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A REVIEW ON SOLID LIPID NANO PARTICLES (SLN'S)

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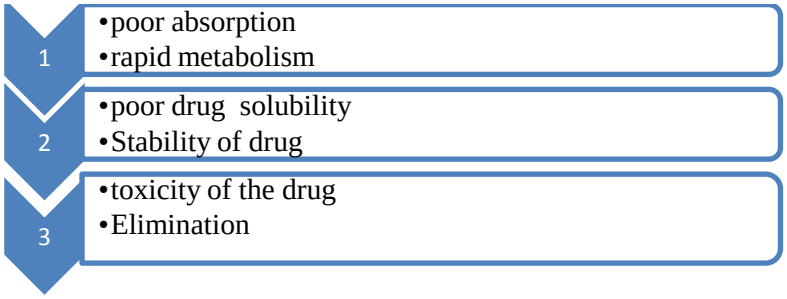
ABSTRACT

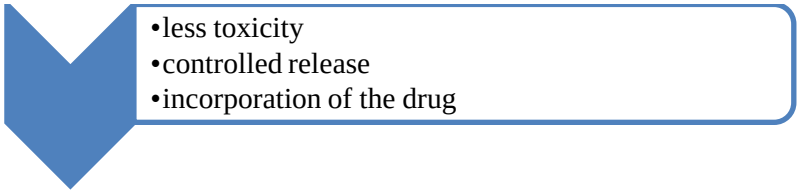
SLN are introduced in 1991 as an alternative carrier system for traditional colloidal carriers, such as liposomes, emulsions and polymeric micro and nanoparticles. A solid lipid nanoparticle is typically spherical with an average diameter between 10 to 1000 nanometers. Solid lipid nanoparticles have a lipoid core it can solubilize both the lipophilic and hydrophilic drugs. The lipid core is stabilized by surfactants (emulsifiers). The term lipid is used here in a broader sense and includes triglycerides (e.g. tristearin), diglycerides (e.g. glycerol behenate), monoglycerides (e.g. glycerol monostearate), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol), and waxes (e.g. cetylpalmitate). Development of the the solid lipid nanoparticles is an emerging field as it has large number of advantages in the delivery of drugs to the various sites in the body. The article gives a brief view on the solid lipid nanoparticles and its evaluation.

INTRODUCTION [1, 4, 5]

Nanoparticles are an emerging field in the delivery of the drugs to the various sites in the body as it provides a large number of advantages in the delivery at the required site. The term nanoparticles means the particle size in the range of about 1-1000nm.Solid lipid nanoparticles is a recently developed field it almost came existence in 1991 as in the forms of the liposomes, emulsions. Solid lipid nanoparticles are the colloidal particles in the size range of 1-1000nm consisting of the lipid core surrounded by the Phospholipid layer it leads to proper targeting of the drug.[1,2,4] As the number of the drugs is increasing in the market there is problem with each and every molecule so there is a need for an proper dosage form to deliver the drug to the required site.Nanopartilces are developed to overcome the following problems:



The solid lipid nanoparticle involves the use of the lipid for the incorporating of the drug in the lipoid core which offers a large number of advantages as:[2]



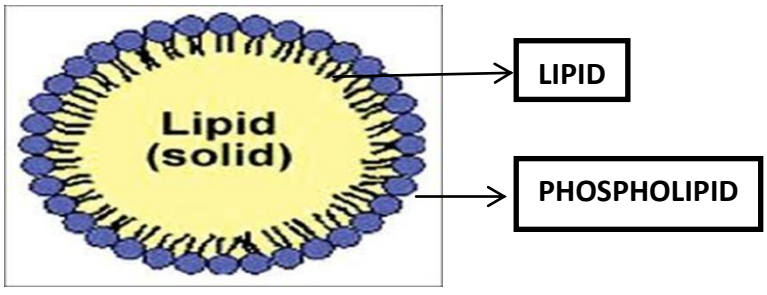
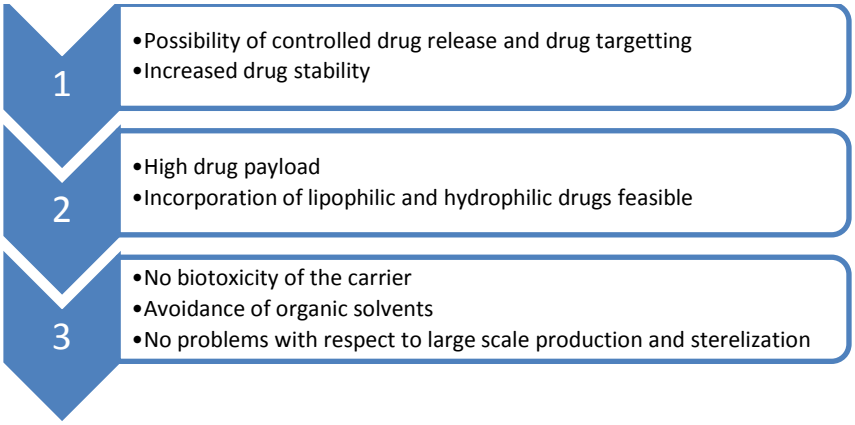


