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REVIEW ON SOLID LIPID NANOPARTICLES

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ABSTRACT

Solid lipid nanoparticles are the new type of colloidal carrier systems; these are the substitute to the conventional carriers such as liposome's, micro-particles, nanoparticles and micro- emulsions based on natural macromolecules or synthetic polymers. These consist of an nm range of spherical solid Lipid nanoparticles spherical in shape, which is dispersed in water or an aqueous surfactant solution. Solid Lipid Nanoparticles enhances the oral bioavailability of water insoluble drugs or poorly soluble drugs. This paper gives an outline of advantages and disadvantages, production methods, different types, drug incorporation methods, drug loading capacity and characterization of SLN's.

KEYWORDS: Colloidal systems, Oral bioavailability, Solid Lipid Nanoparticles, Water Insoluble Drugs.

INTRODUCTION

Solid Lipid Nanoparticles are the new type of colloidal drug carrier systems that combines the advantages of liposome's, polymeric nanoparticles and fat emulsions. Their size ranges from 50-100 nm. These are consists of the nm range of spherical solid Lipid nanoparticles and dispersed in water or an aqueous surfactant solution. Feasibility of incorporation of hydrophilic and lipophilic drugs, easy to manufacture, low cost, easy scale-up, it increases the oral bioavailability of water insoluble drugs and improved physical stability makes solid Lipid Nanoparticles a better choice. However, the loading capacity and complexity should be taken care of.[1-11]

Methods for preparation of SLN's

Various approaches for preparation of Solid Lipid Nanoparticles are.

1. High pressure Homogenization
2. Ultra Sonification/ high Speed Homogenization
3. Solvent emulsion evaporation technique
4. Solvent emulsion diffusion technique
5. Micro emulsion based method
6. Super critical fluid technique
7. Spray drying method
8. Double emulsion technique
9. Membrane contactor technique
10. Precipitation technique

1. High pressure Homogenization

Used for the manufacturing of Solid Lipid Nanoparticles, extremely powerful and reliable technique. Homogenizer pushes the liquid with a pressure of around 100 to 2000 bar through a tiny space in the range of few µ. The fluid accelerates on a very little interval to very high velocity.

Two general approaches of high shear homogenization are described below (Figure 1).

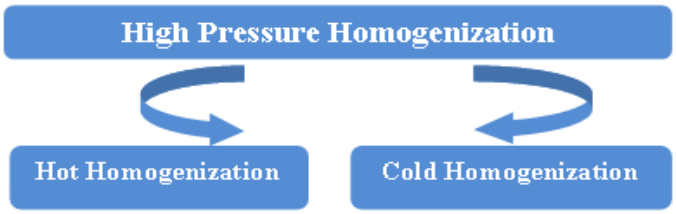

Figure 1: two general approaches for High pressure Homogenizer

1.1 Hot Homogenization

In Hot Homogenization method (Figure: 2) the Drug is dispersed into Lipid melt and this drug lipid melt is further dispersed into the hot solution of surfactant with high speed stirring. Pre-emulsion is carried out at a temperature higher than the melting point of the lipid. High temperature results in lesser particle size. High temperature increases the degradation rate leading to degradation in particle size, however high homogenization pressure enhances the kinetic energy results in increasing in the particle size.

