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SOLID LIPID NANOPARTICLES: A TRENDING OUTLOOK FOR DRUG DELIVERY SYSTEM

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ABSTRACT

Till now a huge type of nanodrug carrier system have been come into existence in medical science by considering target drug delivery and bioavailability improvement. Solid lipid nanoparticle is specific and one of the forefront nanocarrier systems of drug delivery in NDDS. It is (SLNs) as novel, based on lipid nanocarriers with size range comprises between 10 to 1000nm. As various existed research shows that the solid lipid nanoparticles have greater physical stability along with ability to protect the entrapped drug against of decomposition and provision of control drug release, it has greater advantage in comparison of other carrier system. This review paper highlights the types of SLNs, method of preparation along with precise diagrammatic representation, advantages and disadvantages, characterization and finally applications.

KEYWORDS: Bioavailability, Characterization, Control Drug Release, Decomposition.

INTRODUCTION

In this modern trend of various drug delivery system in medical science nano technology drug delivery system have their specific role preferably on the top under which solid lipid nano particles have come into existence which is with modification one of the significant and selective system of drug delivery by considering various advantages in comparison of traditional drug delivery.[1] By developing SLNs new specific frontiers have been opened for improve and enhancing of drug delivery system of drugs specifically for poorly soluble drugs. Nanoparticles comprises of solid colloidal particles running between 10 to 1000nm size range there in the active agent (either drug or biologically active material) is dissolved,

entangled or on it the drug is getting adsorbed or adhered.[2] This system comprises of solid lipid particles of spherical shape which are in nanometer ranges and usually dispersed in surfactant solution of aqueous nature or in water. It seems to be indistinguishable from some degree of oil-in-water emulsion but the solid lipid has replaced the fluid lipid (oil) of the emulsion, i.e. yielding solid and strong lipid nanoparticles.[3] It has been declared that the involvement of solid lipids rather than fluid oils could give controlled discharge pattern of the drug as the maneuverability of the active drug into a solid lipid matrix is comparatively low than a liquid oil.[4]

Some special characteristics feature of nanoparticle such as little molecule size, huge surface region and have capability of changing adjusting their surface properties makes it of advance version against numerous other delivery systems.[5]

SLNs have many beneficial features some of them are good biocompatibility, non-toxic in nature, perfect durability counter to coalition, drug leakage, hydrolysis, and biodegradable, physically durable and astounding transporter for lipophilic drugs.[1] A main additional benefit that is involves the SLNs out turn in the form of powder which can be subsequently loaded into pellets or other dosage form such as capsules or tablets to facilitate improvement in progress of drug delivery.[6]

The exclusive remarkable unique feature of SLNs is that they have capability to easily ferry variety of therapeutics agent comprise tiny drug molecules as well as large bio macromolecules apart from which also include genetic material (DNA/siRNA), and antigens of vaccine too.[7]

Due to their extraordinary size range, nanoparticles show "improved permeability and maintenance of impact" which affirm their potential in explicit targeting on to augment the therapeutic or remedial affects and limit the unwanted impact.[8]

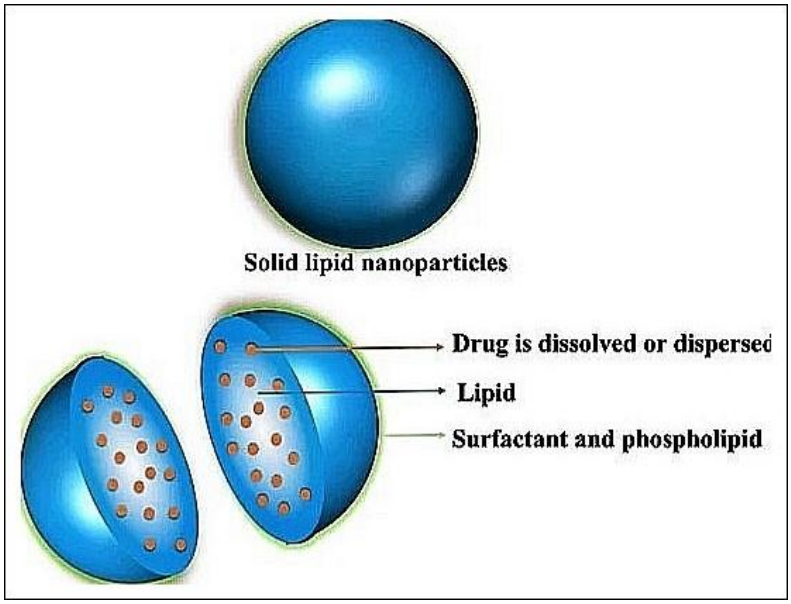

Fig. 1: View of solid lipid nanoparticle.

MODELS OF SLNS

Till now three consecutive drugs incorporated models of SLN have been demonstrated.

Homogenous matrix model

Generation of homogeneous matrix carried out from solid solution of lipid and active drug constituents by utilizing cold homogenization technique without involvement of surfactant. In this, core may coincide the drug either in amorphous swarms or in phase of molecularly dispersed. This present model is commonly examined when profoundly lipophilic agents are incorporated or merge into SLNs.

