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SOLID LIPID NANOPARTICLE: A PROMISING NANOMATERIAL IN DRUG DELIVERY

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ABSTRACT

The virtuous or traditional drug delivery has unsuccessful in enhancement of drug bioavailability and also to decrease toxicity of drugs. In recent times, the targeted drug delivery system has gained its importance in delivering drug with low toxic levels and high bioavailability. Nanotechnology has created an revolution in the field of drug delivery. The solid lipid nanoparticles (SLNs) happens to be best drug carries. SLNs are at spearhead of speedily developing field of the nanotechnology with several applications in the drug delivery, clinical medicine, research, cosmetics, and in other various fields. It is an aqueous dispersion in which colloidal particles are formed from solid lipid that is biodegradable. SLN having size range from 1-1000nm particles use for the drug delivery system. They have been superior stability as compare with various other drug carriers as liposomes. The capability to incorporate drug into the nanoparticulate system, offers latest example in drug delivery that can be used for the drug targeting. Special attention is given to relationship between complexity of SLN dispersions and drug incorporation, SLNs preparation depends upon the nature of drug and methods involve solvent evaporation, ultra-sonication and homogenization using pressure. Bio distribution of drug is an challenge and it's well managed by selecting the perfect route of drug administration. Characterization of SLN includes different methods like Electronic microscopy, particle size determination. The paper gives an overview about latest research and development of SLN according to modern literature is cited.

KEYWORDS: Characterization; Drug incorporation models; Principal of drug release; Route of administration.

INTRODUCTION

Nanoparticle is a narrative multitalented drug delivery approach having targeted and site specific activity many of modern formulations approaches utilizes nanotechnology that is preparation of Nano sized structure containing the active pharmaceutical materials. Nanoparticles is Nano sized particle having size range 1-1000 nm.[1] The nanoparticles are manufactured from synthetic/natural polymers and they are perfectly suitable to optimize the drug delivery and decrease toxic effect. Throughout the year they become known as variable alternative to liposome as drug carrier. The flourishing performance of nanoparticles for delivery of drug depends upon their capability to penetrate through the some anatomical barriers, sustained release of their contents and stability in nanometre (nm) size, to control these limitations the polymeric nanoparticles and lipids have been encourage as alternative carrier, especially for the lipophilic pharmaceuticals, this lipid nanoparticles are called as an solid lipid nanoparticles.[2] Solid lipid nanoparticle is an alternative and improved recent colloidal transporter system to conventional colloidal carriers like emulsion, liposome, polymeric micron and nanoparticles. The nanoparticle as drug delivery was first developed by "Spieser and Co-workers" in late 1960.

Solid lipid nanoparticle

The solid lipid nanoparticles are submicron colloidal carriers consisting of physiological lipid, which diffuse in water or else in aqueous surfactant solution. The structure of SLN is shown in Fig. 1.

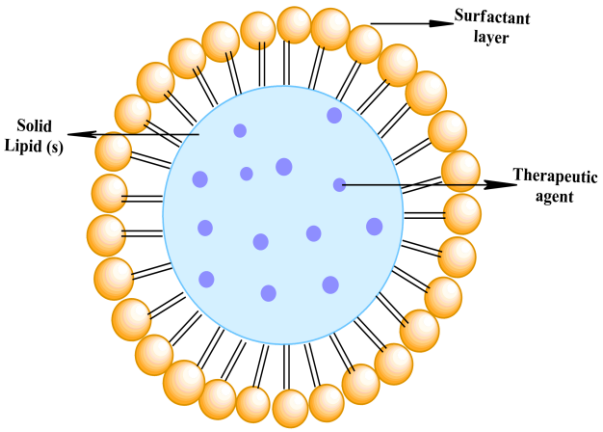

Figure 1: structure of solid lipid nanoparticle.

