IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Solid Lipid-Based Nanoparticles (Slnbs) Drug Delivery System: A Theoretical Review.

[1]Vishal Bhagwan Ambekar* , [2]Mr. Babasaheb Chopade and [3]Dr. Megha T. Salve .

Department of B.Pharmacy.

Shivajirao Pawar Collage Of B.Pharmacy , Pachegaon ,

Ahilyanagar -413725.

Abstract: Solid lipid nanoparticles (SLBN) have been developed as an alternative to other pharmaceuticals such as polymeric nanoparticles, liposomes, and emulsions. Generally speaking, SLBN are divided into two types: solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC). The difference between SLN and NLC lies in the properties of the particle matrix. SLBN can be prepared by various methods, including high-pressure homogenization, solvent emulsion (or diffusion) evaporation, and microemulsion technology. Lipid nanoparticles (SLN) were first reported in 1991 as an alternative to known colloidal agents such as emulsions, liposomes, and polymeric microparticles and nanoparticles. SLN has the advantages and capabilities of the original model, except for avoiding some disadvantages and technical knowledge. This article reviews the manufacturing technology, drug composition, drug transport and release potential of SLN with specific indications for drug delivery. Issues related to the introduction of SLNs into the pharmaceutical industry, such as the status of additives, liposomes and polymeric nanoparticles. This article discusses various lipid matrices, surfactants and other excipients used in SLN formulations, preparation methods, sterilization and lyophilization. The encapsulation efficiency of drug carriers and its effect on physical parameters, drug release and release mechanisms of various compositions are reviewed and discussed. Key points in the behavior and stability of SLNs are described. In vivo tests as well as various in vitro studies conducted by different research groups are discussed. The ability of SLNs to be administered by various administration methods is covered. Passive and active drug targeting using SLNs is described.

***Keywords*:** Solid lipid nanoparticles, SLNs, Nanotechnology, Drug delivery, preparation method, Administration, tumors.

INTRODUCTION: In recent years, the development of lipid nanoparticles (SLNs) has accelerated. The introduction of lipid nanoparticles in 1991 provided an alternative to colloidal materials such as emulsions, liposomes, and polymeric microparticles and nanoparticles [1]. Solid lipid nanoparticles (SLNs) have emerged as an alternative to colloidal systems for application and delivery. They are submicron (50–1000 nm) in size, are made of biocompatible and biodegradable materials, and can mix lipophilic and hydrophilic drugs. SLNs have unique properties such as small size, large surface area, high drug loading and interaction level, and are attractive for their ability to enhance the ability to regulate the display. Nanoparticles have attracted great attention as novel colloidal drug carriers for intravenous injection, as they have been proposed as other infectious agents. The development of lipid nanoparticles is one of the new areas of lipid nanotechnology with many applications in drug delivery, medicine and research, and many other disciplines. Over the years, the primary drug carriers studied have included oil-in-water (O/W) emulsions, liposomes, microparticles, and nanoparticles, often made from synthetic polymers or natural macromolecules.Lipid nanoparticles are a new potential colloidal carrier that can be used as an alternative material for polymers, similar to oil-in-water emulsions for parenteral nutrition, but the liquid lipids In these formulations, lipids

are used in place of emulsions, as depicted in Figure 1.They have advantages such as good biocompatibility, non-toxicity, better lipophilic drugs than lipid nanoparticles, and physical stability. [2,3]

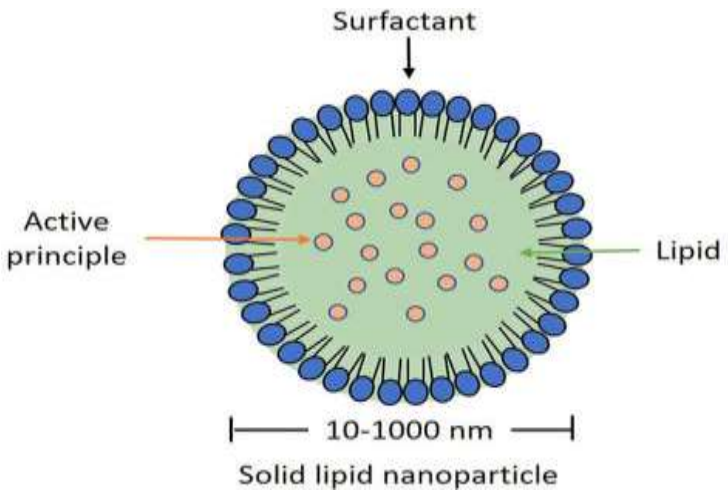

Fig.1: Structure of solid lipid nanoparticle (SLN).[4]

SLN's ADVANTAGES:[5,6]

By using biodegradable physiological lipids, the risk of chronic pain and toxicity can be reduced and the use of organic solvents during production can be avoided.

- ❖ Enhanced Drug Bioavailability: SLNs boost the bioavailability of drugs with limited water solubility, making them more effective.
- ❖ Improved Skin Absorption: When used topically, SLNs help direct drugs to specific areas, increasing their penetration into the skin.
- ❖ Controlled Release and Targeted Delivery: These nanoparticles allow for controlled release and targeted delivery of medications, improving efficacy.
- ❖ Protection for Sensitive Compounds: SLNs safeguard unstable and sensitive molecules, protecting them from intestinal breakdown and external environmental factors.
- ❖ Higher Stability Compared to Liposomes: SLNs offer greater stability than liposomes, another form of drug delivery vehicle.
- ❖ Enhanced Bioavailability of Encapsulated Compounds: SLNs increase the bioavailability of bioactive substances they carry, supporting the stabilization of reactive compounds within the nanoparticle.
- ❖ Focus on Functional Compounds: They effectively deliver functional ingredients precisely to their intended site.
- ❖ Suitable for Lyophilization: SLNs can be freeze-dried, which aids in their storage, stability, and transportability.