Fig 1: Structure of SLN

Aims of solid lipid nanoparticles:

It is stated that nanoparticles as being colloidal in nature provide the advantages and disadvantages of different colloidal carriers. Proposed advantages include:



Advantages:[7]

- Control or target drug release.
- Excellent biocompatibility.
- Improve stability of pharmaceuticals.
- Enhanced bioavailability of entrapped bioactive compound.
- Chemical protection of labile incorporated compounds.
- No special solvent is required.
- Lyophilisation is possible.
- Easy to scale up production than polymeric nanoparticles.
- Can be subjected to sterilization
- Small size and relatively narrow size distribution.
- Easier to validate and gain regulatory approval.

Disadvantages: [11]

- Particle growth
- Poor drug loading capacity
- Particle growth is observed during storage
- Uncertain gelation tendency

SLN production procedures:

Generally the SLN consist of the lipid and the emulsifiers and water. The term lipid is used here in a broader sense and includes triglycerides (e.g. triestearin), partial glycerides (e.g. Imwitor), fatty acids (e.g. stearic acid), and steroids (e.g. cholesterol) waxes (e.g. cetylpalmitate). All emulsifiers play an important role in the stabilizing of the lipoid dispersion.There is a clear advantage in the SLN as there is use of the lipids which is obtained from the various biological sources and offers no toxicity.

Excipients used in the formulation of SLNs:[34]

Lipid matrices: Bees wax, Behenic acid, Caprylic acid, cetylpalmitate, Cholesterol, Glycerylmonostearate, Glyceryltrilaurate, Glyceryltristearate, Glyceryltrimyristate, Glyceryltripalmitate, Glycerylbehenate, Hardened fat, Stearic acid, Solid paraffin, Softisan142.

Emulsifiers: Phosphatidyl choline 95%, Soyalecithin, Egg lecithin, Poloxamer188, Poloxamer 407, Polysorbate 80.

Coemulsifiers: Tyloxapol, Taurocholate sodium, Taurodeoxycholic acid sodium salt, Sodium dodecyl sulphate, Sodium glycholate, Sodium oleate, Cholesterylhemisuccinate.

Cryoprotectants: Trehalose, Glucose, Mannose, Maltose, Lactose, Sorbitol, Mannitol, Glycine, Polyvinyl pyrrolidine, Gelatin.

Chargemodifiers: Stearylamine, Diacetyl phosphate dipalmitoylphosphatidylcholine (DPPC)

SLN Preparation: [11, 12, 13]

1. **HighPressure Homogenization Technique**

High shear homogenization technique was initially used for the solid lipid nanodispersions (Domb, 1993). HSH method is used to produce SLN by melt emulsification. Homogenization is a fluid mechanical process that involves the subdivision of droplets or particles into micro- or nanosize to create a stable emulsion or dispersion.Ahlin et al. used a LakTek rotor–stator homogenizer (Omni International, Gainesville, USA) to produce SLN by melt-emulsification. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of few microns) lipids used in this study include trimyristin, tripalmitin, a mixture of mono, di and triglycerides (Witepsol W35, Witepsol H35) with glycerylbehenate and polaxomer 188 used as stearic stabilizers (0.5%w/w). HPH method involves 2 processing procedures (Mukherjee). They are

a. Hot homogenization, b. Cold homogenization

A.**Hothomogenization**: [13]

This is applied to lipophilic and insoluble drugs. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device (like silversion-type homogenizer).The homogenizer reduces the particle size .The lipid is firstly melted at melting temperature of the specific lipid then the incorporation of the drug is done in the lipid this becomes the organic phase. The aqueous phase is prepared by dissolving the surfactant and cosurfactant in water. Then the aqueous phase is suspended in the organic phase and then it kept for homogenization at a required RPM and for a specific

time. Then the obtained solution is cooled on an ice bath or at room temperature which leads to the formation of solid lipid nanoparticles. The disadvantages of this method are, high temperature shell may doctorate drug content.Ocassionally about 3-5 homogenization cycles at various pressure utilized.