Nanoparticle are the particles which are fabricated of natural or synthetic polymers.[3][3] They are having the size range of 50-500nm. It is new invention of submicron sized lipid emulsion in which the liquid lipid (oil) has been substituted by solid lipid. Solid lipid nanoparticle function as a substitute drug carrier system to other inventive delivery approaches such as emulsion, liposome, and polymeric nanoparticles. In solid lipid nanoparticle there is no significant toxicity and acidity observed in the variety of biodegradable polymeric materials. In contrast to emulsion and liposome, the particle matrix of solid lipid nanoparticle is consist of solid lipid.[4]

Principal of drug release

There is an converse correlation between drug release and partition coefficient of drug. High surface area owing to smaller particle size in nanometre (nm) size range gives higher drug release. The steady drug release can accomplished when drug is homogeneously dispersed in lipid matrix, it depends on type and entrapment model of the solid lipid nanoparticles.[5] For the rapid drug release crystallinity behaviour of the lipid and high mobility of the drug plays a vital role. There is converse relationship between crystallinity and mobility of the drug. Factors affecting to fast release are large surface area, High diffusion coefficient because of there compact size, low viscosity in matrix, and small diffusion distance for the drug.[6]

Aim of SLN

- Chances of controlled drug release.
- Increase drug stability.
- High drug payload.
- No bio toxicity of carrier.
- Prevention of organic solvent.
- Incorporation of lipophilic drug and hydrophilic drug.
- There is no difficulty with respect to huge scale manufacture and sterilization.[7]

Advantages

- Uses of biodegradable lipids minimizes the probability of toxicity.
- Enhancing bioavailability of the low water-soluble active constituents.
- Enhancing the stability of chemically labile drug through protection from external environment.
- Solid lipid nanoparticle have been enhanced stability as compare with other drug carriers as liposomes.
- Higher entrapment efficiency of active constituents.
- The possibility of lyophilisation and spray drying.
- Surface modification can simply done.
- Through autoclaving or gamma irradiation sterilization can be possible.
- Toxic metabolites are not produced.
- Compact size and narrow size distributions provide for site specific drug delivery by solid lipid nanoparticle.[7]

Disadvantage

- Drug loading capacity is limited.
- The unpredictable dynamics of polymeric changes.[8]

Composition

General ingredients includes are

- Solid lipid
- Surfactant
- Co-surfactant
- Water

Lipids used are partial glycerides (Glyceryl monostearate), fatty acids (Lauric and Stearic acid), triglycerides (Trimyristin, Tristearin and Tripalmitin), waxes (Carnauba wax), charge modifiers (Stearylamine), surfactant (Soybean lecithin), Surfactant mixture inhibit particle agglomeration and improvise stability.[9]

Drug incorporation models

Depending upon the production models of solid lipid nanoparticle three models of drug incorporation into them have been reported describes in table 1.

Table 1: Different drug incorporation models in solid lipid nanoparticle.

Sr. No.	Solid solution model	Core-shell mode (drug-enriched shell)	Core-shell model (drug-enriched core)
1.	In the cold homogenization technique this model is formed.	In hot homogenization technique this model is formed.	Dispersion cooling leads to supersaturation of the drug which is dissolve in lipid.
2.	Using no drug-solubilizing surfactant.	Formation of lipid core at the recrystallization temperature of lipid.	Precipitation of drug occurred in melted lipid.
3.	Drug dispersed in the lipid matrix.	Cooling of the obtained dispersion lead to repartitioning of the drug to lipid phase.	Finally, further cooling leads to recrystallization of lipid.
4.	There is strong interaction in lipid and drug	Concentration of the drug in surrounding membrane.	Formation of drug-enriched core

1] Solid solution model/Homogenous matrix model/ solid lipid nanoparticle type I
2] Core-shell model (drug enriched shell)/ Drug enriched shell model/ solid lipid nanoparticle type II
3] Core shell model (drug enriched core)/ Drug enhanced core model/ solid lipid nanoparticle type III.[10]

Sterilization of SLN

1) For the parenteral and the ocular administration of a solid lipid nanoparticle must be sterile.
2) The autoclaving is possible for lecithin stabilized solid lipid nanoparticles but not for sterically stabilized polymer.
3) Physical stability during autoclave cannot be stated, it depend on the composition.
4) Solid lipid nanoparticle dispersion can also be sterilized by filtration.[11]

Route of administration

Solid lipid nanoparticle can be given by following route of administrations are given below.