Drug enriched shell model

This model yields a lipid core free from drug as drug is available just near the shell. Hot high pressure homogenization technique is utilized in this model and lipid precipitation occurs firstly after phase separation on cooling of solution result of which leading of drug free core and due to re-partition in liquid-liquid phase amount of drug increases little by little in outer most shell of lipid core.[9]

Drug enriched core model

This contributes that the nano emulsion is formed when liquefaction of drug in lipid proceed to its saturation and on cooling of nano emulsion the super saturation of active ingredient carried out which leads the precipitation drug's precipitation before lipid precipitation. On expedite cooling process not only drug's precipitation but simultaneously lipid's precipitation

occurs around drug's precipitation and which act as supportive membrane or film toward incorporated drug.[10]

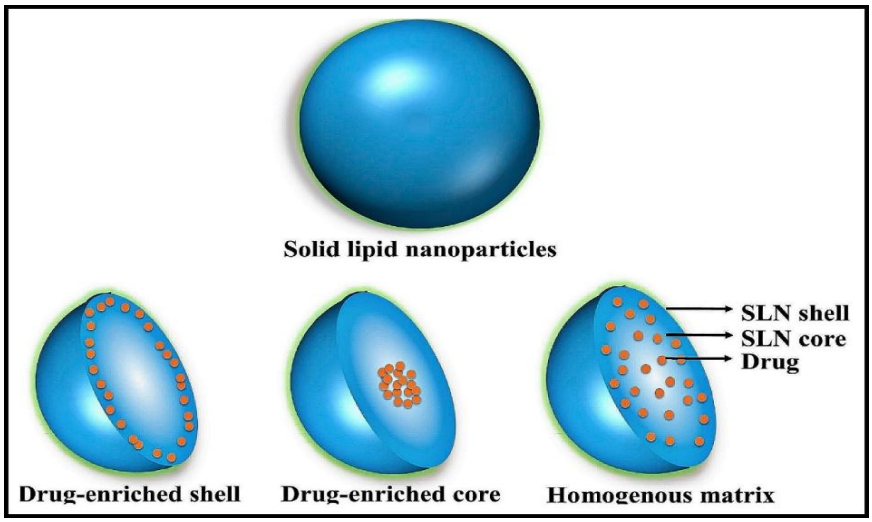

Fig. 2: Models of SLNS.

Principle of Drug Discharge From Slns

- Little molecule measured in the nanometer leads to higher discharge of drug due to large surface area.
- Slow medication discharge is achievable if the lipid matrix consists of drugs uniformly inside it.
- If the drug of high portability then the fast medication release can be attained by making the lipid of crystalline behavior.
- The extent of drug release decreases when there is an increment in the size of particle due to which sustain release pattern of drug could be acquired when there are sufficient particles of large size.
- Surfactant plays momentous role in drug release as its type and amount which present in outer shell of SLNs. Its small amount could lead to prolong drug discharge by giving rise to minimal burst.
- The composition of SLNs, technique of formation, equipment type, lyophillization, sterilization process and tie of production can affect its particle size and behavior of drug release.

PROS OF SLNS

1. As SLNs have small size along with narrow distribution of size result of which site specific drug delivery can be attain.

2. Have excellent stability of shelf life.
3. High entrapment power of active compound and provides chemical protection from degradation
4. Lyophillization can be achieved by process of drying
5. Capability of enhancement of bioavailability of poorly soluble active drug.
6. Acute and chronic toxicity can be decreased by leading control release pattern and using biodegradable and physiological lipids
7. The practicability of inclusion both hydrophilic and hydrophobic medication.
8. Facilitation in sterilization and scale up.[11]

CONS OF SLNS

1. Limited capacity of drug loading.
2. After polymeric transition drug expulsion can occur during storage.
3. Unpredictable gelation tendency.[11]

TECHNIQUES FOR SLNS PREPARATION

High-pressure homogenization (HPH) technique

This facilitate that pushing of a liquid is carried out thru high- pressure homogenizers with the help high pressure generally between100–2000 bar through a gap having size in micron, the fluid quickens to high speed (in excess of 1000 kilo meter/hour) due to applied high pressure and result of which accelerated particles breakdown into submicron size due to shear stress and forces of cavitation. Performance of process can be at exalted temperature (hot homogenization) or beneath room temperature (cold homogenization).[12] In both type of homogenization, the drug is dissolved or may be dispersed in the lipid of molten state almost at 5 to10 °Celsius aloft its melting point.

Hot homogenization

In this the temperature use to carried out this process is usually higher in comparison of lipid melting point and a pre emulsion is formed when combination of lipid and active drug in melting state dispersed in hot aq. with the support of high shear instrument. Further a hot colloidal emulsion is produced by homogenizing the pre emulsion with the aid of homogenizer and after that cooling process of hot emulsion at room temperature is proceeds to generate SLNs which is result of recrystallization of droplet of emulsion.[13]

