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A REVIEW ON SOLID LIPID NANOPARTICLES- A NEW MODEL APPROAX FOR EFFECETIVE DRUG DELIVERY

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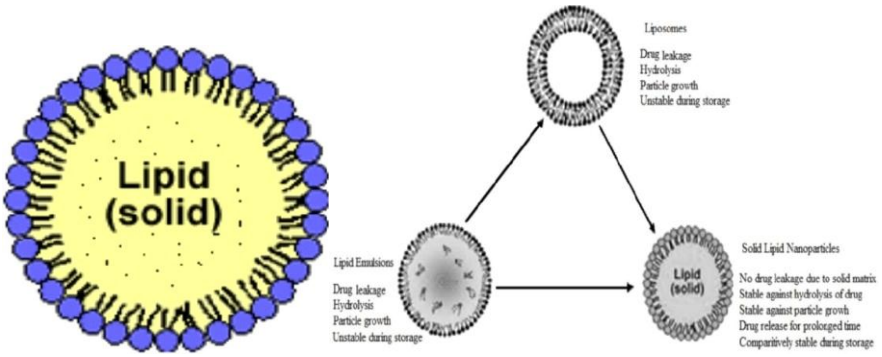
ABSTRACT

Most of the active pharmaceutical ingredients (APIs) under development are poorly water-soluble and have poor bioavailability. Nanotechnology is an approach to overcome the challenges of conventional drug delivery systems. Solid lipid nanoparticles were developed in early 1990s as an alternate to other traditional colloidal carriers like liposomes polymeric nanoparticles and emulsions as they have advantages like controlled drug release and targeted drug delivery with increased stability. It is identical to an oil-in-water emulsion for parenteral nutrition still, the liquid lipid (oil) of the emulsion has been replaced by a solid fat, i.e, yielding solid lipid Nanoparticles. Different production methods that are suitable for large scale production and applications of stable lipid nanoparticles described. In this review article we have focused on different development techniques those are High pressure homogenization, Ultra sonication method, Solvent injection technique, Solvent emulsification- evaporation method, Micro emulsion based method, Solvent evaporation-diffusion method, Spray drying, double emulsion based method. We have discussed appropriate analytical techniques for the evaluation of SLN like photon correlation spectroscopy, measurement of particle size and zeta potential, Invitro drug release, Atomic force, Electron microscopy, Differential scanning calorimetry, determination of incorporated drug (loading efficiency and entrapment efficiency).

KEYWORDS: Solid lipid nanoparticles, Liposomes, Solvent emulsification- evaporation method, Reticulo endoplasmic system.

INTRODUCTION

The targeted delivery system is one of the most challenging research areas in pharmaceutical sciences. By developing colloidal delivery systems like liposomes, micelles, and nanoparticles, a new challenge has opened for improving drug delivery.[1] In 1991 solid lipid nanoparticles (SLN)introduced it represent an alternative carrier system to tradition colloidal carriers such as – polymeric micro- and nanoparticles, emulsions, liposomes.[2]



Solid colloidal particles are nanoparticles size of particles ranging from 10- 1000nm(1.0µm), in which the active drug or biologically active material are dissolved, entrapped, to which the active principle is adsorbed or attached. In system consists of spherical solid lipid particles in the nanometer ranges, which dispersed in water or aqueous surfactant solution. It is identical to an oil-in-water emulsion for parenteral nutrition. Still, the liquid lipid (oil) of the emulsion has replaced by a solid fat, i.e., yielding Solid Lipid

Nanoparticles. Different production methods that are suitable for large scale production and applications of solid lipid nanoparticles are described Nanotechnology, as defined by the National Nanotechnology Initiative (NNI), is the study and use of structures roughly in size range of 1to 100 nm. The overall goal of nanotechnology is the same as that of medicine: to diagnose as accurately and early as possible and to treat as effectively as possible without any side effects using controlled and targeted drug delivery approach. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications nano particles so proposed as an alternative particulate carrier system which are composed of physiological lipid, these are dispersed in water or in aqueous surfactant solution.SLN offer small size, large surface area, high drug loading and the interaction of phases at the interface. These are the unique properties and are attractive for their potential to improve performance of pharmaceuticals. Properties of physio-chemical causes more often challenging. the unique properties of the drug :poor solubility, low permeability, short half-life, and high molecular weight is the commonest challenges for those involved in formulation in pharmaceutical industry it is more important in academic as well as to managers of pharmaceutical industry.