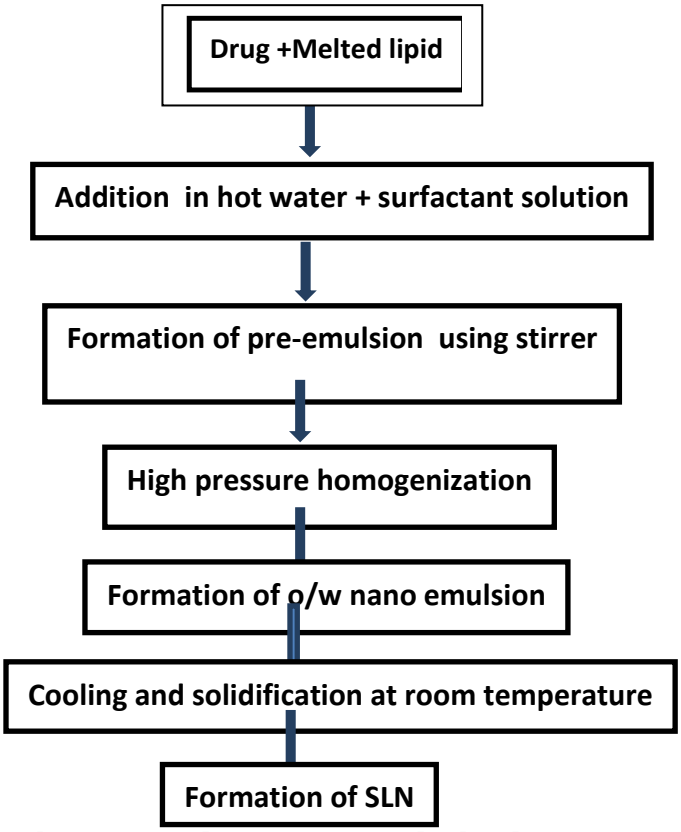


Fig 2: solid lipid nanoparticles preparation by hot homogenization method.

B.**Cold homogenization**:

Cold homogenization is being developed to overcome the temperature problems related degradation problems, loss of drug into aqueous phase and partitioning associated with hot homogenization method. Cold homogenization is carried out with the solid lipid containing drug and therefore called milling of a suspension. First step in between cold and hot homogenization is same but they are differing from next steps. The first step of preparation involves the melting of the lipid and incorporation of the drug in melted lipid. Then, the lipid drug mixture is rapidly cooled by using liquid nitrogen or dry ice to convert it to solid state. The mixture obtained is milled by the means of mortar or ball mill to a micron size and then is suspended into emulsifier solution to yield a pre-emulsion. This pre-emulsion is suspended to high pressure homogenization at room temperature or below the room temperature this action acts as strong field in the breaking of the micro particles to SLN's. The method of cold homogenization minimizes the thermal exposure of the sample does not avoid it due to the melting of the lipid / drug-mixture in the initial step.

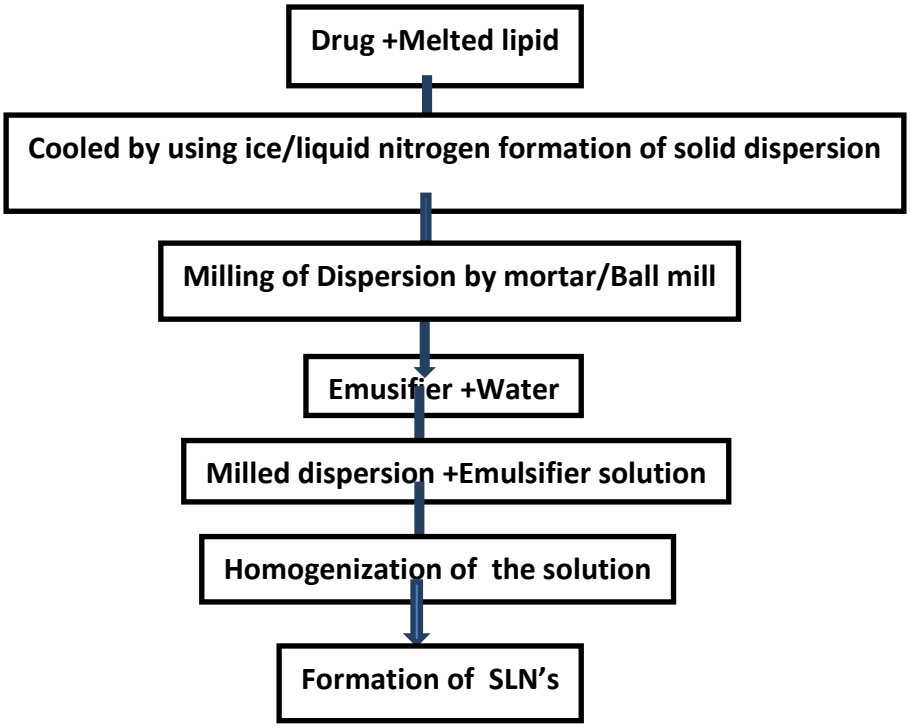


Fig 3: Solid lipid nanoparticles preparation by cold homogenization technique.