1] Paroral administration

Paroral administration forms of solid lipid nanoparticle may include solid lipid nanoparticle loaded traditional dosage form (Tablet, pellets, capsules) or aqueous dispersion. Due to acidity and high ionic strength microclimate of stomach favours particle aggregation. Performance of solid lipid nanoparticle is affected by the food intake.[12]

2] Parenteral administration

Solid lipid nanoparticle is given intravenously to animals. In Pharmacokinetic studies of a doxorubicin, the doxorubicin is integrated into solid lipid nanoparticles and when compared with commercial drug solution it showed the higher blood level after i.v. injection in the rats. Relating to the body distribution, the higher drug concentration of solid lipid nanoparticle found in the lung, spleen and brain, whereas the solution distributed more into the liver and kidney.[13]

3] Transdermal application

Smaller particle size are determined for solid lipid nanoparticles dispersion with lower lipid content (Upto 5%). The low concentration and low viscosity of dispersed lipids are disadvantages for dermal administration. The internalisation of solid lipid nanoparticle dispersion in an ointment or gels is necessary in order to accomplish formulation which can be administered to skin.[14]

METHOD OF PREPARATION

Various method of preparation are given below.

1] High pressure homogenization (Hot and Cold)

It pushes the liquid with high pressure (100-200bar) through hollow gap of some few microns with nearly 100km/h rate and with high viscosity the fluid accelerated to a very short distance very high pressure stress and activations force interrupt the particle down to submicron size range with 5-40% lipid contents.[15] typical solid lipid nanoparticles production conditions are 500 bars and two or three homogenisation cycles. Two general approach of high pressure homogenization (HPH) are cold and hot homogenization. Both working on same conception of mixing the drug in bulk of lipid melt. HPH can be performed below the room temperature or above or at high temperature, called cold-HPH and hot-HPH. In initial stage for both, the lipids and drugs are heated to 5–10 °C greater than melting point of the lipid so drug is dissolved or dispersed in the melted lipid.[16][17] Mostly, concentration of lipid is between 5% to 20% w/v. In next step of the HPH technique, the aqueous phase containing the amphiphile molecules is added to the lipid phase (at the same temperature as the lipid melting) and the hot pre-emulsion is obtained using a high-speed stirring device. The lipid (more added for homogenization) is forced at high pressure (100–1000 bar) through a narrow space (few μm) for 3–5 times, which depends on the formulation and required product. Drug is dispersed or dissolved in the lipid melt Before homogenization.[17] There are certain disadvantage as mentioned further
(1) it's not recommended for drug that are heat sensitive
(2) particle size often increases due to increase in number of rotation or pressure of homogeneity.

However, these disadvantages could be overcome by cold-HPH. As discussed earlier, the first step involves the formation of a suspension of melting lipids and drugs, which i9s followed by instant cooling with the help of dry ice or liquid nitrogen. Further, milling helps to convert powder in to micro-particles. Further in cold aqueous surfactant solution these micro particles are dissolved. Finally, for 5 cycles at 500 bars homogenization is performed to create SLNs.[18]

2] Ultrasonication / High speed homogenization

Solid lipid nanoparticle are also produced by this technique to accomplish smaller particle size, this method based upon the principle that particle size reducing by application of sound waves. Here, To prepare SLN's of size range in 80-800 nm ultrasonication and homogenization with high pressure is performed.[19][20] Fig. 2