Advantages[3]

1. Bioavailability of poor water soluble molecules is improved.
2. Enhanced drug penetration into the skin via dermal application and site specific delivery of drugs.
3. Acute and chronic toxicity is decreased and organic solvents avoidance is achieved by using biodegradable physiological lipids.
4. In-relation to biocompatibility is excellent.
5. Stability of pharmaceuticals is improved.
6. Content of drug is enriched and very high.
7. Controlled arrival of dynamic medication over a long stretch can be achieved
8. Small estimate and generally contract measure dissemination which gives natural chances to site-particular medication conveyance by SLNs.
9. Conventional emulsion producing techniques pertinent

Disadvantages[4]

1. Loading capacity of the drug is very poor.
2. During storage drug expulsion after polymeric transition.
3. Water content of dispersions is very high. it is about in a range from 70-90%.
4. Partitioning effects during the production process causes the low capacity to load water soluble drugs.
5. High water content of SLN dispersions.
6. The low ability to stack hydrophilic medications because of apportioning impacts amid the generation procedure.
7. Poor sedate stacking limit.
8. Unpredictable gelation tendency.
9. Unexpected dynamics of polymerictransitions.

PROPERTIES[5]

- Low systemic toxicity
- Low cytotoxicity
- Sustained release
- It doesn't have avoidance of reticulo endoplasmic system [RES].
- It have large scale production.
- Drug ejection after polymeric move amidcapacity.

APPLICATIONS

- **Solid lipid nanoparticles for delivering peptides and proteins:** Stable lipid particulate systems such as solid lipid nanoparticles (SLN), lipid microparticles (LM), and lipospheres been sought as alternative carriers for therapeutic peptides, proteins and antigens. The Research work developed in the area confirms that under optimized conditions, be produced to incorporate hydrophobic or hydrophilic proteins and seem to fulfill the requirements for an optimum particulate carrier system. Proteins and antigens intended for therapeutic purposes may be combined or adsorbed onto SLN, and further administered by parenteral routes or by alternative ways such as oral, nasal and pulmonary. The formulation in SLN confers improved protein stability, avoids proteolytic degradation, as well as the sustained release of the incorporated molecules.[6]

- **SLN 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 the emulsion system. These are oil-in-water emulsions that degrade rapidly in the body.[7]

- **SLN applied to the treatment of malaria:** Nanosized carriers have been receiving special attention to minimize the side effects of drug therapy, such as poor bioavailability and the selectivity of the drugs. Several nanosized delivery systems have already proved their effectiveness in animal models for the treatment and prevention of malaria. Several strategies to deliver antimalarials using nanocarriers and the mechanisms that facilitate their targeting to plasmodium spp-infected cells discussed in this review. Taking into account the peculiarities of malaria parasites, the focus is placed mainly on lipid-based (e.g.,liposomes, solid lipid nanoparticles and nano and microemulsions)and polymer-based nanocarriers (Nanocapsules and Nanospheres)[8]

- **SLNs in breast cancer and lymph node metastases**: Mitoxantrone-loaded SLN local injections were formulated to reduce the toxicity and improve the safety and bioavailability of drug efficacy of doxorubicin (Dox) reported to been enhanced by incorporation in

SLNs. In the methodology, the Dox was complexed with soyabean-oil-based anionic polymer and dispersed together with a lipid in water to form Dox-loaded solid lipid nanoparticles. The system has enhanced its efficacy and reduced breast cancer cells. [9,10]