SLN's DISADVANTAGE:[7-9]

- ❖ Limited Drug Loading: SLNs have a restricted capacity to hold high doses of drugs.
- ❖ Drug Leakage During Storage: Drugs may unintentionally release over time as structural changes in the polymer occur.
- ❖ High Water Content in Formulations: These dispersions contain large amounts of water (up to 99.9%), which can affect stability.
- ❖ Challenges with Hydrophilic Drug Loading: Due to partitioning effects during preparation, SLNs are less effective at carrying water-soluble drugs.
- ❖ Reduced Targeting Efficiency: Their ability to deliver drugs precisely to target sites is somewhat limited.
- ❖ Potential Impact on Cardiovascular System: Nanoparticles might disrupt autonomic balance, influencing heart and vascular functions.

- ❖ Particle Size Increase: The particles may grow in size over time, which could impact their effectiveness.
- ❖ Unpredictable Gel Formation: SLNs can unexpectedly form gels, making handling difficult.
- ❖ Variable Polymer Dynamics: Changes in polymeric structure can occur unpredictably, affecting stability and performance

AIMS OF SOLID LIPID NANOPARTICLES:

1. Allows for controlled release of medication.
2. Supports loading of both lipophilic and hydrophilic drugs.
3. Improves the stability of drugs.
4. Accommodates a high drug loading capacity.
5. Avoids the use of organic solvents.
6. Carrier is biologically non-toxic. [1][8][10]

NANOPARTICLES:

Defination: Nanoparticles are solid colloidal particles with sizes between 1 nm and 1000 nm, where the active ingredient (either a drug or biologically active compound) is dissolved or encapsulated within a polymeric matrix. [11]

CLASSIFICATION OF NANOPARTICLES:

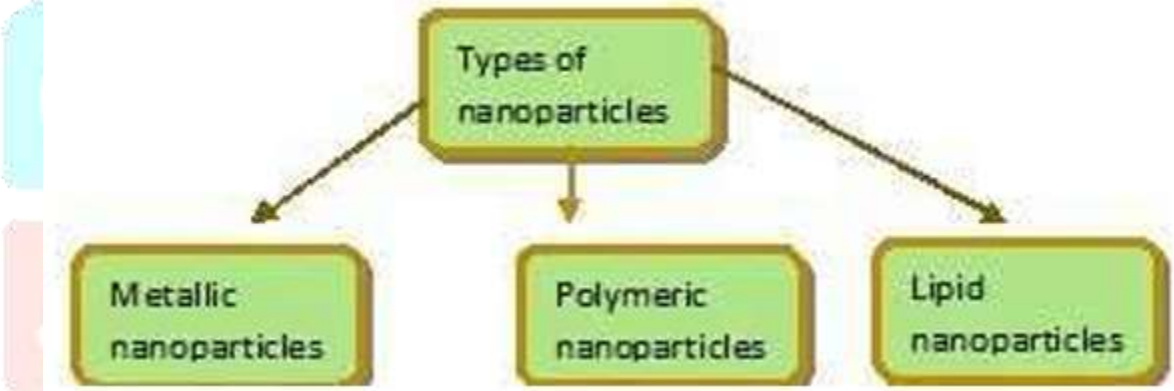

Figure.2: Classification of nanoparticles.[12]

The primary concern with metallic and polymeric nanoparticles is the potential toxicity of the metals and polymers involved in their preparation. On the other hand, the lipids used in these formulations are typically considered GRAS (Generally Recognized As Safe) materials.[13]

A] metallic nanoparticles: In the field of nanotechnology, metallic nanoparticles (MNPs) have exhibited a variety of properties, paving the way for new advancements, especially in targeted drug delivery systems. [14] MNPs are commonly used as carriers for a range of therapeutic agents, including antibodies, nucleic acids, chemotherapy drugs, and peptides. Metals like silver, gold, palladium, titanium, zinc, and copper are known for their enhanced optical properties. Their surfaces can be easily modified to attach targeting agents and active biomolecules through hydrogen bonding, covalent bonds, and electrostatic interactions. Additionally, these nanoparticles can carry multiple drugs, improving their therapeutic efficacy.[15]

B] polymeric nanoparticles: Polymeric nanoparticles (PNPs), with sizes ranging from 1 to 1,000 nm, can either have active compounds adsorbed on the surface of the polymer core or enclosed within the polymer matrix. These nanoparticles are usually organic, and the term "polymer nanoparticle" is commonly used to describe them. They typically take the form of either nanospheres or nanocapsules[16].

C] lipid nanoparticle: Lipid-based nanoparticles (LNPs) are a highly versatile group of nanocarriers that have found extensive use in medical research and pharmacology.[17] They can encapsulate a wide range of therapeutic agents, including small molecules, nucleic acids, and monoclonal antibodies, for various applications.[18,19] LNPs offer numerous advantages, such as protecting drugs from degradation in the

body, improving their solubility and effectiveness, enabling targeted delivery to disease sites, controlling the release of drugs, and altering their distribution within the body.[20]These advanced nanocarriers have the potential to overcome many of the limitations associated with traditional therapies, such as poor efficacy, susceptibility to enzymatic breakdown, low bioavailability, and off-target side effects. [17-21]

METHOD OF PREPARATION OF SOLID LIPID PARTICLES:

SLNs are formulated using lipids, emulsifiers, and water/solvents through different preparation techniques, as detailed below.