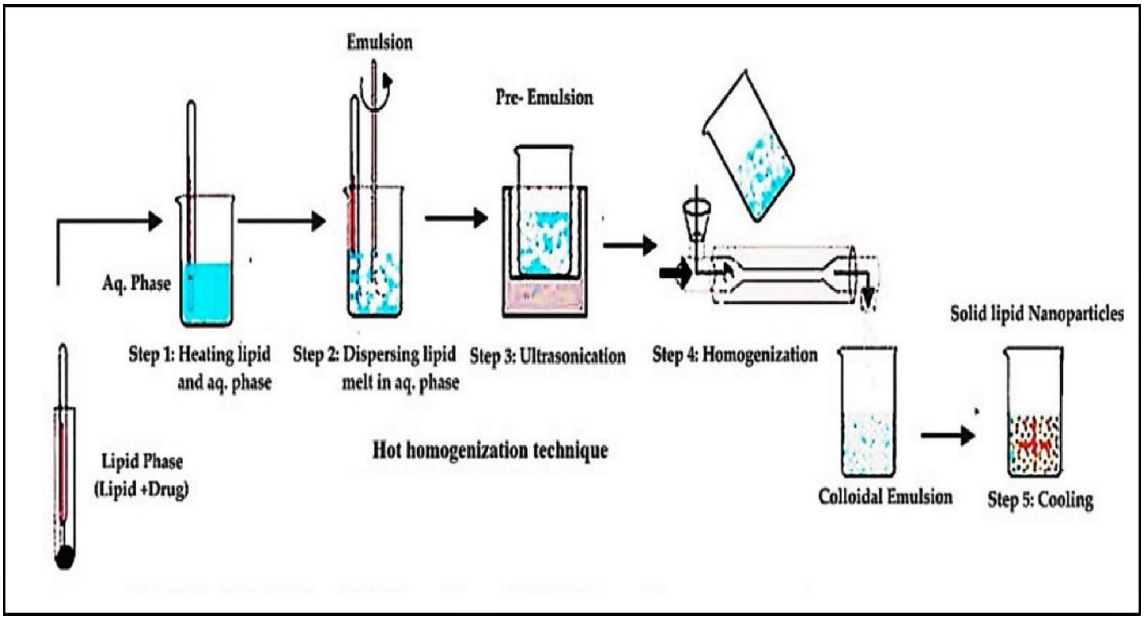

Fig. 3: Hot homogenization process.

Cold homogenization

This technique is analogous to hot homogenization to some extent, the active drug molecule incorporated into melted lipid matrix and then solidification of drug-lipid melt is instantly proceed via rapid cooling thru dry ice or liquid nitrogen. Instantly cooling leads to uniform dispersal of active drug into lipid material. Milling of solidified material is carried out, result of which fine powder is obtain and subsequently a dispersion of fine powder with cold aqueous surfactant solution is produce and finally dispersion is converted into SLNs after applying homogenization along with high pressure.[14]

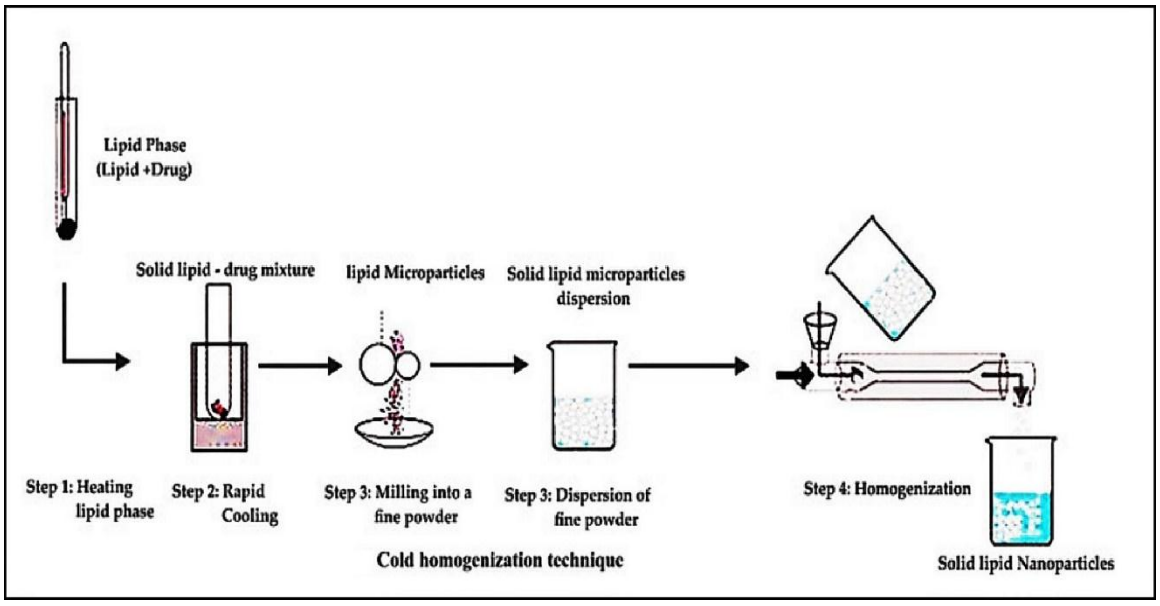

Fig.4: Cold homogenization technique.

High shear homogenization and/or ultra sonication technique

These are techniques of dispersing which leads to carried out the dispersing process of the melted lipid using high sheer homogenization into warm aqueous phase having surfactant to produce an emulsion followed by ultra sonication due to which droplet size of emulsion is reduced and further cooling of warm emulsion beneath temperature of crystallization of lipid produces dispersion of SLNs. Ultra centrifugation can able to yield concentrated form of nanoparticle dispersion.[15]

