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A Glimpse on Theoretical Considerations for Solid Lipid Nanoparticles (SLN) as a Novel Drug Delivery System; a Review

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ABSTRACT

As an alternative to other conventional colloidal carriers such as liposomes, polymeric nanoparticles, and emulsions owing to their benefits such as controlled drug release, targeted drug delivery, and enhanced stability, solid lipid nanoparticles emerged in the early 1990s.[1] The development of solid lipid nanoparticles (SLN) as a next-generation drug delivery technology has opened up new opportunities for the pharmaceutical industry, cosmetics, research, clinical medicine, and other related fields of study. Lipid nanoparticles provide the potential to create novel therapies because of their distinct size-dependent characteristics [2]SLNs have significant promise for site-specific, controlled medication delivery as well as gene delivery. The newest developing drug delivery technique uses polymer-lipid hybrid nanoparticles, lipid drug conjugates, and nanostructured lipid carriers.[3]

INTRODUCTION:

A nanoparticle is a microscopic particle with a size between 1 and 100 nanometers Nanoparticles, invisible to the human eye, can exhibit significantly different physical and chemical properties to their larger material counterparts.[4].With the deep understanding gained in the diverse fields of Biotechnology, Biomedical Engineering, and Nanotechnology, the field of Novel Drug Delivery System is rapidly expanding.[5]Solid lipid nanoparticles (SLNs), which have a diameter size range of 50 nm to 1μm, are colloidal drug carriers.[6]

One of the hardest areas for study in pharmacy is the targeted delivery system. Enhancing medication delivery through the development of colloidal delivery systems including liposomes, micelles, and nanoparticles now faces a new challenge.[7]

Nanoparticles are colloidal particles with a size between 10 and 1000 nm. They are made from artificial or natural polymers and are perfectly suited to enhance drug delivery and lessen toxicity. They have become a versatile alternative to liposomes as drug carriers throughout time. The capacity of nanoparticles to pass through various anatomical barriers, prolonged release of their contents, and stability in the nanometer range are all necessary for their successful application in the administration of drugs. Lipids have been proposed as an alternative carrier, particularly for lipophilic pharmaceuticals, to circumvent the drawbacks of polymeric nanoparticles, such as their high cost and lack of availability of safe polymers with regulatory approval. These solid lipid nanoparticles (SLNs), also referred to as lipid nanoparticles, are drawing a lot of formulator's attention from all over the world.

Since lipids are solid at room and body temperatures, solid lipid nanoparticles (SLN) are medication carriers in the submicron size ranges.[8]

Advantages of SLN

- Reduces the risk of acute and chronic toxicity and prohibits the use of organic solvents in manufacturing processes.
- More precise control over the kinetics of encapsulated substances release.
- Site-specific drug administration, improved drug absorption through dermal application
- The viability of using both hydrophilic and hydrophobic medications.
- Achieved a high concentration of useful compound

- Unlike biopolymeric nanoparticles, much simpler to make.
- Increased bioavailability of compounds that aren't very water soluble
- Potential for scaling up
- The majority of the materials used to make SLNs are inexpensive and simple to scale up for industrial production.
- SLNs are more stable than liposomes, according to research.
- It is possible to make emulsions using traditional techniques.
- Preventing sensitive molecules and chemically labile substances from being degraded in the gut.
- Increase the chemical synthesis of the labile integrated compound and bioavailability of the bioactives that have been captured.
- Lyophilization is conceivable.
- Is susceptible to industrial sterilization techniques
- High-pressure homogenization is a cost-effective preparation process with excellent reproducibility.
- The stability of SLNs over time can be excellent. It is possible to select lipids that don't hydrolyze in aqueous solution.[9-12]

Disadvantages of SLN

- Low capacity for packaging medicines.
- Comparatively large volume of distributed water.
- Medication exclusion after polymeric modification during storage.
- The polymeric transition is moving so quickly.
- Unexpected polymeric transition dynamics.
- Periodically burst release.