1.High pressure homogenization

A. Hot homogenization

B. Cold homogenization

2. Ultrasonication/high speed homogenization
   A. Probe ultrasonication
   B. Bath ultrasonication
3. Solvent evaporation method
4. Solvent emulsification-diffusion method
5. Supercritical fluid method
6. Microemulsion based method
7. Spray drying method
8. Double emulsion method
9. Precipitation technique
10. Film-ultrasound dispersion

1] HIGH PRESSURE HOMOGENIZATION:

SLNs are nanoparticles made of solid lipids, with an average diameter ranging from 50 to 1000 nm, as determined by photon correlation spectroscopy (PCS). These nanoparticles typically consist of solid lipids, surfactants, and water. The term "lipid" broadly refers to substances such as triglycerides (e.g., tristearin), partial glycerides, fatty acids (e.g., stearic acid), hormones (like cholesterol), and waxes (e.g., acetyl palmitate). The choice of surfactants is based on their charge and molecular weight to promote lipid dispersion and stability.[22-24]

A. Hot homogenization:

Hot homogenization is performed at temperatures above the lipid's melting point, which allows for the homogenization of an emulsion. A pre-emulsion is created by mixing the drug-loaded lipid melt with the aqueous emulsifier phase, both at the same temperature, using a high-shear mixing device. High-pressure homogenization (HPH) of the pre-emulsion occurs at temperatures above the lipid's melting point. Typically, higher temperatures lead to smaller particle sizes because they reduce the viscosity of the inner phase. However, elevated temperatures can also increase the degradation rate of both the drug and the carrier. Increasing the homogenization pressure or the number of cycles can result in larger particles due to the increased kinetic energy of the particles.[25-27]

Typically, 3-5 homogenization cycles at pressures ranging from 500 to 1500 bar are sufficient. However, increasing the number of cycles can cause the particle size to grow due to coalescence, which happens because of the high kinetic energy of the particles. While this may enhance particle size, it could also speed up the degradation of both the drug and the carrier. The best results are generally obtained after 3-5 passes through the high-pressure homogenizer (HPH). It is important to note that high-pressure processing raises the temperature of the sample, usually by about 10°C at 500 bar. [28]

B.Cold homogenization:

Drug dissolved/dissolved in molten lipid → Drug-loaded lipid is solidified in liquid nitrogen or dry ice → Grinded in pulverizer (50-100 micron particles) → Lipid is dispersed in semi-solid lipid nanoparticles in cold water dispersion equipment.

The preparation process starts similarly to hot homogenization, where the drug is dispersed, dissolved, or solubilized in the melted lipid. The drug-lipid mixture is then quickly cooled using liquid nitrogen or dry

ice. The solidified drug-lipid blend is milled, often with a mortar or ball mill, to achieve micron-sized particles (50-100 microns). These microparticles are then dispersed in a chilled emulsifier solution to form a presuspension. This presuspension is then subjected to high-pressure homogenization at room temperature or lower, where the cavitation force breaks the microparticles into solid lipid nanoparticles (SLNs). This process minimizes lipid melting, thus reducing the loss of hydrophilic drugs to the aqueous phase. Although cold homogenization reduces thermal exposure to the drug, it does not completely eliminate it due to the initial melting of the lipid/drug mixture. High-pressure homogenization raises the sample temperature (about 10-20°C per cycle). However, increasing the number of cycles or the pressure can lead to larger particle sizes due to coalescence, resulting from the high kinetic energy of the particles. [29-31]

Cold homogenization was introduced to overcome the challenges of hot homogenization, such as the temperature-induced degradation of the drug payload, the loss of drug into the aqueous phase due to partitioning during homogenization, and the unpredictable polymorphic transitions of the lipid. These transitions result from the complex crystallization process of the nanoemulsion, which can lead to various modifications or supercooled melts.[32]