2. **Solvent evaporation method**

Sjo¨stro¨m and Bergenst°ahl described a production method to prepare nanoparticle dispersions by precipitation in o/w emulsions. Solvent evaporation method involves the use of the water immiscible organic solvent (e.g. Cyclohexane).The method involves the dissolving of the lipophilic material and the sample in the water immiscible organic solvent which later on dispersed in the aqueous phase, then it is subjected to high pressure homogenization .The organic solvent was removed by evaporation of the solvent ate the required temperature .The obtained particle size of 25nm mean size.

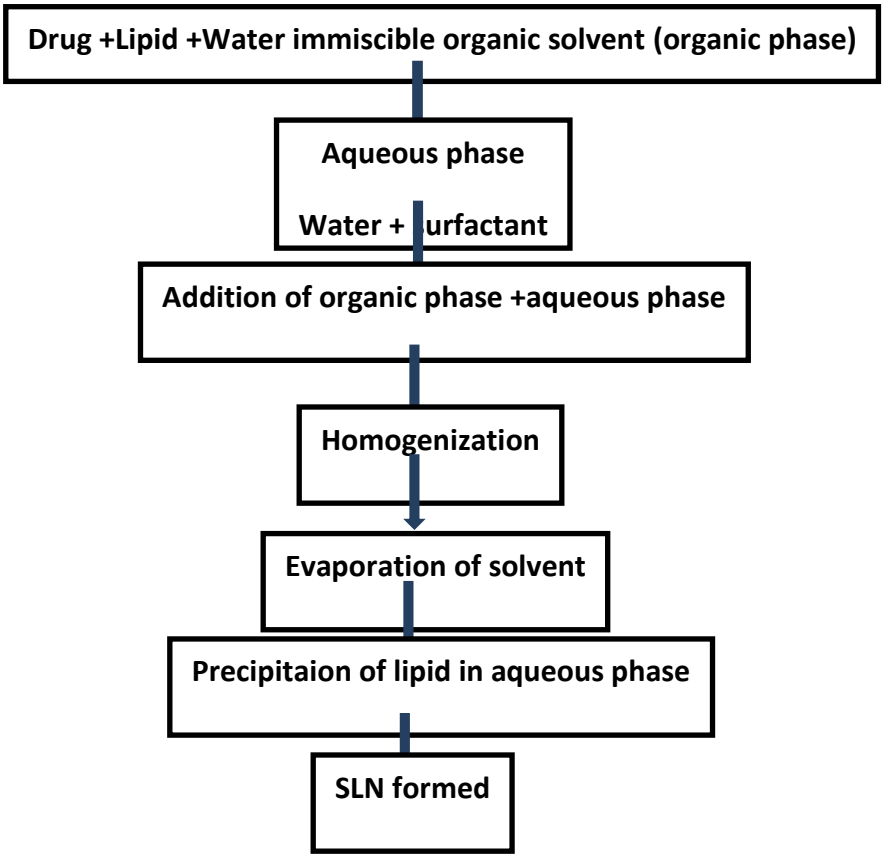


Fig no.4: Solid lipid nanoparticles preparation by solvent evaporation method

3. **Micro emulsion based method**:

Gasco and company (1997) developed SLN'S based dilution micro emulsion. They are made by stirring an optically transparent mixture at 65-70 0 which is typically composed of a low melting fatty acid(stearic acid), an emulsifier (polysorbate 20,polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers(sodium monooctylphosphate) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring (Waghmare et al., 2012). Typical volume ratios of the hot microemulsion to cold water are in the range of 1:25 to 1:50. The dilution process is critically determined by

the composition of the microemulsion. According to the literature, the droplet structure is already contained in the microemulsion and therefore, no energy is required to achieve submicron particle sizes. Fessi produced polymer particles by dilution ofpolymer solutions in water. According to De Labouret et al., the particle size is critically determined by the velocity of the distribution processes. The hydrophilic co-solvents of the microemulsion play a similar role in formation of lipid nanoparticles as acetone for formation of polymer nanoparticles.