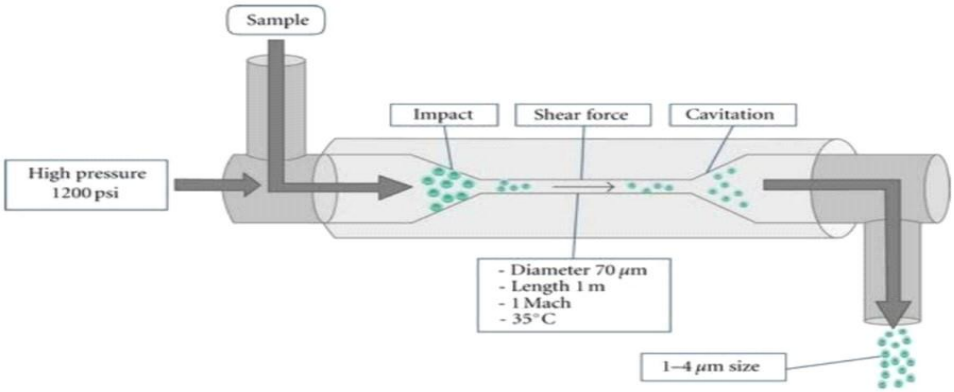
- **Topical application**: Regarding the regularity aspect, topical application is relatively unproblematic. The significant advantages for topical products are the protective properties of SLN for chemically labile drugs against degradation and the occlusion effect due to film formation on the skin. Especially in the area of cosmetics, there are many compounds such as retinol or vitamin C, which cannot be incorporated because of the lack of chemical stability. Incorporation of retinols only possible when applying specific protective measures during production (e.g., noble gas) and using unique packing materials (e.g.,aluminium).[11]

- **SLNs for potential agriculture application:** The essential oil extracted from Artemisia arboreseens L when incorporated in SLN were able to reduce the rapid evaporation compared with emulsions, and the systems used in agriculture as a suitable carrier of ecologically safe pesticides [12]

Preparation of Methods of Solid Lipid Nanoparticles

- **High PRESSURE HOMOGENIZATION**

It is areliable and power full technique, which is employed for the assembly of SLNs. High pressure homogenizers push a liquid with high (100-2000bar) through a narrow gap (in the range of a couple of microns). The fluid accelerates on a really short distance to very high velocity (over 1000Km/h). very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but upto 40% lipid content has also been investigated.



- **HOT HOMOGENIZATION**

Hot homogenization is carried out at temperatures above the melting point of the lipid and may therefore be considered the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and therefore 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 end in lower particle sizes thanks 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.[13-15]

Advantages

- It avoids use of organic solvents.
- It takes short productiontime.
- Its instruments are easilyavailable.
- And there are no regulatoryproblems.

Disadvantages

- Due to high temperature it leads to degradation.
- There are some conformational changes inprotein.
- Coalescence of particles may occur.

- **Cold Homogenization**

- Melt lipid: Active ingredients are solubilized or dissolved in lipid.
- The active lipid mixture is recrystallized or cooled by using lipid nitrogen or dry ice.
- By using a ball mill or a jet mill the active lipid mixture was milled.
- The lipid microparticles are dispersed in cold aqueous surfactant solution.
- At or below low temperature the high pressure homogenization was occurred.

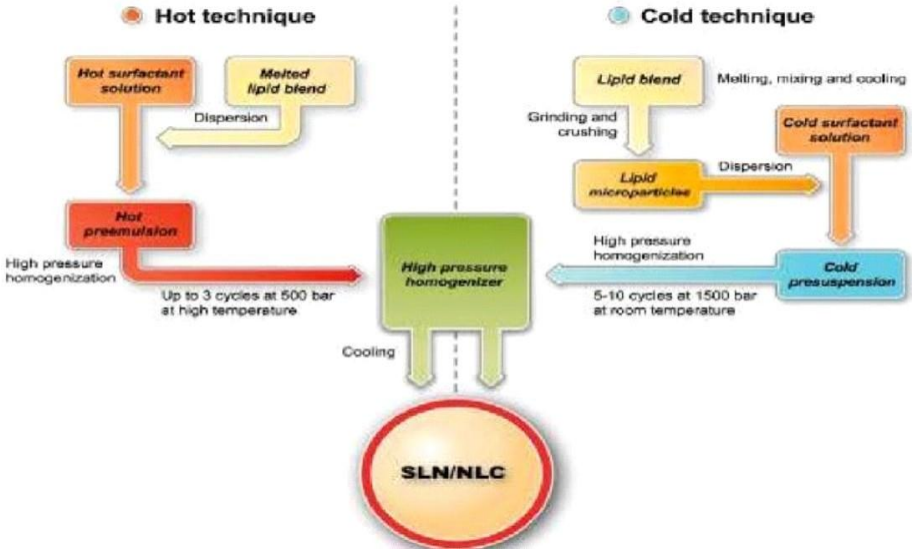
Advantages

It doesn't avoid thermal exposure of the drug completely but it slightly minimizes the exposure of the drug.