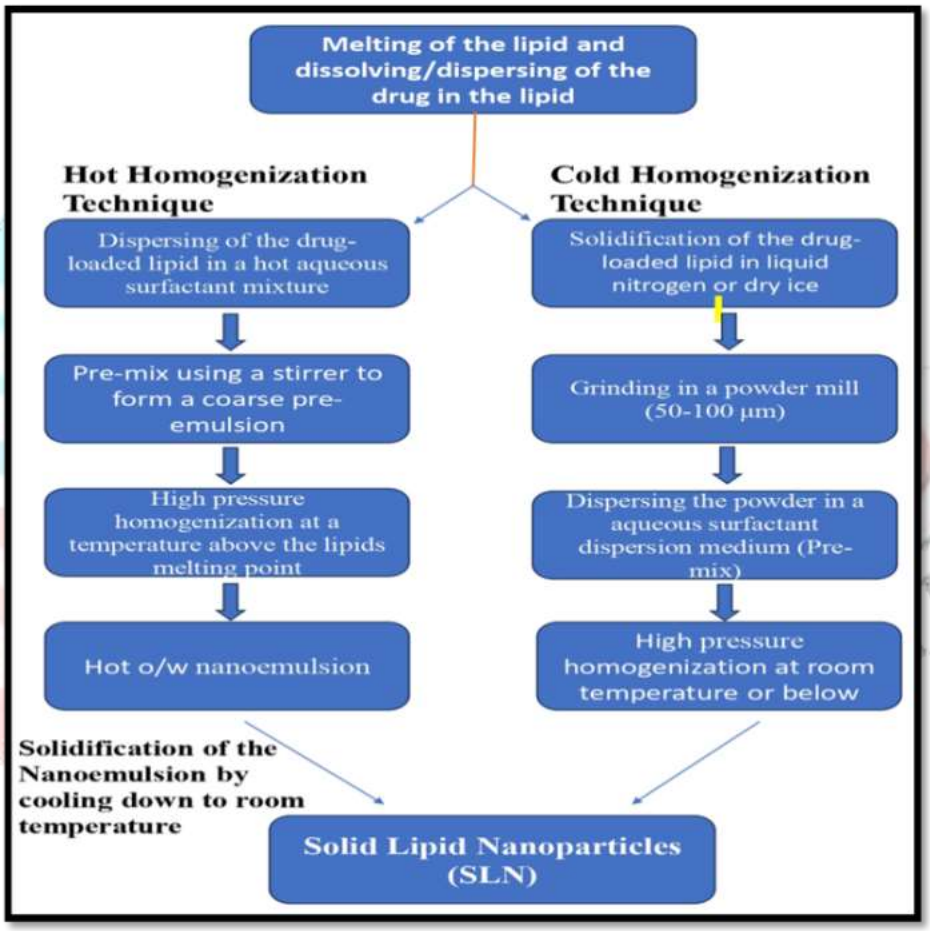

Fig.3: Schematic procedure of hot and cold homogenization techniques for SLN production.[33]

2] ULTRASONICATION/ HIGH SPEED HOMOGENIZATION:

SLNs can be produced using methods like high-speed homogenization or ultrasonic treatment. For achieving smaller particle sizes, a combination of ultrasonication and high-speed homogenization is necessary. Although this method reduces shear stress, it has several limitations, such as the risk of metal contamination and physical instability, including particle growth during storage. This process typically utilizes either a bath sonicator or a probe sonicator. [34,35]

3]SOLVENT EVAPORATON METHOD:

The hydrophobic drug and lipophilic lipid are dissolved in a water-immiscible organic solvent (such as cyclohexane, dichloromethane, toluene, or chloroform), and then emulsified in an aqueous phase using a high-speed homogenizer. The coarse emulsion is subsequently passed through a microfluidizer to improve the emulsification process. The organic solvent is then removed through mechanical evaporation by stirring at room temperature, preferably under reduced pressure using a rotary evaporator, leaving lipid precipitates that form the SLNs.[36]

A nanoparticle suspension is generated by evaporating the polymer solvent, which subsequently diffuses into the surrounding continuous phase of the emulsion. The solvent is removed either by continuous magnetic stirring at room temperature (for more polar solvents) or through a gradual evaporation process under reduced pressure (as with solvents like dichloromethane or chloroform). After the solvent evaporates, the solidified nanoparticles are washed and collected via centrifugation, followed by freeze-drying for long-term storage. This technique facilitates the formation of nanospheres.[37]

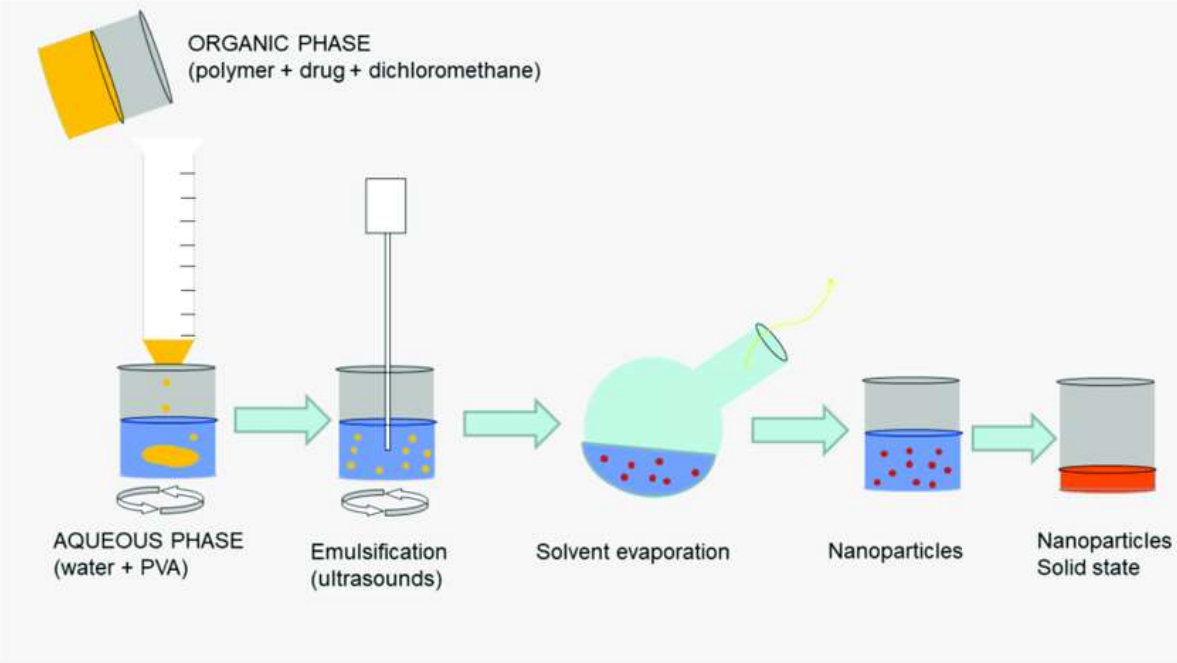

Fig.4:Solvent evaporation method.[38]