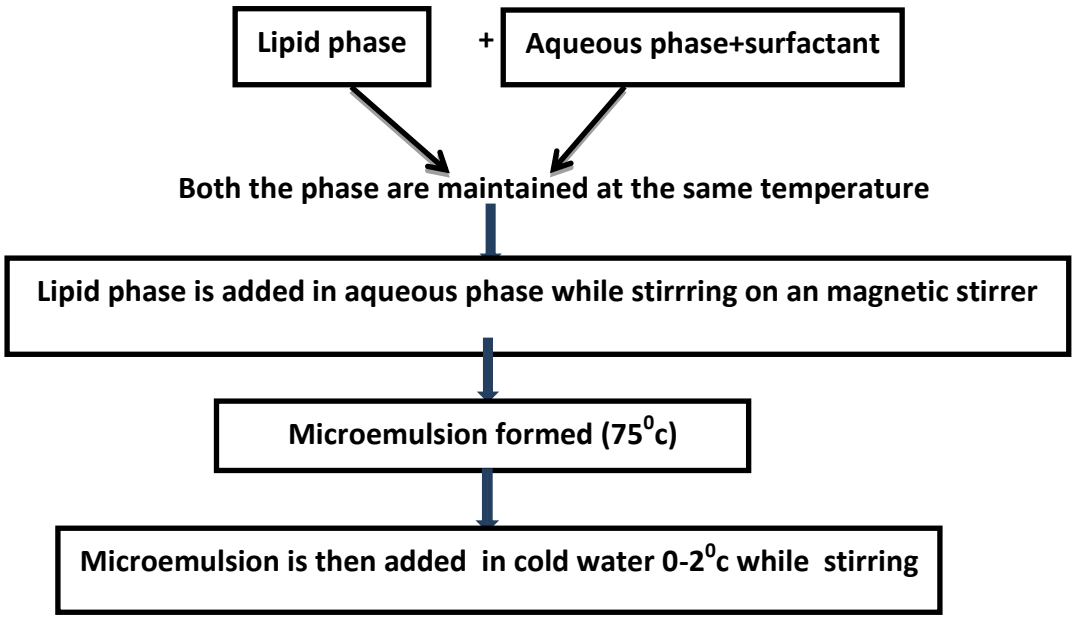
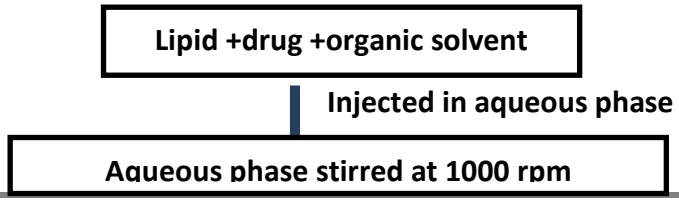


Fig.5.Micro emulsion method

4. **Solvent injection method**

This method is based on the lipid precipitation from the dissolved lipid in in organic solution. Then this lipid solvent mixture was injected through injection needle in to stirred aqueous phase with or without surfactant. The resultant dispersion was then filtered with a filter paper in order to remove any excess lipid. Emulsion within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize SLNs until solvent diffusion gets completed (Schubert et al., 2003). Mishra et al. (2010) prepared and evaluated SLNs using Solvent injection method for delivery of Hepatitis B surface antigen for vaccination using subcutaneous route.



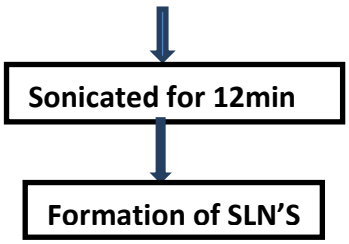


Fig.6.Solvent injection method

5. **Membrane contractor method**

In this technique the liquid phase was pressed at a temperature above the melting point of the lipid through the membrane pores allowing the formation of small droplets. The aqueous phase was stirred continuously and circulates peripherally inside the membrane module, and sweeps away the droplets being formed at the pore outlets.SLN was formed by cooling of the preparation at the room temperature. Vitamin E loaded SLN are prepared using membrane contractor technique to allow large scale production and their stability is promising.

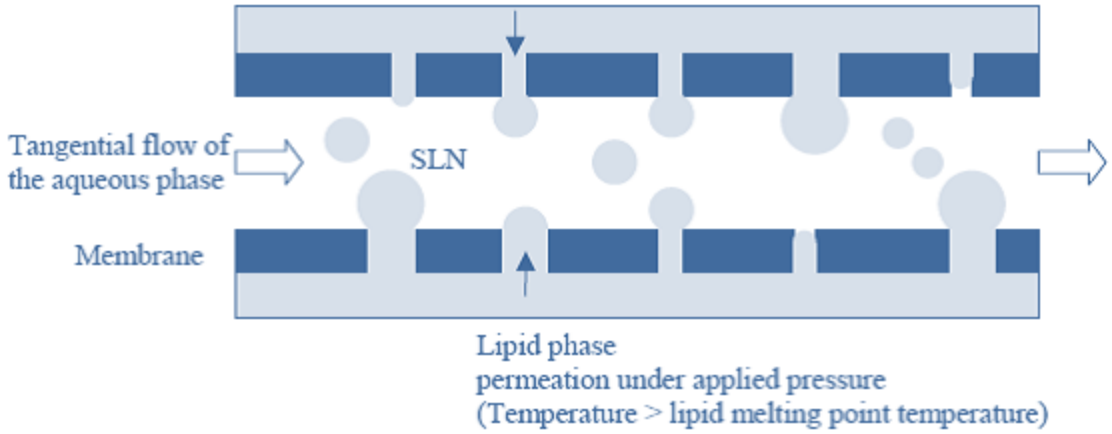


Fig. 7: Shows a Schematic diagram of Membrane Contractor for preparation of SLN.