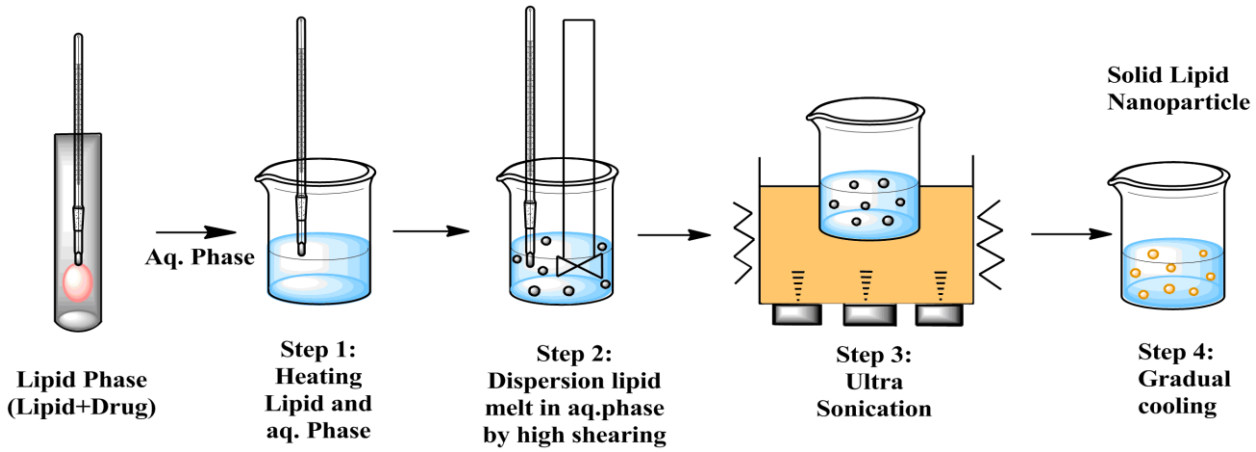

Figure 2: ultra sonication technique.

3] Solvent emulsification/evaporation

For preparation of nanoparticle water-immiscible organic solvent such as cyclohexane and the lipophilic material is mixed then it's emulsified in aqueous phase. The nanoparticle dispersions is formed by evaporation of the solvent produced by precipitation of the lipid in an aqueous medium. The diameter of resulting particles was 25 nm drug used as cholesterol acetate and lecithin /sodium glycocholate blend used as emulsifier. The given results are practically seen and confirmed by Siekmann and Westesen (1996), they experimentally produced cholesterol acetate nanoparticles of size 29 nm.[20] Fig. 3

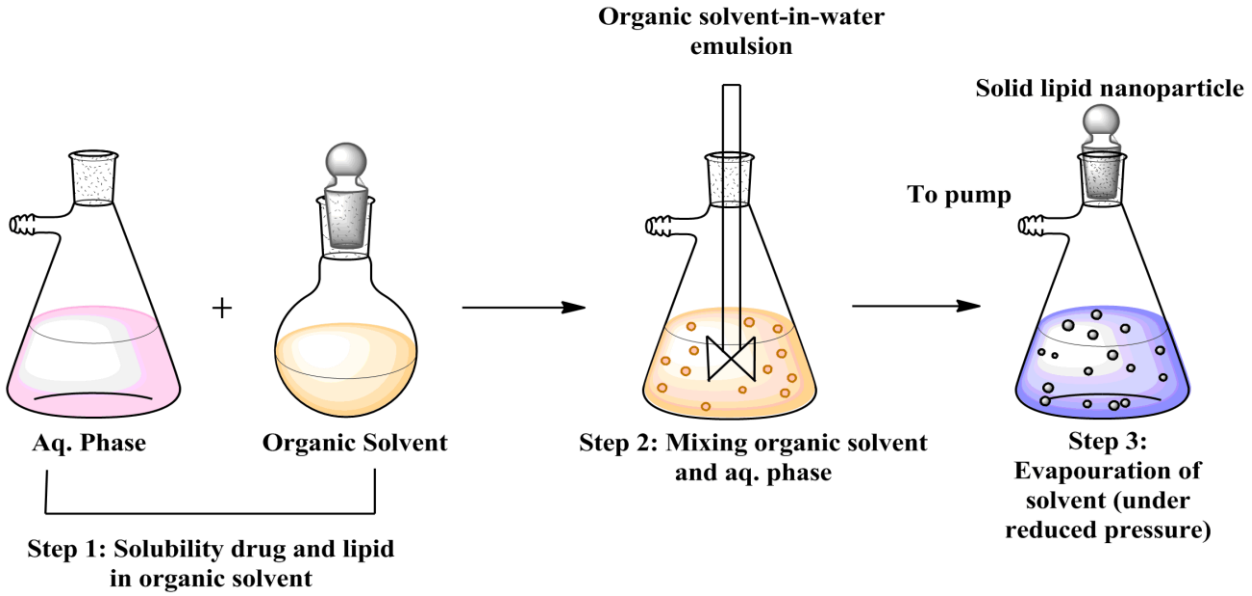

Figure 3: Solvent evaporation technique.