- Low capacity for loading drugs.
- The dispersions have a rather high water content (70-99.9%).
- In the manufacture of tablets and pellets, too much water must be removed.
- Due to partitioning effects, the production cycle's limited capacity for loading water-soluble medicines.
- The limited loading capacity for hydrophilic medicines is a result of production-related partitioning effects.
- In addition to having a low drug loading efficiency and the potential for drug expulsion due to crystallization during storage, SLNs' immaculate crystalline structure has several other disadvantages.[13-15] Preparation techniques for solid lipid nanoparticles:

Methods of preparation of solid lipid nanoparticles

1. Ultrasonication / High-Speed Homogenization:

High-speed homogenization or ultrasonication procedures can be used to prepare SLNs. A combination of ultrasonication and high-speed homogenization is necessary to produce lower particle sizes. One of the simplest techniques for making SLNs is ultrasonication or high-speed homogenization. Work on the concept of mixing the drug in bulk of lipid melt. This method has the benefit of using equipment that is frequently found at the lab scale. However, this approach has drawbacks such as a wider size dispersion that goes into the micrometre range. Other downsides of this method include potential metal contamination and physical instability, such as particle development during storage.[16]

2. High-Pressure Homogenization (HPH) :

Solid lipid nanodispersions were initially created using high shear homogenization procedures. It is a solid and effective method. High-pressure homogenizers force a liquid at high pressure (between 100 and 2000 bar) through a small opening (between a few microns). about a very short distance, the fluid accelerates to a very high velocity (about 1000 km/h). Cavitation forces and extremely high shear stresses cause the particles to break apart at submicron sizes. Although up to 40% lipid content has also been researched, 5-10% lipid content is often used. The two main methods of HPH, heat homogenization and cold homogenization, both involve combining the medication with a large amount of lipid melt.

2.1 Hot Homogenization:

Because hot homogenization is performed at temperatures over the lipid's melting point, it is comparable to the homogenization of an emulsion. By using a high-shear mixing device, it is possible to create a pre-emulsion of the drug-loaded lipid melt and the aqueous emulsifier phase (both at the same temperature). The end result of this procedure is a hot o/w emulsion, which when cooled causes the lipid to crystallize and produce solid lipid nanoparticles.

Above the lipid melting point, the pre-emulsion is homogenized under high pressure. It is preferable to obtain droplets in the range of a few micrometers in size because the quality of the pre-emulsion greatly influences the quality of the final product. Higher processing temperatures result in smaller particle sizes because the lipid phase's viscosity is lessened. The medicine and the carrier, however, degrade more quickly at high temperatures. The temperature of the sample is always elevated during high-pressure processing (about 10° at 500 bar). Most of the time, 3-5 homogenization cycles at 500–1500 bar are adequate. Due to

the high kinetic energy of the particles, increasing the homogenization pressure or the number of cycles frequently causes an increase in particle size.

2.2 Cold Homogenization:

Cold homogenization has been created to address a number of issues with hot homogenization, such as drug distribution into the aqueous phase during homogenization and temperature-induced drug degradation. Due to the difficulty of the nanoemulsion's crystallization step, the lipid undergoes polymorphic transitions that result in many alterations and/or super-cooled melts. The drug is added to melting lipids before cooling the mixture until it solidifies. A mortar mill is used to grind solid material. At room temperature or even significantly below, the obtained lipid microparticle is dispersed in a cold surfactant solution. The lipid must remain in a solid state throughout homogenization, which requires efficient temperature control. Cold homogenized samples often have a wider size distribution and bigger particle sizes compared to hot homogenized samples.[17]

3. Microemulsion Based Method:

This technique relies on diluting microemulsions. Due to the fact that microemulsions (such as o/w microemulsions) are two-phase systems made up of an inner and an outer phase. They are created by stirring an optically transparent mixture, typically made of water, polysorbate 20, polysorbate 60, soy phosphatidylcholine, taurodeoxycholic acid sodium salt, low melting fatty acids (such as stearic acid), and co-emulsifiers (such as butanol and sodium monooctylphosphate). Under stirring, the hot microemulsion is disseminated in cold water (2–3°C). The system is diluted by the precipitation of lipid particles in water, which lowers the amount of solids in the SLN dispersion. The SLN dispersion can be used as a granulation fluid to transfer into solid products (tablets, pellets) by the granulation process, however, if the particle content is low, too much water needs to be eliminated. Along with the microemulsion's composition, the temperature gradient and pH level in microemulsions determine the product's quality.[18]

4. Spray drying method:

It serves as an alternative to the lyophilization procedure. This suggests using lipids with melting points greater than 70 °C. The best results were obtained using 20% trehalose in an ethanol-water mixture or 1% SLN in a trehalose-in-water solution.[17]

5. Solvent evaporation Method :

The lipophilic substance is dissolved in a water-impermeable organic solvent (cyclohexane) that is emulsified in an aqueous phase for the generation of nanoparticle dispersions by precipitation in o/w emulsions. As soon as the solvent evaporates, the lipid precipitates in the aqueous media to create a nanoparticle dispersion. Using lecithin/sodium glycocholate as the emulsifier and cholesterol acetate as the model medication, the produced particles had an average diameter of 25 nm. Siekmann and Westesen (1996), who created the cholesterol acetate nanoparticles with a mean size of 29 nm, validated the reproducibility of the result.[19]