- It is useful in hydrophilic drugs and temperature labile drugs.

Disadvantage

- Higher polydispersity index.



- **Ultrasonication or High SpeedHomogenization**

Drug and phospholipid are dissolved in methanol and mixed with an acetone solution containing a blend of fatty acids. The mixture is then added dropwise to pluronic solution at 70° C. A pre-emulsion is obtained by homogenization using an Ultra – Turrax T25 (IKA-werke GmBH, Germany), at 15000 rpm for 10 minutes at 70°C. This pre-emulsion is ultrasonicated (20w) for 15 minutes to prevent the crystallization of lipids. The o/w emulsion obtained is subsequently cooled down to room temperature with continuous stirring, and the lipid is recrystallized to form SLN.[16]

Advantages

- It is very simple.
- And it doesn't contain any specialized equipment.

Disadvantages

- There is a contamination in metallic particles.
- The particle size isbroad.

- **Solvent Emulsification-Evaporation Method**:

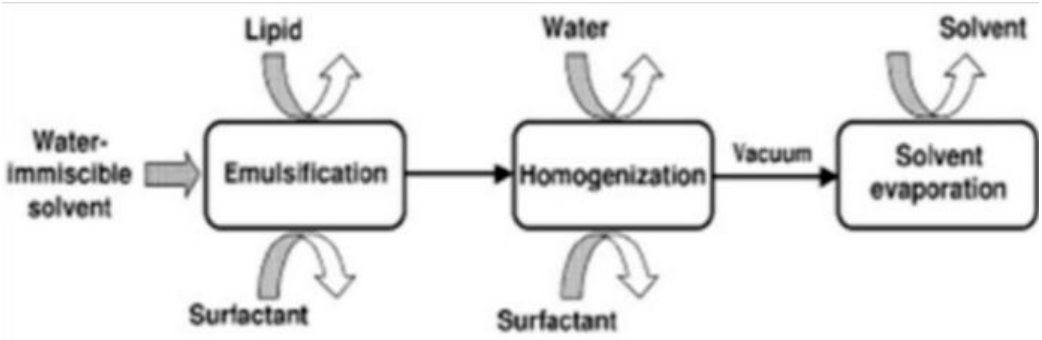
Insolvent emulsification-evaporation method, the lipophilic material and hydrophobic drug were dissolved in a water immiscible organic solvent (e.g. cyclohexane, dichloromethane, toluene, chloroform) and then that is emulsified in an aqueous phase using high speed homogenizer. To improve the efficiency of fine emulsification, the coarse emulsion was immediately passed through the microfluidizer. Thereafter, the organic solvent was evaporated by mechanical stirring at room temperature and reduced pressure (e.g. Rotary evaporator) leaving lipid precipitates of SLNs. The big advantage of this method is that the avoidance of any thermal stress, which makes it appropriate for the incorporation of highly thermo labile drugs a transparent advantage is that the use of organic solvent which may interact with drug molecules and limited the solubility of the lipid in the organic solvent prepared irbesartan soli lipid Nanoparticles using glycery monostearate by solvent emulsification method followed by probe sonication. Formulation was then further evaluated for the pharmacokinetic studies in wistar rats. Irbesartan-loaded SLN of particle \ size 523.7nm and 73.8% entrapment efficiency showed good bioavailability in wistar rats and also showed optimum stability in the studies. The SLN prepared using glyceryl monostearate by solvent emulsification methodleadsto improve bioavailability of the drug.[17]

Advantages

- It is a simple procedure.
- It avoids the heat during production thus it is useful for thermo labile drugs.

Disadvantage

- Solvent residues.