4] Micro emulsion based SLN

Gasco and coworkers (1997) has produced SLNs based on the dilution of microemulsions. These are produced by stirring of mixture that is optically transparent at 65-70°C generally consisting of co-emulsifiers (e.g. butanol, sodium monooctylphosphate), an emulsifier (e.g. polysorbate 20, polysorbate 60, soyaphosphatydylcholine and taurodeoxycholic acid sodium salt), low melting fatty acid (stearic acid), and water. Dispersion of hot microemulsion is done in cold water at (2-3°C) by stirring . Ratio of hot microemulsion and cold water is in range of 1:25 to 1:50.[21][22] The dilution process is determined by composition of the microemulsion. For transferring in product like tablets and pellets, the granulation process of SLN dispersion can be used as granulation fluid, but heavy dehydration is needed in case of low particle content. Solvents such as acetone which distribute instantly in aqueous phase were used to produce nanoparticle where as large particle where produced by use of more lipophilic solvent.[22] Fig. 4.

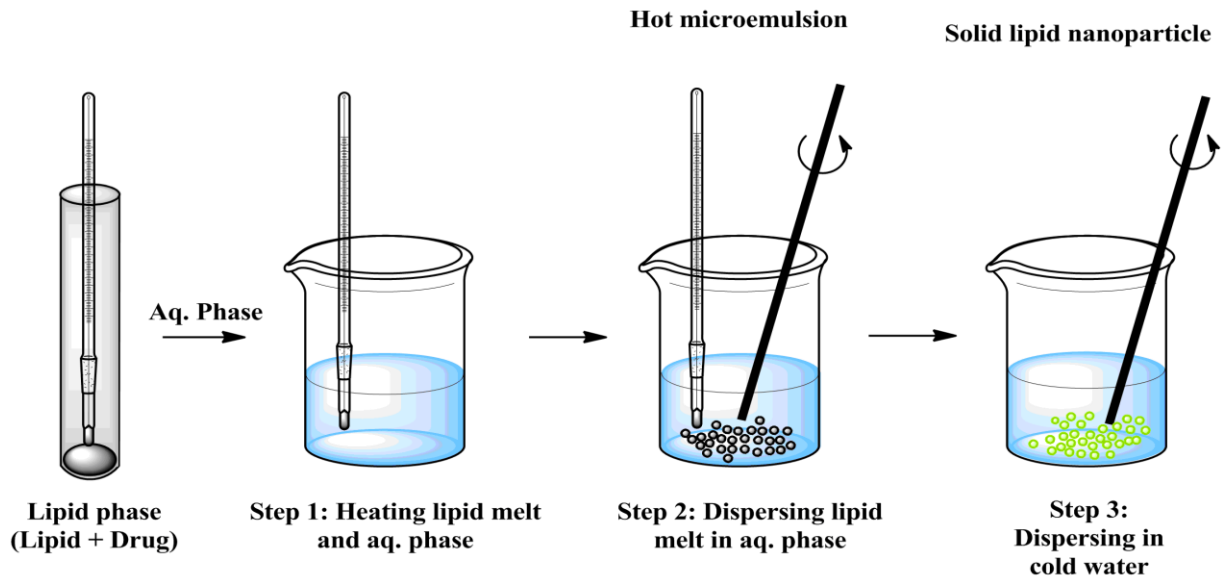

Figure 4: micro emulsion based SLN.