6. Supercritical Fluid Method :

This brand-new method was just used for the creation of SLNs. When a fluid is over its critical pressure and temperature, it is said to be supercritical. The fluid's capacity to dissolve substances grows. This technique includes numerous methods for producing nanoparticles, including supercritical fluid extraction of emulsions (SFEE), the rapid expansion of supercritical solution (RESS), particles from gas-saturated solution (PGSS), and aerosol solvent extraction solvent (ASES). The benefits of this method include avoiding the use of solvents, using dry powder particles rather than suspensions, and only requiring modest pressure and temperature conditions. The best solvent for this procedure is carbon dioxide solution.[20]

7. Double Emulsion Method:

A novel approach based on solvent emulsification-evaporation has been employed to create hydrophilic-loaded SLN. To prevent drug partitioning to the external water phase during solvent evaporation in the external water phase of the w/o/w double emulsion, the drug is here encapsulated with a stabilizer. [20]

8. Membrane contactor technique:

In the membrane contactor method, the liquid phase was forced through the membrane pores at a temperature above the lipid's melting point, resulting in the creation of tiny droplets. The ease of usage of this method and the ability to adjust the SLN particle size by making the right process parameter choices are its benefits. By cooling the preparation at room temperature, SLNs were created. Here, the thermostated bath was utilized to maintain the

necessary temperature for both the aqueous and organic phases, and nitrogen was employed to produce the pressure needed for the liquid phase.[21]

9. Film Ultra Sound Dispersion:

This approach involves combining an organic solution with a medication and a lipid. The organic solution evaporates during rotation and decompression to create a lipid film. The lipid film is then added to an aqueous solution containing the emulsion, which is then exposed to ultrasonic treatment with a probe and diffuser to create equally sized particles.[22]

Applications of SLN:

SLNs as Cosmeceuticals: Sunscreens have been made using SLNs, which serve as a crucial carrier for molecular sunblock and ultraviolet (UV) blockers. According to the in vivo study, when 4% of SLN is added to the regular cream after four weeks, skin moisturization will increase by 31%. SLNs have been demonstrated to be a regulated, novel, occlusive, and topical release method. Wissing and Müller discovered that when moisturizers and sunscreens were made in the form of SLNs, their efficacy increased.[23]

SLN for Parenteral Application: Wissing et al. (2004) conducted a thorough evaluation of SLN parenteral use. Because they contain components that are physiologically well-tolerated and have good preservation properties following lyophilization and/or sterilization, SLNs are ideal for systemic distribution. When administered intravenously, SLN is tiny enough to circulate through the microvascular system and, in the case of hydrophilic coating, impede macrophage absorption. SLN has been proposed for viral and non-viral gene delivery. Electrostatic interactions have shown cationic SLN can directly bind genes, and it may be useful in targeted gene therapy for the treatment of cancer. Additionally, the composition of a particle has the ability to modify its charge, enabling the binding of molecules with opposing charges.

The inability of powerful medications to cross the blood-brain barrier (BBB) frequently limits the ability to treat diseases of the central nervous system, such as brain tumors, AIDS, and neurological and psychiatric problems. Colloids with a hydrophilic coating have better tissue distribution and BBB transit (Kreuter, 2001; Wang et al., 2002). After 24 hours of intravenously administering doxorubicin-loaded stealth and non-stealth SLN, Fundaro et al. (2000) found that the stealth nanoparticles were present in the circulation at higher concentrations than the non-stealth SLN.[17]

SLN for Ocular Application: It has been extensively discussed how to administer ocular medications using SLNs with the goal of ocular drug targeting. SLN's biocompatibility and mucoadhesive properties improve its interaction with the ocular mucosa and extend the drug's time in contact with the cornea. The utilization of SLN as tobramycin carriers in rabbit eyes was studied by Cavalli et al. SLNs greatly increased medicine bioavailability in the vitreous as a result. Cavalli investigated how pilocarpine, a common medication needed to treat glaucoma, was delivered using SLN. For the purpose of increasing drug absorption in the eyes, they discovered very identical results.[24]

SLN in Cancer chemotherapy: Use of SLN in various cancer therapies

- **Liver cancer**

One of the most prevalent malignancies in the world is hepatocellular carcinoma (HCC), a primary malignancy of the liver. HCC has the second-highest cancer-related mortality rate in China. The liver is the most typical organ for tumor metastases in addition to original malignancies. For the in-vitro and in-vivo delivery of antisense oligonucleotide (AS-ODN) to liver endothelial cells, Bartsch and colleagues (2004) proposed stabilized lipid-coated lipoplexes.