- **Solvent Injection Technique**

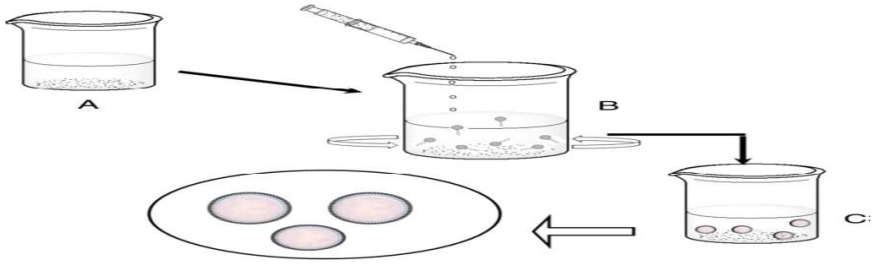
It is a novelapproach to prepare SLN, which has following advantages over other productionmethods like use of pharmalogically acceptable organic solvent, easy handling and fast production process without technically sophisticated equipment. In this technique the solid lipid wasdissolved in water-miscible solvent mixture.Then the lipid solvent mixture was injected through an injection needle into stirred aqueous phase withor without surfactant. The resultantdispersion was thenfiltered with a filter paper in order to removeany excess lipid. The presence of emulsifier within the aqueous phase helps to produce lipid droplets atthe site of injection andstabilize SLN untilsolvent diffusion was complete byreducing the surfacetension between water and solvent.[18-19]

Advantages

- It is a fast production process.
- It doesn't require specialized equipment.
- Easy handling.
- It doesn't need high pressure homogenization.

Disadvantage

- Use of solvent andsurfactant.



- **Micro Emulsion based Method**

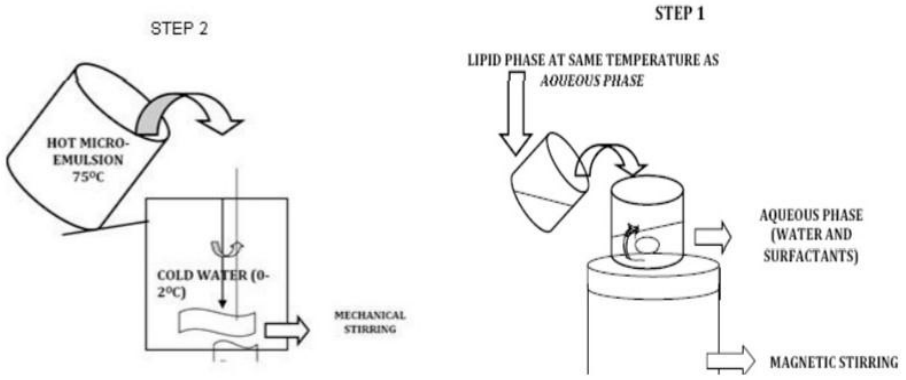
This method is based on the dilution of microemulsions. As micro-emulsion are two- phase systems composed of an inner and outer phase. They are made by stirring an optically transparent mixture at 65-70°C, which typically composed of coffee melting carboxylic acid e.g. stearic acid), an emulsifier e.g. polysorbate 20), co-emulsifiers e.g. butanol) and water. The hot microemulsion is dispersed in cold water 2-3°C under stirring. SLN dispersion are often used as granulation fluid for transferring into solid product by granulation process, but just in case of low particle content an excessive amount of water needs to be removed. High temperature gradients facilitate rapid lipid crystallization and stop aggregation. Due to the dilution step: achievable lipid contents are considerably lower compared with the HPH based formulations.[20]

Advantages

- It doesn't require specialized equipment.
- Doesn't require energyfor production.