6. **Spray drying method**

It is an alternative technique to Lyophilisation in order to transform an aqueous SLN dispersion into a drug product. It is an alternative and cheaper technique to the Lyophilisation process. This recommends the use of lipid with melting point more than 70^{o}C. This method causes particle aggregation due to high temperature shear forces and partial melting of the particle. According to Freitas and Mullera (1998) best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v).

7. **Double emulsion method**

In this method, the drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion. Li et al. (2010) prepared solid lipid nanoparticles loaded with bovine serum albumin (BSA) using double emulsion method. In this technique drug is at first dissolve in aqueous phase and then emulsified in melted lipid phase. The primary emulsion was stabilized upon addition of stabilizer .Then this stabilized emulsion was dispersed in aqueous phase containing hydrophilic emulsifier.

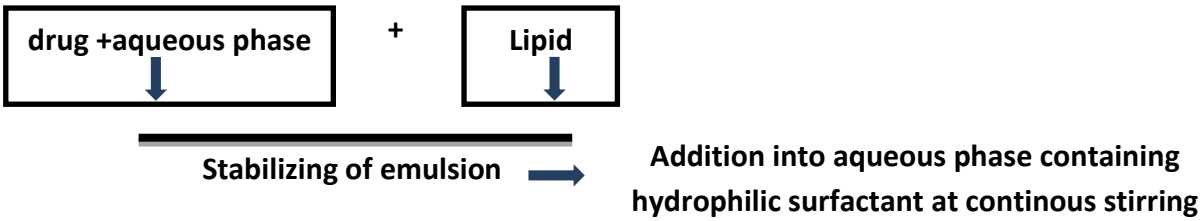


Fig.8.Double emulsion method

8.**Film-ultrasound dispersion**

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

9.**SLN Preparation by Using Supercritical Fluid**

This is a relatively new technique for SLN production and has the advantage of solvent-less processing (Chen, 2006; Kaiser, 2001). There are several variations in this platform technology for powder and nanoparticle preparation. SLN can be prepared by the rapid expansion of supercritical carbon dioxide solutions method. Carbon dioxide (99.99%) was the good choice as a solvent for this method (Gosselin, 2003).

10.**Polymerization Method**

In polymerization methods, monomers are polymerized with subsequent entrapment of drug particles to form nanoparticles or adsorbed on their surface in an aqueous solution. Drug is incorporated either by dissolving in the polymerization medium or by adsorption onto the nanoparticles after completion of polymerization. The nanoparticles suspension is then purified to remove traces of various free stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium.

Formulation variables in the product quality [11, 13, 17, 20, 35]

Particle size

Alteration of the size significantly affects the physical stability, biofate of the lipid particles, and release rate of the loaded drug. Hence the size of the SLNs has to be controlled within reasonable range. Well formulated systems (liposomes, nanospheres and nanoparticles) should display a narrow particle size distribution in the submicron size range (as having size below 1μm), according to the definition of colloidal particles.

Influence of the ingredients on product quality

The particle size of lipid nanoparticles is affected by various parameters such as composition of the formulation (such as surfactant/ surfactant mixture, properties of the lipid and the drug incorporated), production methods and conditions (such as time, temperature, pressure, cycle number, equipment, sterilization and Lyophilisation). Large particle size is obtained at lower processing temperature. The hot homogenization technique gives a smaller particle size, generally below 500 nm, and a narrow particle size distribution as compared to cold homogenization. Mean particle size as well as polydispersity index (PI) values are reported to be reduced at increasing homogenization pressure up to 1500 bar and number of cycles (3-7 cycles).

Influence of the lipids

Using the hot homogenization, it has been found that the average particle size of SLN dispersions isincreasing with higher melting lipids. However, other critical parameters for nanoparticle formation will be different for the different lipids. The examples include the velocity of lipid crystallization, the lipid hydrophilicity (influence on self-emulsifying properties and the shape of the lipid crystals (and therefore the surface area). Further, increasing the lipid content over 5-10% resulted in larger particles (including micro particles) and broader particle size distribution in most cases.

Influence of the emulsifiers

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.

Evaluation of SLN [1, 5, 13, 40]

Analytical characterization of SLN An adequate characterization of the SLN's is necessary for the control of the quality of the product. Several parameters have to be considered which have direct impact on the stability and release kinetics:

• Particle size and zeta potential.

• Degree of crystallinity and lipid modification.

• Co – existence of additional structures and dynamic phenomena.

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. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by particle movement. This method covers a size range from a few nanometers to about 3 microns. PCS is a good tool to characterize nanoparticles, but it is not able to detect larger micro particles. Electron Microscopy provides, in contrast to PCS and LD, direct information on the particle shape. The physical stability of optimized SLN dispersed is generally more than 12 months. ZP measurements allow predictions about the storage stability of colloidal dispersion [35, 36].