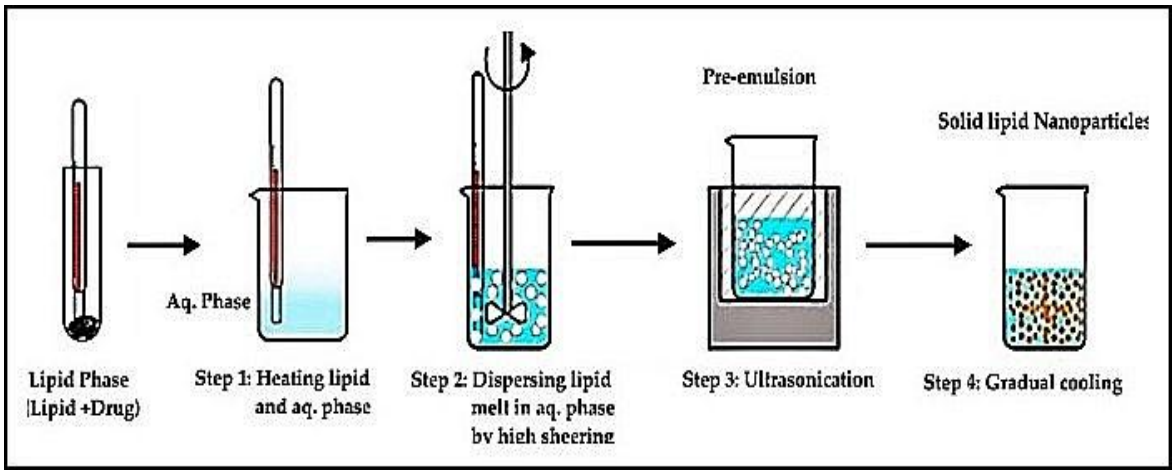

Fig. 5: High shear homogenization and ultra sonication technique.

Membrane contactor technique

This method consist of membrane in cylindrical form having pores and the aqueous phase consisting of surfactant is disseminated in the inner section of membrane, after that lipid in melting form is pressed instantly through the various membrane pores into flowing material inside membrane result of which formation of tiny droplets achieved and they are swept far-out from aqueous phase, it must be taken into consideration that the water temperature maintained at temperature of lipid in melted state and finally by proceeding cooling process of preparation at room temperature, SLNs are formed. Particle size can be attuned by involving membrane of various pore sizes.

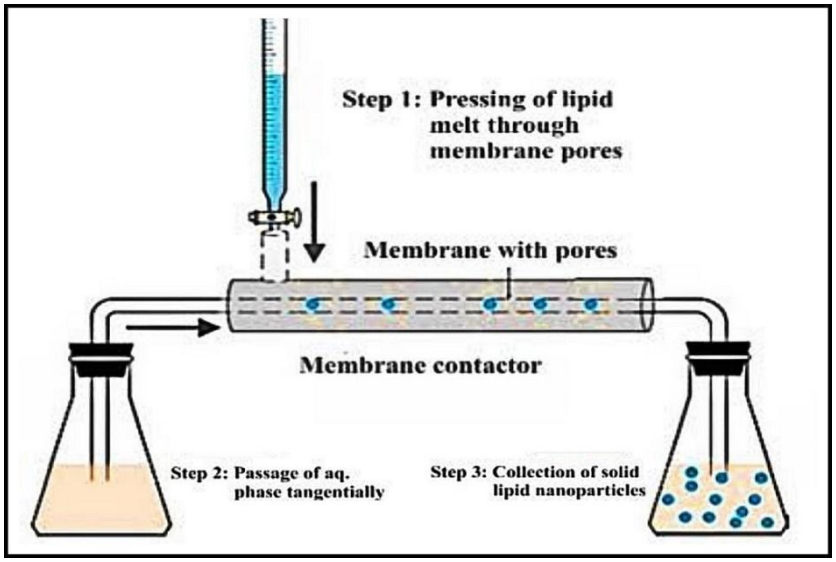

Fig. 6: Membrane contactor technique.

The principle mechanism of formation of particle

1. Lipid phase is tangentially infuses through the multiple pores of membrane, inner section of which have flowing aqueous phase and resulted of process that droplets are formed.
2. Crystallization of droplet initiated to form SLNs.[16]

Double emulsion technique

In this strategy firstly the primary emulsion (w/o) is obtain when melted lipid incorporated the aqueous solution of active drug by blending and dual emulsion (w/o/w) is generated when primary emulsion (w/o) is dispersed in emulsifier's aq. Solution having hydrophilic nature. Particles formed are relatively large but hydrophilic molecules possibility cause surface modification. Lipid crystallization is the primary mechanism of particle formation on solidification.[17]

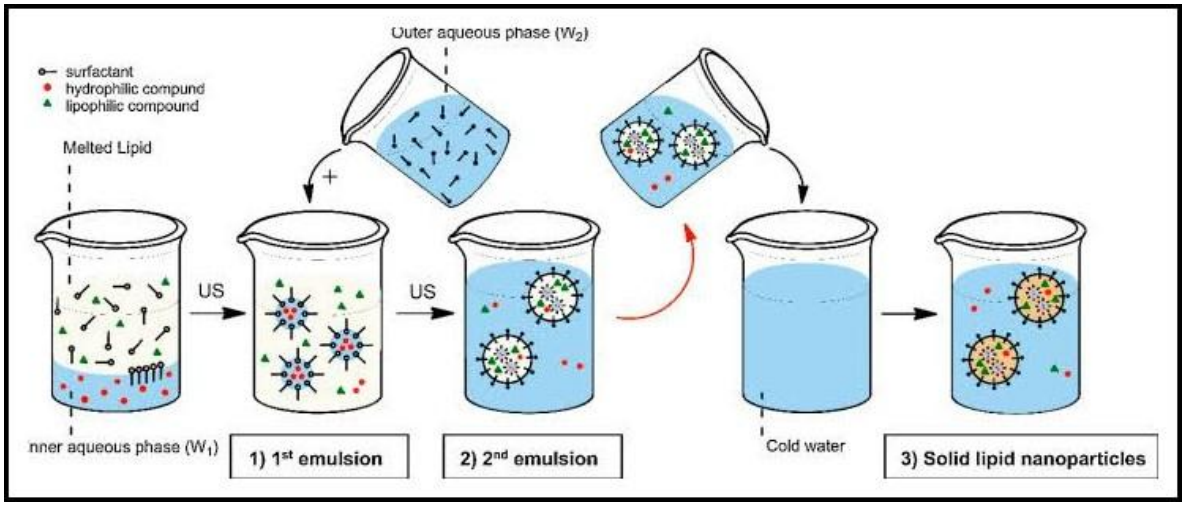

Fig. 7: Double emulsion technique.

