centrifugation of aqueous dispersion. More than 90 percent of the EE% was reported for SLNs are prepared by shear homogenization and ultra sonication which showed long term stability upon storage for one month.

Larger number of drugs loaded with SLNs were prepared and their EE % is compared. Few examples of drugs prepared by different methods :

Siu, et al. measured Entrapment Efficiency and size of Insulin loaded SLNs which is prepared by double emulsion technique by changing the Stabilizer (Poloxamer 188) and Surfactant (Sodium Cholate) concentrations. The final results have shown that by increasing the concentration of surfactant by 0.05% (w/v) resulted in particle size reduction and EE enhancement . Later Zang, et al, Prepared the insulin loaded SLNs by both solvent emulsification evaporation method and microemulsion techniques and it was found that, compared to micro emulsion technique, the SLNs prepared by solvent emulsification evaporation method showed higher EE of 68%.

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6) Surface Morphology:

Direct observation of nanoparticles can be done by Scanning electron microscopy and Transmission electron microscopy methods. Surface morphology observation can be done more effectively by scanning electron microscopy.

7) Nuclear Magnetic Resonance (NMR) :

Both the Qualitative nature and the size of nanoparticles are determined by NMR. The Physicochemical status of the molecules with in the nanoparticles can be understood with molecular mobility by NMR.

APPLICATIONS :

1) SLNs acting as Cosmeceuticals:

In recent years, Cosmeceuticals had become the major application for these carriers. Solid lipid nanoparticles were prepared to meet the specific needs of manufacturing units like qualification, validation, low cost etc.{4}

SLNs are used as active carrier for UV blockers. Better Therapeutic effect is shown on skin layers when SLNs are formulated with glyceryl behenate. A Recent invivo study showed that the skin hydration is induced by 31% when 4% SLNs is added to the conventional cream and also SLN have shown the promising controlled release action when used as occlusive topicals.

2) SLN as adjuvants in vaccination:

In several immune deficiency disorders, adjuvants in vaccines play an important role in immunization to enhance the immune response. Several new vaccines are not so effective in immunization. Therefore, adjuvants are required. Best example is Lipid components of solid lipid nanoparticles in solid state will degrade more slowly thus, providing a longer exposure to the immune system.

3) SLPs for ultrasonic drug & gene delivery :

Ultrasonic sound release the drug from the micelles by shear stress & shock waves.SLP are used in ultrasonic drug delivery into invivo and Invitro studies. Smaller packing of SLPs allows to extravasate drug into tumor tissue

4) SLNs in TB Chemotherapy :

Anti-TB Drugs like Pyrazinamide, Rifampicin loaded with SLN were able to decrease the dosing frequency. Anti-TB drug loaded with SLNs were prepared using solvent diffusion method.{4}

5) SLNs for topical use:

Therapeutic agents like corticosteroids used in the treatment of psoriasis (skin diseases). SLNs products applied for topical use helpful in targeting corticosteroids to specific dermal sites there by, decreasing the drug absorption. The Flurbiprofen loaded SLN , Isoretinoin loaded SLN gels used for topical application. Doxorubicin used to target the dermal sites will produce higher tissue concentrations.

6) SLNs in diabetes :

Diabetes is one of the most common metabolic disease which causes hyperglycemia due to insulin deficiency. Several proteins and proteins are protected by SLNs acting as carriers. Octaarginine is a peptide which can penetrate into cell and helpful in the facilitation of cellular uptake of few drugs in treating diabetes. The octaarginine loaded with SLN had proven to show sufficient hypoglycemic effect(3 Fold increase) in rats.

7) SLNs as a targeted carrier for cancer therapy :

SLNs used as drug carriers to treat Neoplasms. Ramoxifen, an anti tumor drug loaded in SLN used to promote the drug release upon i.v. administration in breast cancer and will induce the permeability effect

List of Examples of drugs developed using solid lipid nanoparticle technology.

Drug	Lipid used	Applications
5-Fluoro uracil	Dynasan 114 and Dynasan 118	Prolonged release in simulated colonic media
Calcitonin	Trimyristin	Improvement of efficacy of proteins
Idarubicin	Emulsifying Wax	Delivery of oral proteins
Lopinavir	Campritol 888 ATO	Bioavailability Enhanced
Tetracycline	Glycerylmonostearate and stearic acid	Sustained release

MARKETED PRODUCTS :

S.NO	BRAND NAME	DRUG	USES	MFG COMPANY
1	FLAGFOL	Propofol	Anaesthetic	FLAGSHIP

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			agent	BIOTECH INTERNATIONAL PVT LTD.
2	DIAZEMULUS	Diazepam	Reduce Muscle spasm	RL FINE CHEM CHEM LTD
3	LIMETHASONE	Dexamethasone-sulfate	NSAIDS	LI BIOPHARMA
4	FLUOSOL-DA	Fluosol	For Coronary Antiplastry Treatment	GREEN CROSS OF JAPAN
5	AMIDATE	Etomidate	Anesthetic Agent	BACHEM

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