5] Spray drying method

To transform an aqueous SLN dispersion into a drug product it's an alternative technique to lyophilization. It is an cost-effective method as compare with lyophilization and recommended that to use lipids with melting point >70°C. Due to partial melting of particle and high temperature shear forces there is particle aggregation. Good results were obtained with 20% trehalose in ethanol-water mixtures (10/90 v/v) or SLN concentration of 1% in a solution of trehalose in water.[23]

6] Supercritical fluid extraction of emulsion (SFEE)

It is novel technique for the manufacture of solid lipid nanoparticles. Carbon dioxide is key ingredient in this method which helps in removing solvent from o/w emulsions. Though carbon dioxide cannot dissolve ample amount of drugs still it is better choice. Alternative for supercritical fluid extraction of emulsion is supercritical anti-solvent precipitation (SAS). This technique are use of solvent is avoided, Instead of suspension dry powder of particles is obtained, low temperature and pressure required.[24]

7] Double emulsion technique

In this technique drug mostly hydrophilic drug was dissolved in aqueous solution, and then wax is emulsify in melted lipid. By adding the stabilizer (Gelatin, poloxamer-407) the primary emulsion was stabilized. Then the stabilized primary emulsion was dispersedin aqueous phase containing hydrophilic emulsion. After that double emulsion was stirred and it is isolated by filtration. In the double emulsion technique it is not necessary to melt lipid for formulation of peptide-loaded lipid nanoparticle and surface of nanoparticle can customized in order to stabilize them by incorporation of lipid-PEG derivative. Sterically stabilization considerably enhanced the resistance of colloidal system in gastrointestinal fluids.[25]

CHARACTERISATION OF SLN

1] Zeta potential measurement and Particle size

The two most influential techniques for calculation of particle size are photon correlation spectroscopy (PCS) and laser diffraction (LD). Photon correlation spectroscopy (PCS) is also better-known as dynamic light scattering. Due to particle movement fluctuation in scattered light's intensity produced which is measured by this. Photon correlation spectroscopy covers a size range from few nm to about 3 micron. PCS is a good instrument to characterised nanoparticles but it is unable to detect large micro particles, electron microscopy provides, in contrast to the PCS and LD, the straightforward information on particle shape is provided. The physical stability of an optimized solid lipid nanoparticle dispersed is generally above 1 year. Zeta potential measurements permit prediction about storage stability of colloidal dispersion.[26]

2] Electron microscopy

The transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are used to measure the shape and morphology of lipid nanoparticles. It determines the particle size and distribution. SEM uses electron transmitted from surface of the sample where as TEM uses electrons transmitted through the sample.[27]

3] Atomic force microscopy (AFM)

It is an advanced microscopic technique which is applied as a new tool to image the original unchanged shape and surface properties of particles. This technique measures the force acting between the surface of sample and the tip of a probe, when the probe is kept in close proximity to the sample which results in spatial resolution of up to 0.01 nm for imaging.[28]

4] Differential scanning calorimetric (DSC)
The geometric scattering of the radiation from crystal planes in solid allow presence or absences of the former to conclude the degree of crystallinity to be assess. This may used to find out nature and speciation of crystallinity in the nanoparticles through the measurement of glass and the melting point temperature.[29]

5] Drug content determination
1 ml formulation diluted with 5ml of 0.5% surfactant solution, sonicate it in bath sonicator. Afterwards, the preparation is subjected to centrifuge at 12000 rpm for 30 minutes at 4°C. The supernatant is then collected and absorbance is measured at wavelength 430nm by using ultraviolet-visible spectrometer.[30]

6] The entrapment efficiency
It is calculated by taking 1ml formulation afterward sit is centrifuge at 2000 rpm for 5 minutes. The supernatant was collected and then with polar solvent settled particles were washed. Again the centrifuges and supernatant were added collectively and absorbance was calculated at corresponding wavelength in nm in particular drug by using ultraviolet-visible spectrometer [31]

7] In vitro release
It is evaluated using the dialysis bag diffusion method. 2gm of drug loaded with solid lipid nanoparticles be put in dialysis bags. The bag was fixed at both ends. Place the bags in 100ml of phosphate buffer solution (PH-7.4) at 37± 1 °C and under 100 rpm stirring. 5ml of sample were withdraw at predetermined time interval and replace with same volume of fresh dialysis medium and withdraw sample were assayed for drug content by measuring absorbance at 254nm against blank using ultraviolet spectrophotometer.[32]

8] Stability studies
For both solid lipid nanoparticles dispersion and lyophilized solid lipid nanoparticles stores at frozen condition (2-8°C) at temperature 25°C ± 2°C (ambient) for 1 month and assay be evaluated instantly after production of solid lipid nanoparticles and during 1 month (after 7,15,30 days) of storage at various temperature conditions. The finishing formulations were also examined visually for the indication of caking and discoloration.[33]