- **Breast Cancer**

As the second highest cause of cancer-related fatalities in women, breast cancer is one of the most common cancers in women. However, because of advancements in breast cancer therapy and prevention since 1989, the annual rate of breast cancer mortality has fallen by 1.8%. The development of resistance to several chemotherapeutic medicines, often known as multidrug resistance (MDR), is a significant clinical barrier in cancer therapy. Chemoresistance can typically be caused by one of two things. First, by physically impeding delivery to the tumor (such as by insufficient absorption, excessive metabolism/excretion, and/or insufficient drug diffusion into the tumor mass); second, through intracellular mechanisms that raise the threshold for cell death. It is well known that nanoparticles are effective tumor-targeting agents because of their enhanced permeability and retention (EPR) effect, which allows them to target tumors passively. As an added benefit, hiding the particles with a polyethylene glycol/oxide (PEG/PEO) surface modification prevents the reticuloendothelial system from absorbing them, extending their circulation time.[25]

SLN for Respiratory Application: Nebulizing SLNs containing anti-tubercular, anti-asthmatic, and anti-cancer medications have been demonstrated to be effective in boosting drug bioavailability and lowering dosage rates to improve pulmonary action. When used as inhalers, paclitaxel-loaded SLNs created by Rosière et al. have increased therapeutic effectiveness for lung cancers.[23]

SLN for Nasal Application: Due to fast absorption, quick start of action, avoidance of labile drug degradation in the GI tract, and insufficient transport across epithelial cell layers, nasal administration was a prospective alternative noninvasive method of drug delivery. Efforts have been made to enhance drug absorption through the nasal mucosa using methods like formulation development and prodrug derivatization. SLN has been suggested by many research groups as an alternate transmucosal delivery route for macromolecular therapeutics and diagnostics. In a recent study, polymeric nanoparticles that had been coated with PEG as vaccination carriers demonstrated excellent outcomes. Improved transmucosal transport of the enclosed bioactive chemical thanks to PEG coating of polylactic acid nanoparticles. This concept is applicable to solid lipid nanoparticles.[26]

Characterization of SLNs: The characterization of SLNs can be done by following parameters.

Visual size and distribution

- **Photon correlation spectroscopy (PCS):** PCS uses particle mobility to gauge differences in scattered light. It measures between a few nanometers and three microns in size. The radius of the particle is affected by the diffraction angle.

- **Laser diffraction (LD):** The advantage of LD is that it covers a broad range from nanometers to lower millimeter. The sensitivity of LD to tiny particles was enhanced by differential polarization intensity scattering.[27]

Zeta potential: Zeta potential analyzers or zetameters can be used to analyze its measurement. In the aqueous suspension of SLN, the zeta potential reveals the strength of electrostatic attraction or repulsion between particles.[27]

Atomic force microscopy (AFM): This method creates a topological map of the sample based on the forces acting between the probe tip and the surface by rastering a probe tip with atomic scale sharpness across the sample. The specifics of the specific force used serve to

differentiate between the sub techniques. The probe can be moved across the sample (contact mode) or left to hover slightly above (noncontact mode). AFM is a useful tool because it can map a sample according to features other than size, such as colloidal attraction or resistance to deformation, and it is capable of achieving ultra-high resolution.[19]

X-ray diffraction and differential scanning calorimeter (DSC): The degree of crystallinity can be measured thanks to the geometric scattering of radiation from crystal planes within a solid, which enables the detection of the former or its absence. Drug properties and degree of crystallinity in nanoparticles can be assessed using DSC.[23]

Electron microscopy: TEM and SEM are used for direct nanoparticle observation. The SEM has a small size limit of detection and is utilized for better morphological examination.[23]

In-vitro drug release studies: In dialysis tubing, the release profile of a drug's active ingredient can be monitored. Solid lipid nanoparticles are placed into previously washed dialysis tubing, which is hermetically sealed, and dialyzed against disintegration media at a fixed temperature with constant mixing during the process of dialysis. Tests were performed under various conditions, combined or centrifuged, and assessed for the presence of drugs. The quick discharge rate of drugs from colloidal carriers cannot be determined using this method. In vivo drug release is studied using the following techniques as Dialysis bag diffusion technique and Reverse dialysis bag technique.[28]

Conclusion: Significant advancements in medical therapies that combine the benefits of polymeric nanoparticles, liposomes, and fat emulsions are possible thanks to solid lipid nanoparticle technology. By potentially reducing the solubility, permeability, and toxicity issues related to the individual therapeutic molecules, SLN administration can be a creative way to administer molecules into the target region in a controlled manner. For SLNs, having high physical stability and drug loading is advantageous.

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