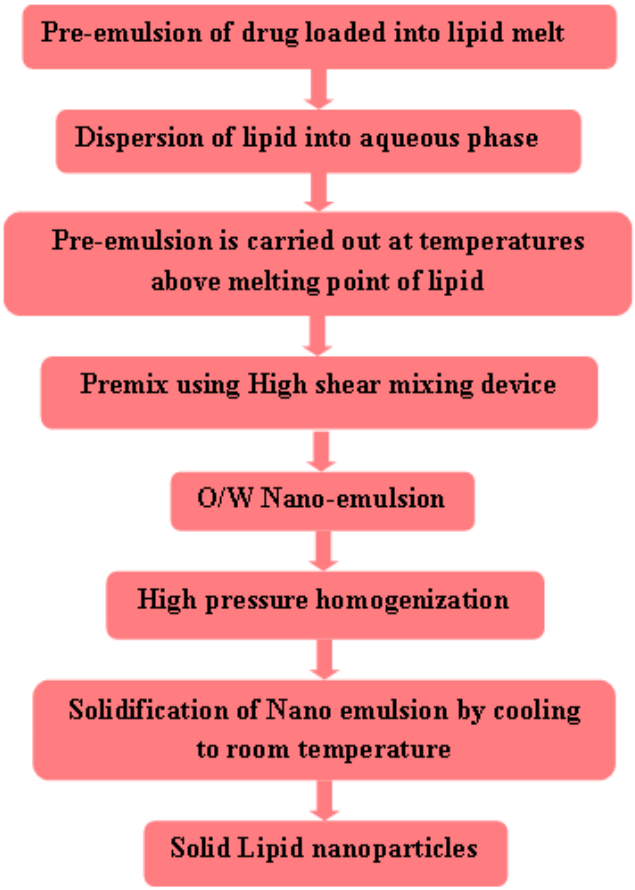

Figure 2: Hot Homogenization Method

1.2 Cold Homogenization method

To overcome the flaws associated with hot homogenization method, they develop cold homogenization method. Problems are drug distribution into aqueous phase, drug degradation, complexity. In this method drug is dispersed into lipid melt and cool the drug contained lipid melt.

Solid lipid is ground to lipid micro-particles and these lipid micro-particles are dispersed into cold surfactant solution and produces pre-suspension. The formed pre-suspension is homogenized at lower than the room temperature. Gravitational force among the molecules is strong enough to break the lipid micro-particles into SLN's.

Cold homogenization method preparation is described below in figure: 3.

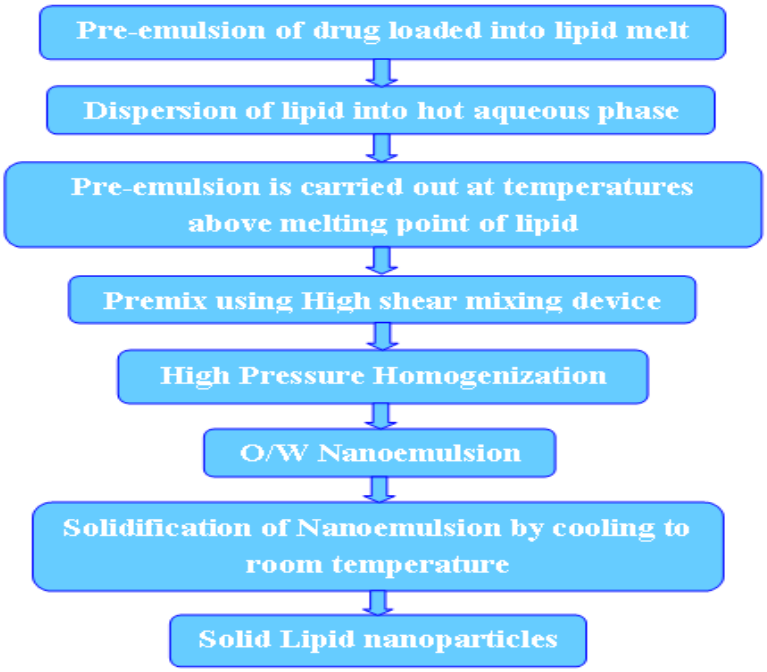

Figure 3: Cold Homogenization Method

2. Ultra Sonification/ High Speed Homogenization

SLN's are manufactured by Ultra Sonification or High Speed Homogenization. The combination of both techniques ultra Sonification and high speed homogenization are required to get small particle size. Ultrasonification types (Figure: 4) and High Speed Homogenization process is described below (Figure: 5).[12-27]