Solvent injection technique

This contributes that lipid and drug combination is dissolved in a water-soluble organic solvent (isopropanol and ethanol) and under stirring condition the solution is injected into water by using a syringe and needle. When it becomes in contact with aqueous solution then lipid is converted into drug entrapped nanoparticle.[18]

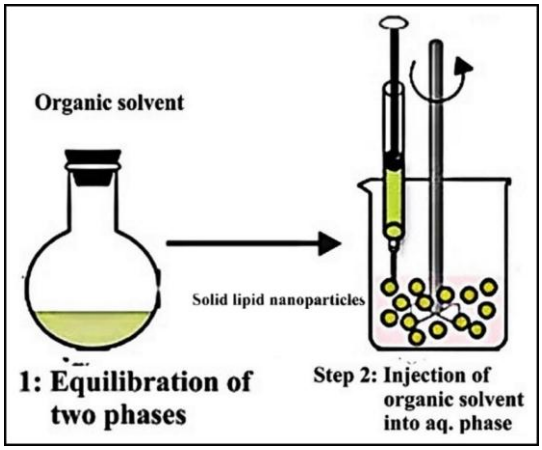

Fig. 8: Solvent injection technique.

Coacervation technique

In coacervation technique the polymeric stabilizer stock solution is formed by warming into high temp water and then a fatty acid's sodium salt is dispersed uniformly in stock solution, further above krafft point of fatty acid's sodium salt, the solution is proceed for heating under stirring condition leads to clear arrangement of solution. The drug that is solubilized in ethanol is included into clear arrangement of solution under consistent and continuously blending until a solitary phase is achieved. On successively addition of coacervating solution to this mixture resulted a suspension which on cooling under consistent agitation yields drug loaded nanoparticle.

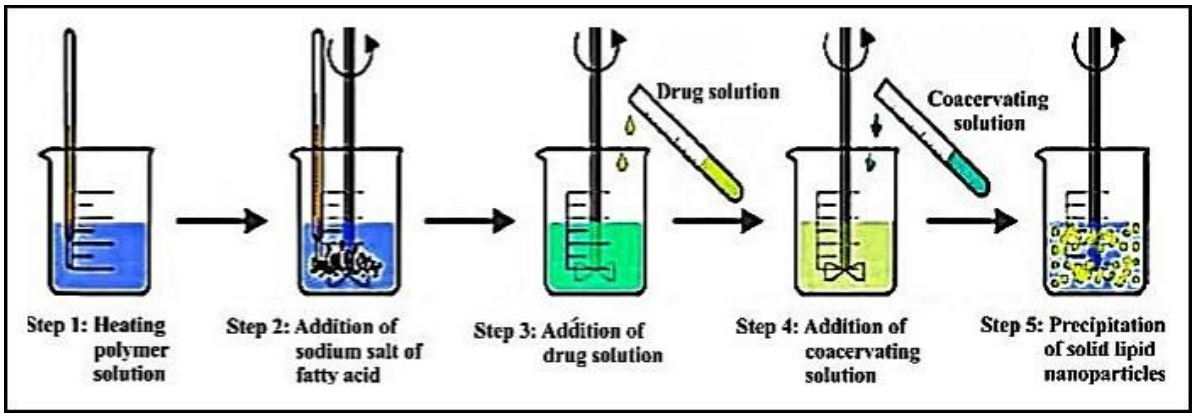

Fig. 9: Coacervation technique.

Emulsification solvent diffusion technique

For solubilization of solid lipids solvents which are quite miscible in water, bring into utilization. Saturation of organic solvent along with water was done to confirm the initial thermodynamic equilibrium. The oil/water emulsion which is transient is instill into water under constant and ceaseless blending result of which is that the solidification phenomenon of dispersed phase carried out leads to generating lipid nanoparticles because of organic solvent dissemination. Dissemination of solvent from inside organic phase to outside aq. phase causes lipid crystallization which is main mechanism of formation of particle.[15]