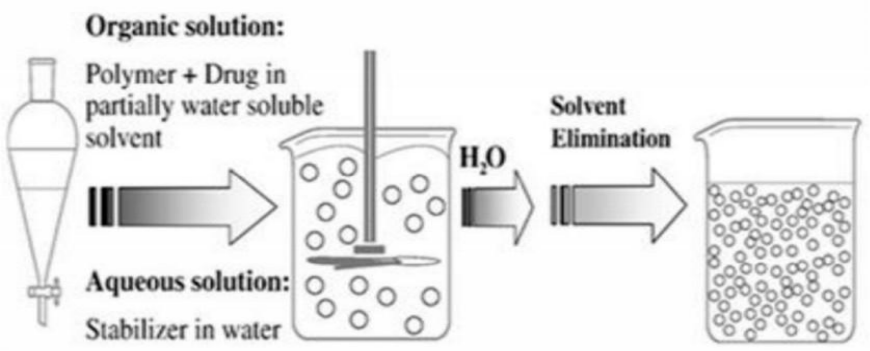
Disadvantages

- It requires high concentrations of surfactants and co-surfactants.
- Large amount of water is present in the system.



- **Solvent Evaporation-Diffusion Method**

SLN also can be prepared ranging from emulsion precursor, whose organic phase is constituted by a solvent, which can be either volatile or partially water miscible. O/W or W/O/W emulsions can be prepared: O/W emulsions are used for lipophilic dugs that are dissolved within the inner organic phase of the system, alongside the lipid. W/O/W emulsions are suitable for hydrophilic drugs, that are dissolved in the inner aqueous phase, while the lipid is dissolved within the intermediate organic phase of the multiple system. Nanoparticles are formed when the solvent is removed either by evaporation (solvent evaporation technique for volatile solvents) or by water dilution (solvent diffusion technique for partially water miscible solvents): owing to solvent removal lipid precipitates as nanoparticles encapsulating the drug.[21]



- **Spray Drying Method:**

It is an alternate and cheaper technique to the lyophilization process. This recommends the utilization of lipid with freezing point quite 70°C. The best results were obtained with SLN concentration of 1% during a solution of trehalose in water or 20 % trehalose in ethanol-water mixture. The addition of carbohydrates and low lipid content favor the preservation of the colloidal particle size in spray drying. The melting of the lipid can be minimized by using ethanol-water mixtures instead of pure water due to cooling leads to small and heterogeneous crystals, the lower inlet temperatures.[22-24]

Double Emulsion Based Method

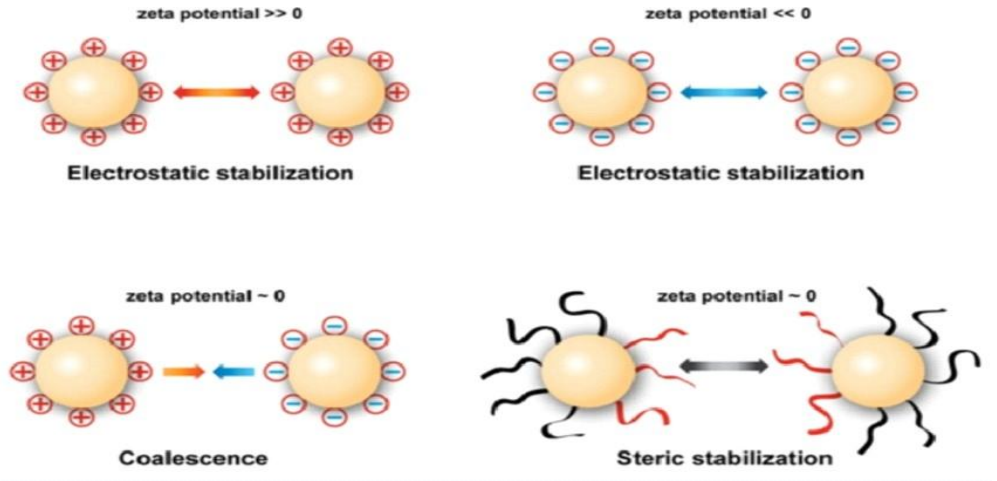
Warm w/o/w double microemulsions can prepared in two steps. Firstly, w/o microemulsions made by adding an aqueous solution containing the drug to a mixture of melted lipid, surfactant, and co-surfacant at a temperature slightly above the melting point of fat to obtain a transparent system. In the second step, formed w/o microemulsion is added to a mixture of water, surfactant, and co-surfacant to get an open w/o/w system. SLNs can be obtained by dispersing the warm micro double emulsions in the cold then washed with dispersion medium by ultra-filtration system. Multiple emulsions have inherent instabilities due to coalescence of the internal aqueous droplets within the oil phase, the coalescence of the oil droplets, and the rupture of the layer on the surface of the inner droplets. In the case of SLNs production, they have to be stable for few minutes, the time between the preparations of the apparent double microemulsions and its quenching in a cold aqueous medium, which is possible to achieve price.[25,26]