Dynamic light scattering (DLS)

DLS also known as PCS records the variation in the intensity of the scattered light on the microsecond time scale.

Static light scattering (SLS)/fraunhofer diffraction

SLS is an ensemble method in which the light scattered from a solution of particles is collected and fit into fundamental primary variable.

Acoustic methods

It measures the attenuation of the scattered sound waves as a means of determining size through the fitting of physically relevant equations.

Nuclear magnetic resonance (NMR)

NMR can be used to determine both the size and qualitative nature of nanoparticles. Electron microscopy

Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) are the direct method to measure nanoparticles, physical characterization of nanoparticles with the former method being used for morphological examination. TEM has a smaller size limit of detection.

Atomic force microscopy (AFM)A probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on forces at play between the tip and the surface.

Measurement of crystallinity and lipid modifications

Powder X - ray diffraction and differential scanning calorimetry (DSC)-

The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus the degree of crystallinity to be assessed. DSC can be used to determine the nature and the speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperature.

Thermodynamic stability, lipid packing density and quantification are a serious challenge due to the increase, while drug incorporation rates decrease in the following order:

Super cooled melt < α-modification < β9-modification < β-modification.

Due to the small size of the particles and the presence of emulsifiers, lipid crystallization modification changes might be highly retarded. Differential scanning calorimetry (DSC) and X- ray scattering are widely used to investigate the status of the lipid. Infrared and Raman spectroscopy are useful tools for investigating structural properties of lipids. Their potential to characterize SLN dispersions has yet to be explored [37].

Co – existence of additional structures

The magnetic resonance techniques, nuclear magnetic resonance (NMR) and electron spin resonance (ESR) are powerful tools to investigate dynamic phenomena and the nano-compartments in the colloidal lipid dispersions. Dilution of the original SLN dispersion with water might cause the removal of the surfactant molecules from the particle surface and induce further changes such as crystallization changes of the lipid modification [5].

Parameter Method of analysis

Molecular weight Gel chromatography

X-ray photoelectron spectroscopy

Entrapment efficiency

This is the prime importance in SLN, since it influences the release characteristics of drug molecule. The amount of drug encapsulated per unit weight of nanoparticles is determined after separation of the entrapped drug from the SLN formulation. This separation can be carried out using the techniques such as ultracentrifugation, centrifugation filtration and or gel permeation chromatography.

Centrifugation filtration

Filters such as ultra free – mc or ultra sort – 10 are used along with classical centrifugation techniques. The degree of encapsulation can be assessed indirectly by determining the amount of drug remaining in supernatant after centrifugation filtration/ultra-centrifugation of SLN suspension or alternatively by dissolution of the sediment in an appropriate solvent and subsequent analysis.

In vitro and ex vivo methods for the assessment of drug release from SLN [23, 24, 25, 30]

A large number of drugs including very hydrophilic molecules have been postulated to be incorporated into SLN.

Various methods used to study the in vitro release of the drug are:

• Side by side diffusion cells with artificial or biological membrane20.

• Dialysis bag diffusion technique.

• Reverse dialysis bag technique.

• Agitation followed by ultracentrifugation or centrifugal ultra filtration25.

In vitro drug release [2, 3, 4, 5]

Dialysis tubing

In vitro drug release could be achieved using dialysis tubing. The solid lipid nanoparticle dispersion is placed in pre - washed dialysis tubing which can be hermetically sealed. The dialysis sac then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analyzed for the drug content using a suitable analytical method.

Reverse dialysis

In this technique a number of small dialysis sacs containing 1 mL of dissolution medium are placed in SLN dispersion. The SLN's are then displaced into the medium.

Everted Gut Sac Experiment Using Rat Intestine

Intestinal permeability studies using everted gut sac were performed using established methods adopted from literature [13, 14] (Ruan et al., 2006, Mariappan and Singh, 2006). Male Wistar rats (body wt. 250-300 g, n = 4) were used for the study. Prior to the surgical procedure, the rats were fasted overnight (16–20 h) with water ad libitum. The rats were anesthetized with pentobarbital sodium (60 mg/kg, i.p.). The intestine of the rats was exposed by a midline abdominal incision and a 20-25 cm segment of the proximal rat jejunum was excised and placed in oxygenated TC 199 medium. The intestine was gently everted over a glass rod, divided into segments of length of approximately 4 cm each, filled with oxygenated