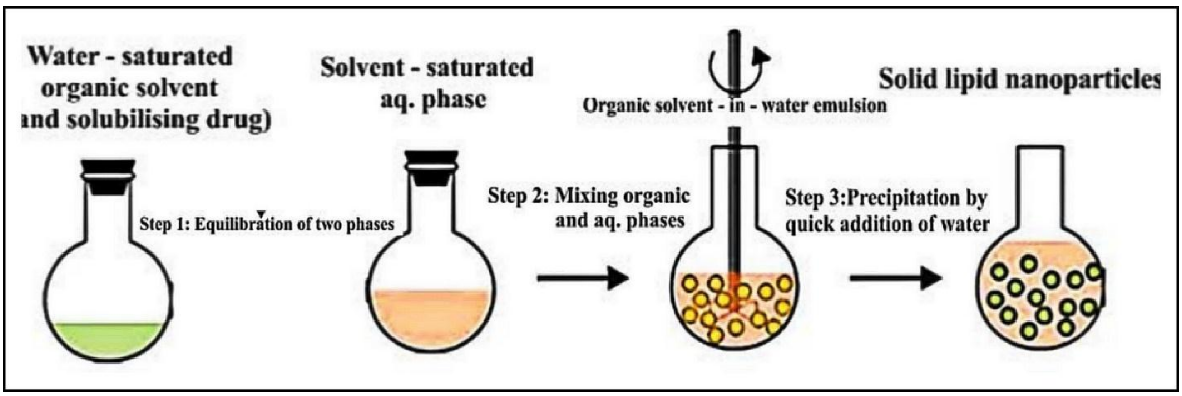

Fig. 10: Emulsification solvent diffusion technique.

Emulsification-solvent evaporation technique

Appropriate volume of organic solvent is used to dissolve lipophilic material by magnetic stirring to produce organic phase and this organic phase incorporate into aqueous solution by utilizing rapid homogenizer to generate coarse pre-emulsion coarse pre-emulsion then further nano dispersion is attain by instantly passing of coarse pre-emulsion through a homogenizer of high pressure and finally nanodispersion is kept over nigh on a magnetic stirrer. Nano dispersion is made by occurring of lipid material precipitation into the aqueous medium upon solvent evaporation then for removal of lipid and agglomerates of drugs, the resulted nano dispersion is filtered by using a sintered glass filter. Nanoparticles formed by this technique, high entrapped efficiency. Due to solvent evaporation lipid crystallization is carried out which is prime mechanism of particle formation.[19]

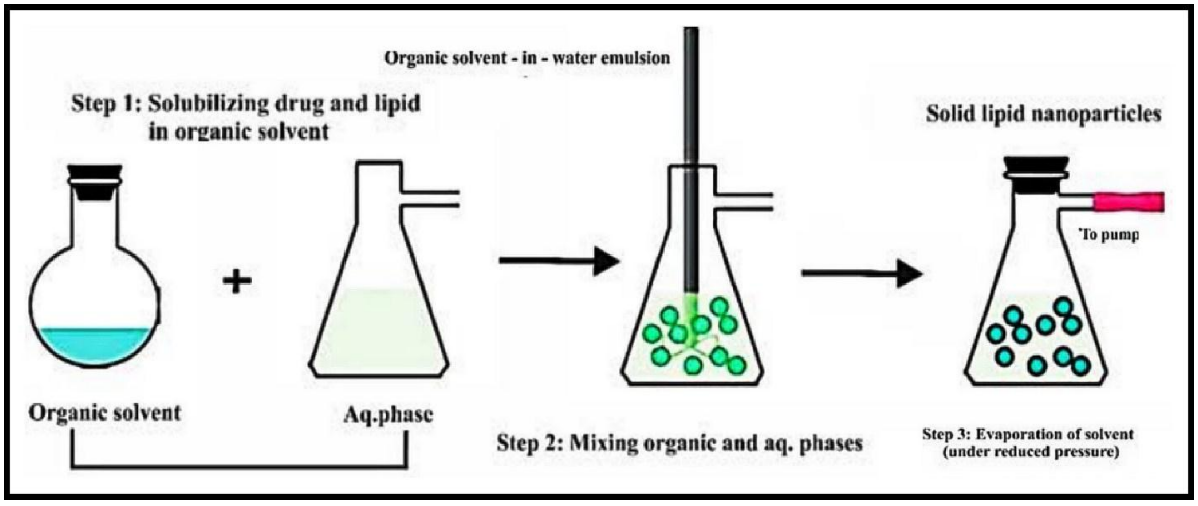

Fig. 11: Emulsification solvent evaporation technique.

Supercritical fluid (SCF) technique

Solid lipid nanoparticles are prepared from emulsions utilizing SCF innovation [20]. the preparation of organic solution is carried out by solubilization of the lipid material and alongside drug into organic solvent (chloroform) with the inclusion of convenient surfactant and this organic solution is dispersed into aq. solution (consist of a co-surfactant), a high-pressure homogenizer comes into process through which the mixture is passed to generate an oil in water emulsion. From one strand of the extraction column the obtained o/w emulsion is inserted (usually at the top) at consistent and uniform flow rate, and the selected supercritical liquid which is sustained at stable temperature and pressure, is introduced concurrently with a consistent and uniform degree of flow. Solvent is extracted continuously from the o/w emulsion leads to formation of lipid nanoparticle dispersion.