APPLICATIONS

1] Targeted drug delivery
The fundamental area in drug delivery is accurately targeting drug to cells or tissues of choice. Fate of drug that has entered the body should in control of drug targeting. Today's delivery technologies are far-off from the design of so called "magic bullet" in this drug is exactly targeted to the accurate side of action. Nanotechnology offers an additional challenge to come to this goal a bit closer, to deliver drug in right place at right time. Targeting is the capability to direct the drug-loaded system to the site of interest.[34]

2] Health implication of solid lipid nanoparticle
It is important to distinguish between 'free' and 'fixed' nanoparticles. The former pose direct health threat because they are more challenging to contain due to airborne and can inhaled. Nanoparticles can enter the human body in various ways via lungs where rapid translocation through the blood streams to vital organ is possible, including crossing the blood brain barrier (BBB) and absorption by the intestinal tract and skin.

3] For lymph node metastases and breast cancer
To diminish the toxicity and to increase safety and bioavailability of drug mitoxantrone solid lipid nanoparticles local injections were produced. The efficacy of doreorubic in the reduction of breast cancer cells was reported to be increased when prepared as solid lipid nanoparticles.[35]

4] For topical application
Solid lipid nanoparticles are suited colloidal transport systems for skin application due to their many desired effects on the skin. Recently, studies were carried out on solid lipid nanoparticles with compounds such as ascorbyl pamitate, vitamin E, retinol, clotrimazol, triptolide, podophylotorein for topical application.

5] Potential agriculture application
Upon extraction of volatile oil from artemisia arborescent L, and is incorporated into solid lipid nanoparticles, it decrease the rapid evaporation as compared to its incorporation into emulsions. The system is used in agriculture asproper transporter of ecologically safe pesticides.[36]

6] For Cosmetics use
It is used for manufacturing of sunscreen and they act as an important carrier for molecular sunscreen and ultraviolet (UV) blocker. The in-vivo study discovered that skin moisturization would be built by 3% after four weeks when 4% of solid lipid nanoparticle added to conventional cream.

7] Stealth nanoparticle
This is new system for drug-transport. It deflect the fast clearance of the drug by immune system, By using antibody labelled shealth lip bodies, Devious researches approved the improved delivery to the unreachable sites of target tissue.[37]

8] For treatment of malaria
Nanosized carrier have special attention to reduce the adverse effect of drug therapy like poor bioavailability and selectivity of drugs, some of the nanosized delivery systems have previously proven their effectivness in animals models for management of the prophyaxis of malaria.

9] Ocular application

Interaction of solid lipid nanoparticle with ocular mucosa is improvised by properties such as mucoadhesive and bio compatibility and they prolonged the corneal resistance time of an drug, with the goal of ocular drug targeting. The evaluated SLNs as carriers for the ocular delivery of a Tobramycin in the rabbit eyes. As result they significantly increased the bioavailability of a drug in aqueous humor.[38]

10] Nasal application

Nasal administration shows potential secondary non-invasive route of drug administration because of rapid absorption and onset of action, avoid degradation of the labile drugs (peptides and proteins) in gastrointestinal tract and inadequate transport across epithelial cell layers. For the improvement of drug absorption by the nasal mucosa, various approaches such as prodrug derivatisation and formulation development have been employed. Solid lipid nanoparticle is an efficient alternative proposed for Tran's mucosal drug delivery systems of macromolecular therapeutic agents and diagnostics by different research groups.[39,40]

CONCLUSION

In the solid lipid nanoparticles, the large scale up is achievable and drug could be effective with lesser dose incorporation. Furthermore this particle are in submicron size because of this, more efficient surface area and excellent bioavailability is believable. Nanotechnology focus on the very tiny and it is uniquely suitable to creating system that better delivers drugs to small area inside body. This article covered the difference production method of solid lipid nanoparticles, characterization, advantages and disadvantages of solid lipid nanoparticle, route of administrations and applications. High physical stability and drug loading are advantageous to solid lipid nanoparticle.

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