4]SOLVENT EMULSIFICATION-DIFFUSION METHOD:

SLNs can also be prepared using the solvent emulsification-diffusion method. The size of the particles is influenced by the lipid concentration in the organic phase and the type of emulsifier used, with particle sizes typically ranging from 30 to 100 nm. One of the main advantages of this method is that it avoids the use of heat during preparation. In this process, the lipid matrix is dissolved in a water-immiscible organic solvent, which is then emulsified into an aqueous phase. The solvent is evaporated under reduced pressure, causing the lipid to precipitate in the aqueous medium and form nanoparticles.[39,40]

In the solvent emulsification-evaporation method, the lipophilic material and hydrophobic drug are dissolved in a water-immiscible organic solvent (such as cyclohexane, dichloromethane, toluene, or chloroform) and then emulsified into an aqueous phase using a high-speed homogenizer. To improve the emulsification process, the coarse emulsion is immediately passed through a microfluidizer. Following this, the organic solvent is evaporated through mechanical stirring at room temperature and reduced pressure (using a rotary evaporator), resulting in the formation of lipid precipitates that create SLNs. [41]

5]SUPERCRITICAL FLUID METHOD:

This novel method for producing SLNs offers the benefit of being solvent-free. It serves as a flexible platform technology for the creation of powders and nanoparticles in different forms. One promising approach is the rapid expansion of supercritical carbon dioxide solutions (RESS), which is employed to fabricate SLNs. Carbon dioxide (99.99%) is used as the solvent in this process, making it an effective option. [42]

6]MICROEMULSION BASED METHOD:

This method is based on the dilution of microemulsions, which are two-phase systems consisting of an inner and outer phase (e.g., oil-in-water microemulsions). These microemulsions are prepared by stirring an optically transparent mixture at 65-70°C, typically composed of a low-melting fatty acid (e.g., stearic acid), an emulsifier (e.g., polysorbate 20), co-emulsifiers (e.g., butanol), and water. The resulting SLN dispersion

can be used as a granulation fluid to form solid products, such as tablets or pellets, via the granulation process. However, if the particle content is low, excess water needs to be removed. High temperature gradients promote rapid lipid crystallization and prevent aggregation. Due to the dilution step, the lipid content obtained is generally lower than that in formulations produced with high-pressure homogenization (HPH). [43]

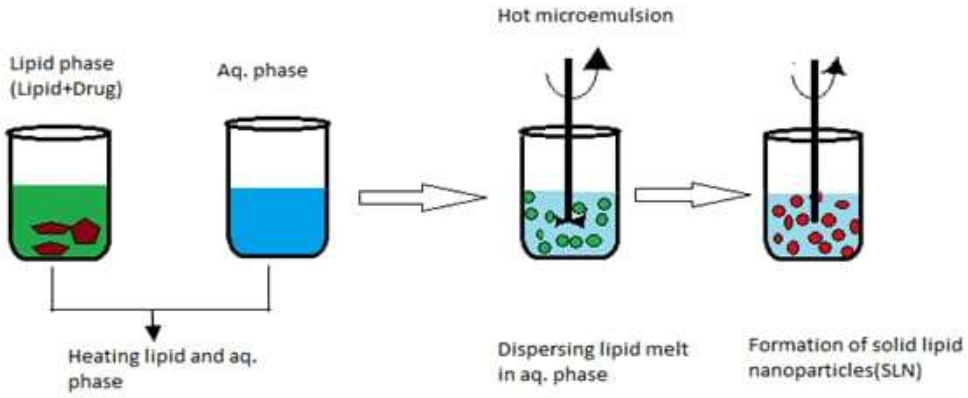

fig.5:Microemulsion based method [44]

7]SPRAY DRYING METHOD:

This technology offers an alternative to lyophilization, which is typically used to create pharmaceutical products from aqueous SLN dispersions. Although spray drying is a more economical option compared to lyophilization, it is not widely used for lipid synthesis due to particle aggregation caused by the high temperatures and shear forces applied during the process. Research suggests that lipids with melting points above 70°C are more suitable for spray drying. [45,46]

8]DOUBLE EMULSION METHOD:

In the double emulsion method, hydrophilic drugs are first dissolved in an aqueous solution and then emulsified into melted lipid. The resulting primary emulsion is stabilized by adding a stabilizer like gelatin or poloxamer-407. This stabilized primary emulsion is then dispersed into an aqueous phase containing a hydrophilic emulsifier, such as PVA. The double emulsion is stirred and then separated by filtration. This approach avoids the need to melt the lipid for the preparation of peptide-loaded lipid nanoparticles, and the nanoparticles' surface can be modified for steric stabilization by incorporating a lipid/PEG derivative. The steric stabilization significantly enhances the system's resistance to gastrointestinal fluids. This technique is mainly used for encapsulating hydrophilic drugs like peptides.[43]

9]PRECIPITATION TECHIQUE:

An emulsion in the aqueous phase is formed by dissolving the lipid in an organic solvent, such as chloroform. After the solvent evaporates, the lipid precipitates, leading to the formation of nanoparticles. The glycerides are dissolved in the organic solvent (e.g., chloroform), and the solution is then emulsified in an aqueous phase. Once the solvent evaporates, the lipid precipitates to form nanoparticles. [47,48]