Mechanism of particle formation

SFE (dissemination) of organic solvent and lipid crystallization which is result of expansion of organic phase.[21]

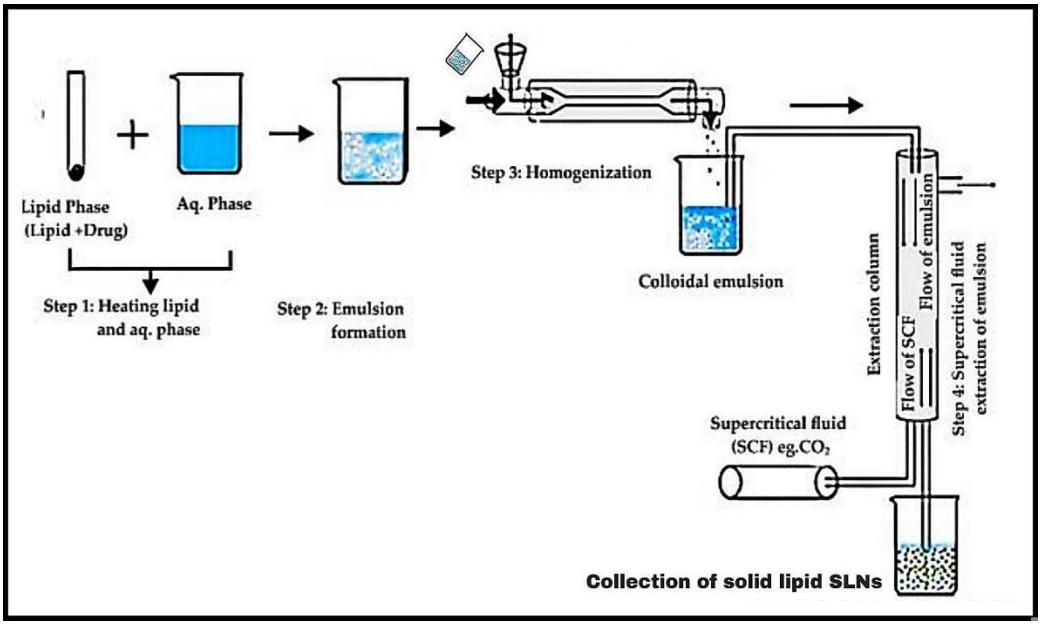

Fig. 12: Supercritical fluid (SCF) technique.

CHARACTERIZATION OF SLNS

Particle size analysis and zeta potential

The size of particles is utilized to estimating the physical durability of SLNs. The most premium techniques for assessing particle size are Laser Diffraction (LD) and Photon Correlation Spectroscopy (PCS). The PCS additionally called dynamic light scattering by which intensity of scattering light can be measured which is result of motion of particles randomly.

The PCS is particularly used to estimation of particles size having range in 3 nm to 3 µm whereas laser diffraction is used to estimate the particle size of range 100 nm to 180 µm and larger size of micro-particles can also be determined by pcs technique. An important criterion is that effect of the particle size on the diffraction on which LDS technique depends. Smaller particles produce stronger scattering with high angle of diffraction as compared to larger particles.[11]

Zeta potential is estimated by the use of zeta potential analyzer and for determination of size along with zeta potential the SLNs dispersion is firstly diluted 50-folds with the primary dispersion preparation medium. The increased value or degree of zeta potential could offer ascent to the disaggregation of the particles. Zeta potential determination makes it conceivable to anticipate the storage stability and strength of colloidal dispersion.[22,23]

Electron microscopy

This provides approach to straight forwardly observation of nanoparticles is usually estimated by Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). Morphological assessment in better way is determined by SEM whereas TEM has small size restriction of detection.[24]

Atomic force microscopy (AFM)

In this strategy, for production a topological map a probe tip alongside atomic scale sharpness is reestablish across a sample and the forces complies amid the tip and surface is that on which topological map is based. Across the sample (contact mode) the probe can be hauled just directly above (non-contact mode), with the definite nature of the appropriate force occupied serving to differentiate between the sub strategy. With this outlook the ultra-high resolution can be obtain which having the proficiency to map or delineate a sample as per properties thereto size, e.g., makes AFM can be a valuable tool by colloidal attraction or refusal to deformation.[25]

Dynamic light scattering (DLS)

DLS and PCS are very fast and prominent technique for estimating the particle size. Brownian nanoparticles in colloidal dispersion having size in the nano and submicron range are usually determined by DLS. Light hits the moving particles by striking monochromatic light (laser) into a spherical particles soln. (in case of random Brownian motion) bring out Doppler Shift result of which, the wavelength of the coming light is changed and it was revealed that this change is linked to the particle's size. Use of the autocorrelation function, determination of size distribution, the particle movement in the medium, the diffusion coefficient of particle, determination of size distribution can also be determined by DLS. The PCS is the commonly applied method for the accurate assurance of particle size and the distribution of size based on DLS.[26]

Nuclear magnetic resonance (NMR)

For both qualitative nature and measurement of nanoparticle's size, NMR can be included. Chemical shifting balances and the susceptibility to molecular flexibility are the results on which selection of NMR technique depends to furnish important data and information regarding the physicochemical state of constituent inside the nanoparticles.[3]

Acoustic methods

In acoustic spectroscopy technique by measuring the sound waves attenuation and applying physical equation, particle size determination can be carried out. Information on the surface charge can be attain by oscillating electric field which is created by movement charged particle under control of acoustic energy.