Evaluation Tests

- **Measurement of Particle Size and Zeta potential:**

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the foremost powerful techniques for routine measurements of particle size.PCS (also referred to 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's unable 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.[27,28]



In-VitroDrug Release

Dialysis Tubing

In vitro drug release could be achieved using dialysis tubing. The solid lipid nanoparticle dispersion placed in pre-washed dialysis tubing, which can be hermetically sealed. The dialysis sac then dialyzed against a suitable dissolution medium at room temperature; at appropriate intervals, the samples withdrawn from the dissolution medium, using a suitable analytical method. Centrifuged and analyzed for the drugcontent.[29]

Reverse Dialysis

In this technique, several small dialysis sacs containing 1ml of dissolution medium placed in SLN dispersion. The SLNs then displaced into the medium.[30]

Franz Diffusion Cell

The SLNs dispersion placed in the donor chamber of the Franz diffusion cell fitted with a cellophane membrane. The distribution then analyzed against a suitable dissolution medium; the samples withdrawn from the dissolution medium at appropriate intervals and analyzed for drug content using appropriate methods like spectroscopy and HPLC methods.[31]

Atomic Force Microscopy

In this procedure, a probe tip with atomic-scale sharpness is restored across a sample to produce a topological map based on the forces at play between the tip and the surface. The probe can drag across the example (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. That ultrahigh resolution is obtainable with this approach, which alongside the power to map a sample consistent with properties additionally to size, e.g., colloidal attraction or resistance to deformation, makes AFM a valuable tool.[32]

ELECTRON MICROSCOPY

Solid lipid nanoparticles were seen by transmission microscopy. Tests of SLN were weakened to ten time and after that mounted on gold plate. The mounted plates were dried and inspected under a transmission electron magnifying instrument without utilizing any sort of stain. The CCD camera an delicate picture framework was utilized with the transmission electron magnifying instrument to envision SLN.[33]

Differential Scanning Calorimetry (DSC)

It is a widely used technique that measures differences in the amount of heat required to increase the temperature of a sample compared to a reference. Variations in heat flow may be positive or negative and presented as a function of the cold. A phase transition, there are differences in the sample compared to the reference. rate of crystallinity using DSC estimated by comparision of the melting enthalpy/g of the bulk material with the melting enthalpy of the dispersion.[34-36]

Determination of Incorporated Drug

Amount of drug incorporated in SLNs influences the discharge characteristics hence it's vital to live the quantity of incorporated drug. The amount of drug encapsulated per unit wt. of nanoparticles is determined after separation of the free drug and solid lipids from the aqueous medium and this separation can be done by ultracentrifugation, centrifugation filtration or gel permeation chromatography. The drug are often assayed by standard analytical technique like spectrophotometer, a spectroflurophotometry, HPLC or liquid scintillation counting.[37]

CONCLUSION

SLN constitute an attractive colloidal drug carrier system due to successful incorporation of active compounds and the irrelated benefits. The present review has focused on increasing awareness about the nano -technological field in drug delivery with the emergence of several promising

approaches like solid lipid nanoparticles, nano-structured lipid carriers, lipid drug conjugates etc. SLN as a colloidal drug carrier combines the advantage of polymeric nanoparticles, fat emulsions, and liposome; due to various positions, including the feasibility of incorporation of lipophilic and hydrophilic drugs, improved physical stability, low cost, ease of scale- up, and manufacturing. SLNs are prepared by various advanced techniques. Disadvantages include low drug-loading capacities, the presence of alternative colloidal structures (micelles, liposomes, mixed micelles, drug nanocrystals), the complexity of the physical state of the lipid (transformation between different modifications) and the possibility of super cooled melts which cause stability problems during storage or administration (gelation, particle size increase, drug expulsion).

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