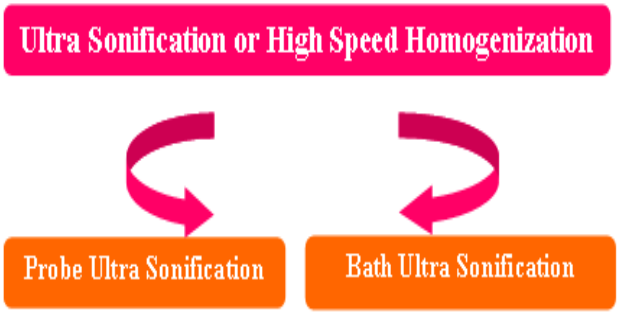

Figure 4: Ultra Sonification types

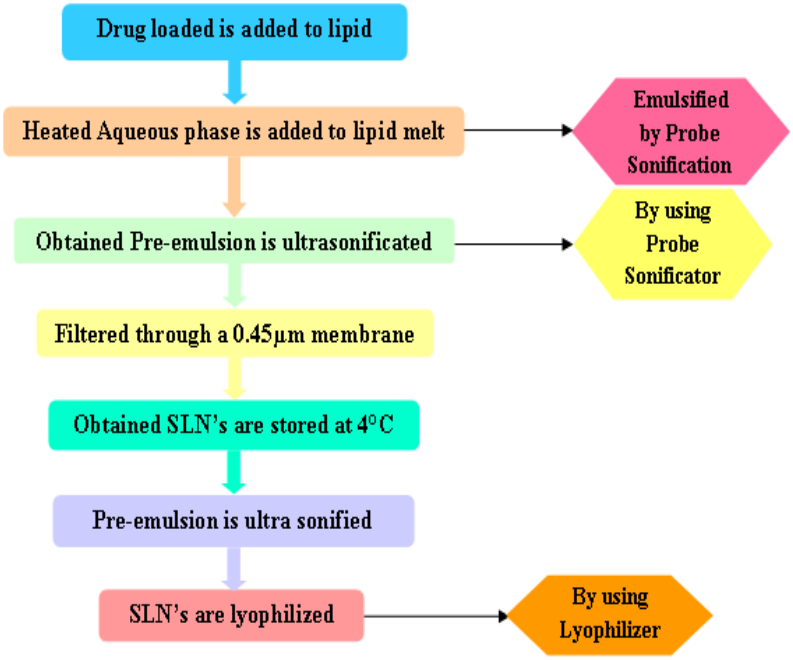

Figure 5:: Description of High Speed Homogenization

3. Solvent emulsion evaporation technique

SLN's are also manufactured by solvent emulsion evaporation method. Lipophilic material and hydrophilic drug are dissolved in a water immiscible organic solvent and then that is emulsified in an aqueous phase using high shear homogenizer. To improve the efficiency of emulsification, the coarse emulsion is passed through the micro fluidizer. The organic solvent is evaporated by stirring at room temperature and reduced pressure. Nanoparticles dispersion is formed by leaving precipitants of lipids in aqueous medium giving SLN's.

4. Solvent emulsion diffusion technique

The solvent used in this technique is miscible with water and this can be executed either in aqueous or in the oil phase. By this technique the particle size with 20-100nm can be obtained. Voidance of heat is an advantage in this technique. The process is described below (Figure 6).

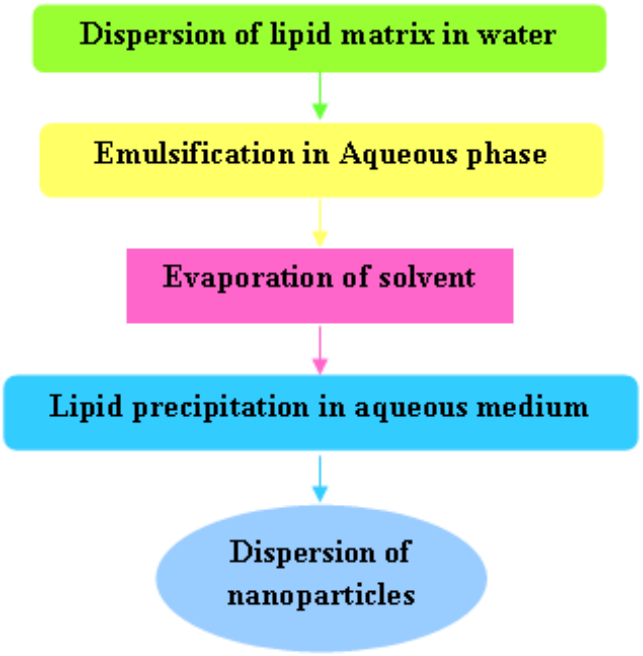

Figure 6: Description of Solvent emulsion diffusion technique

5. Micro emulsion based technique

This technique is based on micro-emulsions dilution. Micro-emulsions are two phase systems composed of inner phase and outer phase. Micro-emulsions are prepared by stirring a transparent mixture at 70-75°C. Micro-emulsions contain low melting fatty acids, emulsifiers, Co-emulsifiers and water. Hot micro-emulsion is dispersed into water (cold) under stirring. SLN's dispersion is used as granulation fluid and it is transferred into solid products like tablets, capsules, pellets by granulation process.

Step: 1(Figure: 7) and Step 2 (Figure: 8) is described below.