10]FILM-ULTRASOUND DISPERSION:

The lipid and drug are dissolved in suitable organic solvents, and after the organic solvents are evaporated through decompression and rotation, a lipid film is created. Then, an aqueous solution containing emulsifiers is added. To achieve dispersion, ultrasound with a probe is applied, resulting in the formation of SLNs with small and uniform particle sizes. [25]

ADMINISTRATION ROUTES OF SLNS:

1. Oral administration
2. Parenteral administration
3. Rectal administration
4. Nasal administration
5. Topical application
6. Ocular administration

1.Oral administration:

SLNs are reported to exhibit controlled release behavior that helps protect the encapsulated drug from degradation in the stomach and intestines, enabling its potential absorption and transport through the intestinal mucosa. Nevertheless, it is important to assess the stability of these colloidal carriers in gastrointestinal fluids to evaluate their effectiveness for oral delivery. [49]

2. Parenteral administration:

SLNs were initially developed to address challenges associated with parenteral nanoemulsions. Over the past twenty years, SLN and NLC formulations have expanded to various new applications. SLNs have successfully resolved issues related to the rapid drug release from parenteral nanoemulsions. With proper surface modifications, such as stabilization with poloxamers and poloxamines, SLNs can deliver controlled and prolonged effects following intravenous administration[50]. Peptide and protein drugs, typically administered parenterally due to their degradation in the gastrointestinal tract, benefit from SLNs by reducing side effects and increasing bioavailability. These systems are particularly effective for targeted drug delivery. [1,51-52]

3. Rectal administration:

Rectal drug administration is often preferred for pediatric patients due to its simplicity. Submicron emulsions and SLNs have an advantage over traditional rectal solutions because they avoid the use of organic solvents (such as ethanol, propylene glycol, and benzyl alcohol) commonly found in commercial formulations. Sznitowska et al. evaluated the bioavailability of diazepam in rabbits after rectal administration of three formulations: an organic aqueous solution, a submicron emulsion (20% miglyol), and acetylpalmitate SLNs. The SLNs demonstrated a lower relative bioavailability (47%) compared to the solution form. This decrease in bioavailability was attributed to the poor diffusion of the drug through the lipid matrix, which hindered its efficient release and absorption.As a result, a lipid matrix that remains solid at body temperature is not an optimal choice for rectal drug delivery, even when formulated as submicron dispersions.[53]

4. Nasal administration:

The nasal route is favored for drug administration due to its quick absorption, fast onset of action, and ability to avoid drug degradation in the gastrointestinal tract, which can occur due to enzymes and limited transport through epithelial cell layers.[49]

5.Topical application:

The skin, with its vast surface area (approximately 20 square feet), presents a valuable option for drug delivery. Topical drug delivery is mainly aimed at providing localized effects, which can (i) reduce the need for systemic treatments, (ii) lower the required dose to target the skin, and (iii) minimize off-target side effects. Examples of topical products include anti-fungal treatments, sunscreens, keratolytics, local anesthetics, antiseptics, and anti-inflammatory drugs for skin conditions like psoriasis. In contrast, transdermal drug delivery is designed for systemic effects, with the skin serving as the entry point for the drug into the bloodstream. For instance, transdermal patches are used for delivering nicotine in smoking cessation, buprenorphine and fentanyl for pain management, and hyoscine (scopolamine) for motion sickness.[54]

6.Ocular administration:

SLNs have proven to be a promising delivery system for pilocarpine and tobramycin. SLNs, which contained an ion-pair complex of tobramycin with hex acetylphosphate (1:2 molar ratio), were prepared using the warm o/w microemulsion technique. The precorneal retention of SLNs was evaluated by instilling fluorescent SLN dispersions into the lower conjunctival sac of rabbit eyes. These dispersions created a stable film on the cornea and were retained in the eye for an extended duration. When tobramycin-loaded SLNs were topically applied to rabbits, they led to a significant increase in the bioavailability of tobramycin in the aqueous humor, compared to commercial eye drops. This enhanced availability may be due to the entrapment and prolonged retention of SLNs within the mucin layer on the corneal epithelium, as well as the potential improvement in drug penetration through the cornea facilitated by Epikuron 200.[55]

APPLICATION:

1) SLNs as gene delivery carrier
2) SLNs for targeted drug in solid tumors
3) SLNs is cosmetic formulation
4) SLNs in breast cancer treatment
5) SLN as vaccines adjuvants
6) SLNs fotr anti tubercular treatment
7) Stealth nanoparticles
8) Solid lipid nanoparticles for delivering peptides and proteins.[56]

CONCLUSION:

This review offers a thorough overview of the preparation, characterization, and applications of Solid Lipid Nanoparticles (SLNs) in drug delivery. SLN formulations provide several benefits and limitations when compared to other drug delivery systems. The high-pressure homogenization technique is an effective method for SLN production and can be easily scaled for large-scale industrial production. It allows the incorporation of both lipophilic and hydrophilic drugs into SLNs. SLNs show potential as an alternative colloidal drug delivery system. Nonetheless, more research is necessary to fully comprehend the molecular structure and behavior of SLNs in both in vitro and in vivo settings.

Acknowledgement: The author would like to thank Mr.Babasaheb L. Chopade,Dr.Megha T. Salve,Dr.Abhijeet R. Shete and all persons directly or indirectly involved in the preparation of this article.