Surface charge

The intensity and nature of surface charge are the specific units by which the nanoparticles interaction with their biological environment and their interaction of electrostatic type with bioactive compounds are determined. The stability (colloidal) of the nanoparticles is measured by zeta potential which is a specific measurement of the surface charges. The estimation of zeta potential makes it conceivable to anticipate the stability and strength of the colloidal dispersion during storage. The high degree of zeta potential whether negative or positive values, assures the colloidal particle's stability and absence of aggregations too. The degree of surface hydrophobicity then can be estimated from zeta potential value. Information on the behavior and nature of the drug which is to be encapsulated within the nano capsule or absorbed on its surface can easily obtained by zeta potential.[27]

APPLICATIONS OF SLNS

SLNs in parenteral administration

It has been cleared that SLN is a very good tool for administration of the drug via parenteral route because of various reasons. Firstly, they have small size which helps them to circulate the system of micro vascular and regarding of hydrophilic coating prevent uptake of macrophages. Secondly, they have physiologically well tolerated excipients along with the API and after lyophilization and sterilization they possess good storage capabilities. Delivery of viral and non- viral gene can also be done by SLNs where cationic SLNs can bind gene through electronic interactions. Hence they are used in gene therapy in cancer treatment.[28]

SLNs in nasal administration

Nasal route is adopted as an alternative non-invasive route due to quick absorption, quick beginning of medication activity and avoidance of drugs deterioration in GIT and inadequate transport across layers of epithelial cells. Pro drug derivatization and formulation development are the perfect approaches which have been used for improving absorption of drugs various research groups have stated that SLNs as an alternative to trans mucosal systems of delivery of macromolecular therapeutic agents and diagnostics.[11]

SLNs in topical administration

Dermatological conditions can be treated with SLNs by targeting the corticosteroids to sites of disease and reducing systemic drug absorption. They are preferred for use on injured or aggravated skin as usually they depend on non-irritant and non- poisonous lipids. For treatment of skin diseases like eczema and psoriasis, corticosteroids are generally used therapeutic agents.[29]

SLNs in respiratory administration

Radio-labeled SLN when inhaled and assessed, the data displayed a momentous uptake of SLNs into the lymphatic system. In treatment regarding cancer of lungs SLNs have been approached as carriers of anti-cancer drugs and also for peptide drug for bioavailability increment. Nebulization of SLNs has improved bioavailability and lead to reduction in dosing frequency that manages pulmonary TB.[30]

SLNs as vaccine adjuvants

The more secure new subunit vaccines are not as much efficacious and successful in immunization and henceforth, viable adjuvants are requisite. Adjuvants of Immunologic are substances that are utilized to boost the degree, incitement and clout of vaccines. The slow degradation of lipid component of SLNs gives a long enduring exposure to immune system.[31]

SLNs for drug targeting in brain

SLNs have been proposed as one of the specific drug targeting system in treatment of various CNS disease as they boost the capability of drug to infiltrate the BBB. SLNs are advantageous than polymeric nano particles because their low cytotoxicity, good production scalability with higher drug loading capacity. The critical issues which come under development of appropriate brain targeting formulations are addressed by physiochemical properties of SLNs.[32]

SLNs for peptides and proteins delivery

Incorporation of hydrophobic or hydrophilic proteins can be attained by SLNs when processed under optimized conditions. Administration of proteins can be done thru parenteral routes or other selective routes include oral, nasal and pulmonary routes after incorporated into SLNs or adsorbed on the surface of it. This system improves or boosts protein stability,

escape proteolytic deterioration, and uninterrupted discharge of the incorporated drug molecules.[33]

SLNs in cosmeceuticals

By considering the preparation of sunscreens SLNs have come into existence as an active or effective transporter specialist for UV blockers and molecular sunscreens. It has been declared that SLNs have controlled release pattern and involve as innovative occlusive topical. In consideration of vitamin a with glyceryl behenate provided with better localization in upper skin layers with glyceryl behenate has provided with better localization.[34]

SLNs as gene carriers

In gene vector formulation solid lipid nanoparticle can be used. According to recent studies, diametric hiv-1 hat peptide (TAT 2) incorporation into SLNs gene vector was carried out to optimization of gene transfer.[35] Cationic SLNs can well bind deoxy ribonucleic acid (DNA) directly via interaction of ionic type and intervene gene transfection. Liquid nano phase consisting of water and also an organic solvent miscible in water was used to prepare lipid nucleic nanoparticle where lipid and DNA both are solely dissolved thru organic solvent removal, formation of durable and size of approximate homogenous range lipid-nucleic acid nanoparticle between 70-100 nm was carried out and it's called genospheres.[36]

SLNs for cancer chemotherapy

For delivering of chemotherapeutic drugs SLNs have been considered as best suitable carrier because they have provided improved or stability of drugs along with encapsulation of drugs of cancer with multifarious physicochemical properties, augment drug efficacy, upgraded pharmacokinetics and minimum *in-vitro* toxicity. The major problem has been reported in targeting tissues is colloidal particles removal by the res macrophages. Delivering of anticancer compound by using SLNs is very prominent way as several obstacles can be at least partially overcome by SLNs, some obstacles which include tissue toxicity of normal rating, inferior specificity problems alongside stability issues and a high prevalence of medication obstructive tumor cells are involved.[37,38]

SLNs for cancer (breast cancer) and lymph node metastasis treatment

Various studies have shown that SLN local injections of mitoxantrone were formulated result of which reduction in toxicity, improve and boosted the safety and simultaneously drug's bioavailability.[39]

SLNs in tuberculosis treatment

Drug delivery system based on SLNs via pulmonary route has been used to deliver anti-tubercular drug. Reduction in the frequency of dose and improvement in patient compliance was achieved by several drugs loaded SLNs systems for tuberculosis. Utilization of solvent diffusion technique has been come into process for preparation of anti-tubercular drugs in the form of SLNs.[30]

CONCLUSION

By extracting all important information from numerous research articles ,it has been concluded that number of research and scientist groups are progressively fascinating towards solid lipid nanoparticle because of its exclusive properties alongside pros counter to traditional dosage forms and hence SLNS have a durable nature which is propitious for delivery of poorly water soluble drugs and by considering bioavailability too.

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