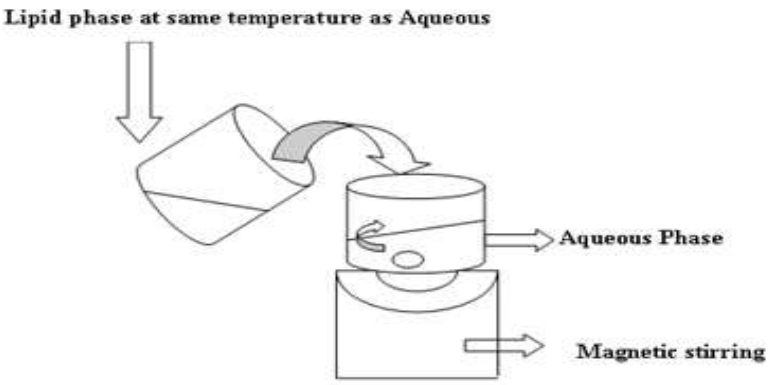

Figure 7: Step-1 of Micro emulsion based method

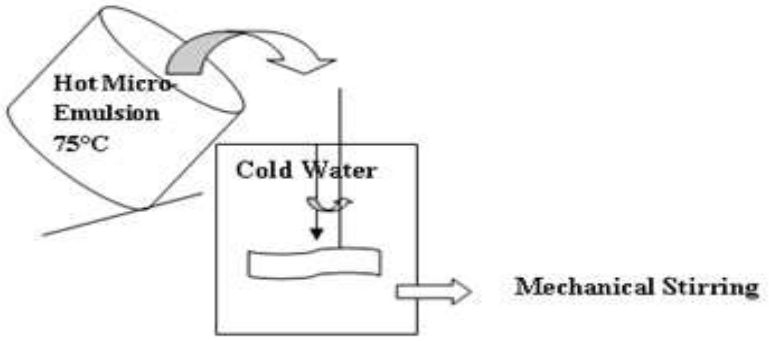

Figure 8: Step-2 of Micro emulsion based method

6. Super critical fluid technology

It is a substitute method for preparation of solid lipid Nanoparticles by PGSS (Particles from gas saturated solutions). It is relatively new method for production of SLN's and it has the benefit of solvent less processing. The pressure and temperature of the fluid goes beyond their respective critical value then the fluid is called as supercritical fluid. Beyond the critical temperature it is not possible to liquefy a gas by using pressure. SLN's can be made by RESS (rapid expansion of super critical carbon dioxide method).

7. Spray drying Method

It is a substitute method to lyophilisation process in order to convert aqueous solid lipid nanoparticles dispersion into a drug substance. Spray drying method is cheaper than lyophilisation technique. In this method high temperature causes particle aggregation, partial melting and shear forces. This method suggests using of the lipids with melting point > 75°C. The best results are obtained with SLN's concentration of 20% trehalose in ethanol.

8. Double emulsion method

In this technique, the drug is dissolved in aqueous solution and emulsified in lipid melt. By adding stabilizer primary emulsion is stabilized. Then the stabilized emulsion is dispersed in aqueous phase and forms the double emulsion. Then the formed double emulsion is stirred and isolated by using filtration. This technique avoids the necessity to meet the lipid for the production of peptide loaded lipid nanoparticles. The surface of nanoparticles can be altered in order to sterilize them by incorporation of lipid polyethylene glycol derivative. Sterilization significantly increases the ability to fight these colloidal systems in GI fluids.

9. Membrane contactor technique

It is a novel technique for the manufacture of SLN's. In this technique, the liquid phase is pressed at temperature higher than the lipid melting point through the membrane pores allowing the tiny droplets. In the membrane contactor technique aqueous phase is stirred continually and circulated tangentially and sweep away the droplets which are formed at the pore outlet. By cooling the preparation at room temperature SLN's are formed. To maintain the required temperature two phases are placed in the thermostatic bath and nitrogen is used to produce pressure for the liquid phase. The influence of various parameters like velocity, lipid phase pressure, lipid and aqueous phase temperature, membrane pore size are studied. For the preparation of polymeric nanoparticles this method is also used. Process of membrane contactor technique is described below in (Figure: 9).

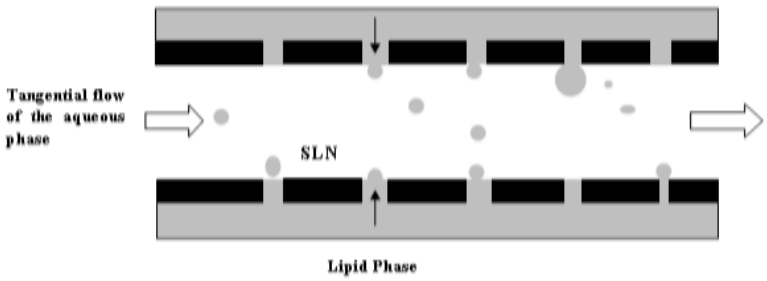

Figure 9: Membrane contactor technique.