REFERENCES:

1. Ekambaram P, Abdul hasan sathali A, Priyanka K. solid lipid nanoparticles: a review. Sci. Revs. Chem. Commun., 2012, 2(1), 80-102.
2. Muller, R.H., Karsten, M., Sven, G. Solid lipid nanoparticles (SLN) for controlled drug delivery—A review of the state of the art. Eur J Pharm Biopharm 2000, 50: 161-77.
3. Stevens, P.J., Sekido, M., Lee, R.J. Synthesis and evaluation of hematoporphyrin derivative in a folate receptor-targeted solid lipid nanoparticle formulation. Anticancer Res 2004, 24(1): 161-5.
4. https://images.app.goo.gl/cuzKbNN3gjwP8F1t5.
5. Geszke-Moritz M., Mortiz M., Solid lipid nanoparticles as attractive drug vehicles: composition, properties and therapeutic strategies. Mater Sci Eng C Mater Biol Appl 68: 2016, 982-994.
6. MuÈller B.W., Mikroemulsionen als neue Wirkstoff TraÈgersysteme, in: R.H. MuÈller, G.E. Hildebrand (Eds.), Pharmazeutische Technologie: Moderne Arzneiformen, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1998, 161-168.
7. Wolfgang Mehnart and Karsten Mader, Adv. Drug. Deliv. Rev., 47, 165-196 (2001). 10. Houli Li, Xiaobin Zhao, Yukun Ma and Guangxi Zhai, Ling Bing Li and Hong Xiang, Lou. J. Cont.Release, 133, 238-244 (2009).

8. Melike Uner, Gulgun Yener, Int. J. Nanomedicine, 2(3), 289-300 (2007).
9. Annette Zur Mehlen, Cora Schwarz and Wolfgang Mehnart, Eur. J. Pharm. Biopharm., 45, 149-155(1998).
10. Indu Pal Kaur, Rohit Bhandari, Swati Bhandari and Kakkur. Potential of solid lipid nanoparticles in brain targeting. J. Cont. Rel. 2008, 127, 97 109.
11. P. Ekambaram, A. Abdul hasansathali K. Priyanka, solid lipid nanoparticles: a review Scientific Reviews Chemical Communications, 2(1), 2012, 80-102.
12. Verma Surender, Makkar Deepika, Solid lipid nanoparticles: a comprehensive review, Journal of Chemical and Pharmaceutical Research, 2016, 8(8):102-114.
13. Jaiswal S., Gupta G.D, Recent advances in solid lipid nanoparticles and challenges. Iajpr 3(12): 2013, 1601 1611.
14. Cooper ER. Nanoparticles: a personal experience for formulating poorly water soluble drugs. J. Control. Release. 2010;141(3):300–302.
15. Thanki K, Gangwal RP, Sangamwar AT, Jain S. Oral delivery of anticancer drugs: challenges and opportunities. J. Control Release. 2013;170(1):15–40.
16. Khan I., Saeed K., Khan I. (2019). Nanoparticles: Properties, applications and toxicities. *Arab. J. Chem.* 12 908–931.
17. Gurevich, E. V.; Gurevich, V. V. Beyond traditional pharmacology: new tools and approaches. *Br. J. Pharmacol.* **2015**, *172* (13), 3229– 3241.
18. Tenchov, R.; Bird, R.; Curtze, A. E.; Zhou, Q. Lipid Nanoparticles─From Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement. *ACS Nano* **2021**, *15* (11), 16982– 17015.
19. Mittal, D.; Kaur, G.; Singh, P.; Yadav, K.; Ali, S. A. Nanoparticle-Based Sustainable Agriculture and Food Science: Recent Advances and Future Outlook. *Frontiers in Nanotechnology* **2020**, *2*,.
20. Shah, S.; Dhawan, V.; Holm, R.; Nagarsenker, M. S.; Perrie, Y. Liposomes: Advancements and innovation in the manufacturing process. *Adv. Drug Deliv Rev.* **2020**, *154–155*, 102– 122.
21. Beck, H.; Harter, M.; Hass, B.; Schmeck, C.; Baerfacker, L. Small molecules and their impact in drug discovery: A perspective on the occasion of the 125th anniversary of the Bayer Chemical Research Laboratory. *Drug Discov Today* **2022**, *27* (6), 1560– 1574.
22. Morel S., Terreno E., Ugazio E., Aime S., Gasco M.R., NMR relaxometric investigations of solid lipid nanoparticles (SLN) containing gadolinium (III) complexes, Eur. J. Pharm. Biopharm. 45 : 1998, 157 163.
23. Carli F., Physical Chemistry and Oral Absorption of the Nanoparticulate Pharmapeptides 1999. Systems, 5e Rencentre
24. Schwarz C., Mehnert W., Lucks J.S., MuÈller R.H., Solid lipid nanoparticles (SLN) for controlled drug delivery. I. Production, characterization and sterilisation, J. Control. Release 30 : 1994, 83-96.
25. Krishna Sailaja A, Amareshwar P, Chakravarty P. Formulation of solid lipid nanoparticles and their applications. CPR 2011, 1(2), 197-203.
26. Ahlin P, Kristl J, Kobar S. Optimization of procedure parameters and physical stability of solid lipid nanoparticles in dispersion. Acta Pharm. 1998, 48, 257-67.
27. Jahnke S. The theory of high pressure homogenization, in: Muller RH, Benita S, Bohm B. editors. Emulsions and nanosuspensions for the formulation of poorly soluble drugs, Stuttgart Medpharm Scientific Publishers. 1998, 77-2005.
28. jahnke S. The theory of high pressure homogenization. In: Muller RH, Benita S, Bohm B, editors. Emulsions and nanosuspensions for the formulation of poorly soluble drugs. Stuttgart: Medpharm Scientific Publishers; 1998. pp. 177–200.
29. S.P, Vyas, R.k. Khar, Targeted & Controlled Drug Delivery Novel Carrier System, C.B.S. Publication, First Edition, 15-16, 46-348.
30. S.P.Vyas, Theory & Practice in Novel Drug Delivery System, C.B.S. Publication, First Edition, 299-315.
31. C. Shah, V. Shah, U. Upadhyay, solid lipid nanoparticles: a review current pharma research, 1(4), 2011, 351-368.