TC 199 medium and tied using surgical suture (Braided silk wax, Pearsalls Ltd, USA) to prepare sacs. The sacs were placed in flasks containing 20 ml of caffeine, paracetamol and sulfasalazine (prepared in TC 199 at a concentration of 100 μM each) either separately or in a combination of all three drugs. Lucifer yellow (10μg/ml) was added to all the solutions as an internal standard. The flasks containing sacs were incubated for the period of 60 min, at 37°C in an oscillating water bath (80 cycles per min). After the incubation period, the sacs were cut open and the contents obtained were centrifuged at 3000 g for 5 min at 4 °C. The supernatants were analyzed for marker compounds using the validated method described earlier. Lucifer yellow was quantified by spectrofluorimetry at excitation and emission wavelengths of 485 nm and 530 nm, respectively, using POLARstar OPTIMA (BMG LABTECH, Germany), controlled by FLUOstar OPTIMA (version 1.30 R3). The apparent permeability coefficient (Papp) of the marker drugs was calculated by using the following equation: Papp = [V/ (A*T)]* (C60/C0)Where V is volume ofserosal content, A is the area of the intestinal segment, T is the time of incubation, C0 is the initial concentration on mucosal side, while C60 is the concentration of the compound on serosal side after 60 minutes.

Applications of SLN[11,23,27,30]

1. **Per oral administration**

Per oral administration forms of SLN may include aqueous dispersions or SLN loaded traditional dos-age forms, e.g. tablets, pellets or capsules. The microclimate of the stomach favors particle aggregation due to the acidity and high ionic strength. It can be expected, that food will have a large impact on SLN performance. The plasma levels and body distribution were determined after administration of CA–SLN suspension versus a CA solution (CA-SOL). Two plasma peaks were observed after administration of CA–SLN. The first peak was attributed to the presence of free drug; the second peak can be attributed to controlled release or potential gut uptake of SLN.

2.**Transdermal application**

The smallest particle sizes are observed for SLN dispersions with low lipid content (upto5%). Both the low concentration of the dispersed lipid and the low viscosity are disadvantageous for dermal administration. In most cases, the incorporation of the SLN dispersion in an ointment or gel is necessary in order to achieve a formulation which can be administered to the skin. The incorporation step implies a further reduction of the lipid content of the SLN dispersion resulting in semisolid, gel-like systems, which might be acceptable for direct application on the skin (Prow, 2006).

3.**SLNs as gene vector carrier**

SLN can be used in the gene vector formulation Rudolph). In one work, the gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide (TAT 2) into SLN gene vector. There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids (Hayes, 2006; Pedersen, 2006). The lipid nucleic acid nanoparticles were prepared from a liquid anaphase containing water and a water miscible organic solvent where both lipid and DNA are separately dissolved by removing the organicsolvent, stable and homogeneously sized lipid-nucleic acid nanoparticle (70-100 nm) were formed. It is called genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle.

4.**Parenteral administration**

SLN have been administered intravenously to animals. Pharmacokinetic studies of doxorubicin incorporated into SLN showed higher blood levels in comparison to a commercial drug solution after i.v. injection in rats. Concerning the body distribution, SLN were found to cause higher drug concentrations in lung, spleen and brain, while the solution led to a distribution more into liver and kidneys. Parenteral application is a very wide field for SLN. Subcutaneous injection of drug loaded SLN can be employed for commercial aspect, e.g., erythropoietin (EPO), interferon-β. Other routes are intraperitonial and also intra-articular.

5.**Ophthalmic administration**

Many investigations have been made to use nanoparticles for prolonged release of drugs to the eye. The basic problem of ophthalmologic formulation is the fast removal from the eye, which implies clearance of the applied drug through the nose. It could be shown for nanoparticles that an increased adhesiveness is available leading to higher drug levels at desired site of action. However, the basic problem was that the nanoparticles are of limited toxicological acceptance.

6.**Pulmonary administration**

A very interesting application appears to be the pulmonary administration of SLN. SLN powders cannot be administered to the lung because the particle size is too small and they will be exhaled. A very simple approach is the aerosolization of aqueous SLN dispersions. The important point is that the SLN should not aggregate during the aerosolization. The aerosol droplets were collected by collision of aerosol with a glass wall of a beaker. This basically demonstrates that SLN are suitable for lung delivery. After localization into the

bronchial tube and in the alveoli, the drug can be released in a controlled way from the lipid particles.

CONCLUSION

SLNs delivery can be an innovative way to administer molecules into the target site in a controlled manner by possibly overcoming or alleviating the solubility, permeability and toxicity problems associated with the respective drug molecules. High physical stability of these systems is another advantage. So SLNs is a new era technology which has been taken over by the pharmaceutical industry. The possibility of incorporating both the lipophillic and hydrophilic molecules and the possibility of the several administration make the SLNs delivery system all the more promising. SLNs will open a new channel for an effective delivery of a vast variety of drug molecules including analgesics, antitubercular, anticancerous, antiaging, antianxiety, antibiotics, antihypertensive and antiviral agents to the target site.

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