10. Precipitation method

In this method glycerides are dissolved into chloroform and form a solution. The formed solution is emulsified in an aqueous phase. After chloroform evaporation, the lipid will be precipitated and form nanoparticles.[28-35]

Types of SLN's

SLN's are divided into 3types

1. Type-I or Homogenous model
2. Type-II or drug enriched shell model
3. Type-III or drug enriched core model

The types of Solid lipid nanoparticles depends on

- ❖ The nature of active pharmaceutical ingredient and lipid
- ❖ The solubility of actives
- ❖ Nature and concentrations of surfactants
- ❖ Type of production and temperature of production

1. Homogenous model

The homogenous model is derived from active ingredient solid solution and lipid solid solution. Solid solution can be obtained when solid lipid nanoparticles are manufactured by cold homogenization method. The Production of lipid blends having the active ingredient in molecular dispersed form. After lipid blend solidification, it is ground to minimize or avoid the active molecules enrichment in different parts of nanoparticles.

2. Drug enriched shell type

This model can be attained when SLN's are manufactured by hot homogenization method and the concentration of active ingredient in the lipid melt should be low during the cooling process of the O/W hot Nano-emulsion. First the lipid will precipitate, leading to a steadily increase the active molecules concentration in the remaining lipid melt, an outer shell will solidify and it consists of both lipid and active ingredient. Enhancement of the external area of the particles causes burst release. In controlled shell model, the active ingredient percentage assigned in outer shell can be modified by incorporating a co-enzyme Q10.

3. Drug enriched core type

This model can be accomplished when the concentration of active ingredient in the lipid melt is immense and it is comparatively close to its saturation solubility. In most of the cases cooling down of hot oil droplets will reduce the solubility active ingredient in lipid melt. The active ingredient saturation solubility becomes more, precipitation forms leading to the formation of enriched core model.

Drug Incorporation of SLN's

Drug incorporation techniques are described below (Figure: 10).

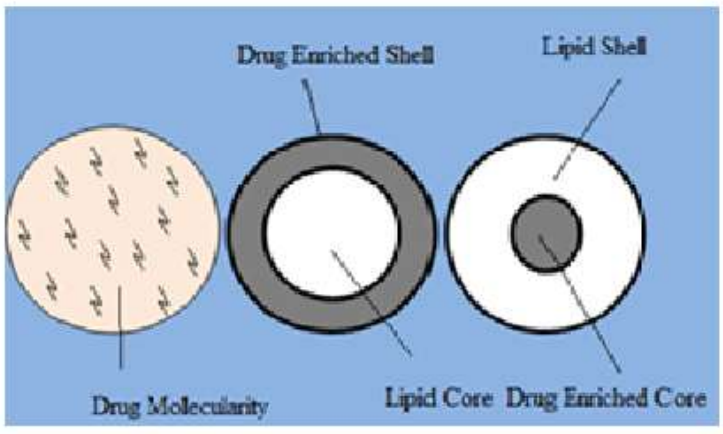

Figure 10: Drug Incorporation Techniques

Drug incorporation of SLN's is as follows

1. Drug solubility in the lipid melt
2. Chemical structure and physical structure of solid lipid matrix
3. Miscibility of the drug and lipid melt
4. Polymorphic state of lipid matrix and solid matrix.

Drug incorporation and drug loading capacity

Drug loading size, particle size and size distribution of Solid Lipid Nanoparticles are found to vary with lipid, emulsifier, and method of preparation.

Factors determining the drug loading capacity in the lipid

- Solubility of lipid melt
- Drug Miscibility in the lipid
- Physical and chemical structure of lipid matrix
- Polymorphic state of lipid material.[36-41]

Characterization of Solid Lipid Nanoparticles

Characterization of solid lipid nanoparticles is a challenging process due to small particle size and complexity of the system.

Various parameters need to be considered as

1. Particle size and Zeta potential measurement
   - Photon correlation spectroscopy
   - Electron microscopy
   - Atomic force microscopy
2. Determination of incorporated drug
3. Invitro drug release
   - Dialysis tubing
   - Reverse dialysis
4. Rheology
5. Storage stability
6. Crystallization tendency and polymorphic behaviour of SLN's.

1. Particle size and Zeta potential measurement

Laser diffraction and Photon correlation spectroscopy (PCS) are most robust techniques for measurement of particle size and Zeta potential. PCS is also identified as dynamic light

scattering. It measures scattered light fluctuation intensity. This is caused by movement of particles. This method covers from few Nanometres to above 3µ. To characterize a Nanoparticles this tool is useful, but it is incapable to identify larger micro particles.

Electron microscopy provides similar to Laser diffraction & Photon correlation spectroscopy. It gives straight information on the shape of the particles. The physical stability of optimized SLN's are dispersed generally >11 months. Zeta potential measurements permit predictions about colloidal dispersions storage stability.

2. Determination of incorporated drug

The quantity of drug incorporation in SLN's influences the characteristics of drug release hence it is important to measure the incorporated drug amount. The incorporated drug amount per unit weight of nanoparticles is determined after solid lipids and free drug separation from the aqueous medium. This separation can be done by centrifugation filtration, gel permeation chromatography or ultra centrifugation. The drug can be assayed by using standard analytical techniques such as spectroflurophotometry, spectrophotometer, HPLC or liquid scintillation counting.

3. Invitro drug release

3.1 Dialysis Tubing: By using dialysis tubing, invitro drug release can be accomplished. The dispersion of SLN is placed in hermitically sealed pre-washed dialysis tubing. At room temperature dialysis sac is dialyzed against an appropriate dissolution medium; from dissolution medium samples are collected at suitable intervals. Samples are centrifuged and the drug content is analyzed by using suitable analytical method**.**

3.2 Reverse Dialysis: In this reverse dialysis method, a number of tiny dialysis sac containing dissolution medium (1ml) are placed in the dispersion of SLN. Then SLN's are replaced into the medium

4. **Rheology:** Rheology measurements of SLN's can be performed by using brook field viscometer. Viscosity depends on the lipid content dispersion. As there will be increased dispersed lipid content, the flow becomes non- Newtonian from Newtonian.

5. Storage Stability: The SLN's physical stability during storage can be determined by observing the changes in the particle size, viscosity and drug content. This can be done by using TLC (Thin Layer Chromatography).

6. Crystallization tendency and polymorphic behaviour of SLN's: Particles which are in solid state play an important role as it decreases the incorporated drug mobility and it prevents leakage of the drug from the carrier. Basic techniques to establish particles physic-chemical state include X-ray diffraction and thermal analysis. Most commonly used techniques in the thermal analysis are differential scanning calorimetry and thermal analysis.[42-50]

Polymers used in the preparation of nanoparticles

Polymers which are used in the formulation should be compatible with the body in the terms of non-toxicity and non-antigenicity. It should be biocompatible and biodegradable. Polymers used in the preparation of nanoparticles are listed in table 1.

Table 1: List of Polymers used in the preparation of Nanoparticles.

NATURAL POLYMERS	SYNTHETIC POLYMERS
Chitosan, Cellulose, Alginates, Carrageenan, Gellan gum, pectin, Starch, Xanthum gum	Poly(acrylic acid), Poly(cyanoacrylates), Poly(amides), Poly (lacticacid), Poly (anhydrides), Poly (Vinyl alcohol), Poly (isobutylcyanoacrylate), Poly(ethylene oxide)

Applications

Table 2: Applications of Nanoparticles.

SI. No	APPLIED FIELD	APPLICTIONS
1	Nanomedicines	Nanodrugs, Medical devices, Tissue engineering
2	Chemicals and Cosmetics	Coatings, nanoscale chemicals and compounds
3	Food Sciences	Nutraceuical food, Nanocapsules
4	Materials	Biopolymers, Nanoparticles, Carbon Nanotubes, Coatings
5	Scientific Tools	Atomic Force, Microscopic tunnelling and Scanning tunnelling
6	Agriculture	Atomic Force, Microscopic tunnelling and tunnelling microscopy

CONCLUSION

SLN's are a new type of colloidal drug carrier system combines the advantages of liposome's, polymeric nanoparticles and fat emulsions due to various benefits including feasibility incorporation of hydrophilic and lipophilic drugs, manufacturing, low cost, easy scale up and improves physical stability. Sustained release and the site specific delivery can achieve better by using SLN's. Disadvantages include low drug loading capacity, the physical

state of lipid complexity, presence of the alternative colloidal structure. The suitable characterization of lipid dispersion requires different analytical methods in addition to the identification of the particle size. Nanoparticles are used for applications in diagnostics, drug discovery, delivery and much more in the medical field. These are very complicated systems with clear benefits and undesired effects over other colloidal carriers.

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