32. Mullen zur A. Feste Lipid-Nanopartikel mit prolongierter Wirkstoffliberation: Herstellung, Langzeitstabilitat, Charakterisierung, Freisetzungsverhalten und mechanismen. Ph.D. Thesis, Free University of Berlin. 1996.
33. https://in.images.search.yahoo.com/search/images;_ylt=AwrKCT06FRNnKQIAaeq7HAx.;_ylu=Y29sbwNzZzMEcG9zAzEEdnRpZAMEc2VjA3BpdnM-?p=Schematic+procedure+of+hot+and+cold+homogenization+techniques+for+SLN+production.&fr2=piv-web&type=E210IN826G0&fr=mcafee#id=24&iurl=https%3A%2F%2Fjournals.innovareacademics.in%2Findex.php%2Fijcpr%2Farticle%2Fdownload%2F49387%2F28798%2F229926&action=click.
34. Pardeike J, Hommoss A, Muller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. Int J Pharm. 2009 Jan 21;366(1-2):170-84.
35. Venkateswarlu V, Manjunath K. Preparation, characterization and *in vitro* release kinetics of clozapine solid lipid nanoparticles. J Control Release. 2004 Mar 24;95(3):627-38.
36. Sathali AH, Ekambaram P, Priyanka K. Solid lipid nanoparticles: a review. Sci Rev Chem Commun. 2012;2(1):80-102.
37. Szczęch M., Szczepanowicz K. Polymeric Core-Shell Nanoparticles Prepared by Spontaneous Emulsification Solvent Evaporation and Functionalized by the Layer-by-Layer Method. Nanomaterials. 2020;10:496.
38. https://in.images.search.yahoo.com/search/images;_ylt=AwrKDovdFhNnHAIAIXm7HAx.;_ylu=Y29sbwNzZzMEcG9zAzEEdnRpZAMEc2VjA3BpdnM-?p=solvent+evaporation+method+for+nanoparticles&fr2=piv-web&type=E210IN826G0&fr=mcafee#id=2&iurl=https%3A%2F%2Fwww.researchgate.net%2Fpublication%2F324012783%2Ffigure%2Ffig1%2FAS%3A608428338737157%401522072028442%2FSchematic-diagram-of-the-emulsion-solvent-evaporation-method.png&action=click
39. Muller, R.H., Mader, K., Gohla, S.H. Solid Lipid Nanoparticles for Controlled Drug Delivery- A Review of the State of the art. Eur J Pharm Bio Pharm. 2000, 50(1), 161-177.
40. Trotta, M., Debernardi, F., Caputo, O. Preparation of Solid Lipid Nanoparticles by a solvent emulsification-diffusion technique. Int J Pharm. 2003, 257, 153-160.
41. Waghmare A. S., Grampurohit N.D., Gadhave M.V., Gaikwad D.D., Jadhav S.L, Solid lipid nanoparticles: a promising drug delivery system, International research journal of pharmacy, 2012
42. Tabatt K, Sameti M, Olbrich C, Muller RH, Lehr CM. Effect of cationic lipid and matrix lipid composition on solid lipid nanoparticle-mediated gene transfer. Eur J Pharm Biopharm. 2004 Mar 1;57(2):155-62.
43. N.K.Jain, Pharmaceutical Product Development, C.B.S. Publication, First Edition, 445.
44. https://images.app.goo.gl/eLTbiDu6uP2jD8bx6
45. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: a modern formulation approach in drug delivery system. Indian J Pharm Sci. 2009 Jul;71(4):349-58
46. Ghasemiyeh P, Mohammadi Samani S. Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: applications, advantages and disadvantages. Res Pharm Sci. 2018 Aug;13(4):288-303
47. Shah R, Eldridge D, Palombo E, Harding I. Lipid nanoparticles: production, characterization and stability. New York, NY, USA. Springer International Publishing; 2015.
48. Sailaja AKS, Amareshwar PA, Chakravarty PC. Formulation of solid lipid nanoparticles and their applications. J Curr Pharm Res. 2011;1(2):197-203
49. S.P.Vyas, Theory & Practice in Novel Drug Delivery System, C.B.S. Publication, First Edition, 299-315.
50. Schöler N, Olbrich C, Tabatt K, Müller RH, Hahn H, Liesenfeld O. Surfactant, but not the size of solid lipid nanoparticles (SLN) influences viability and cytokine production of macrophages. International journal of pharmaceutics 2001;221(1), 57-

67.http://www.sciencedirect.com/science/article/pii/S037851730100660357-67. (accessed October 2013).
51. Melike Uner, Gulgun Yener. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives Int J Nanomedicine. 2007, 2(3), 289-300.
52. Lippacher A, Fluessigund halbfeste SLN Dispersionen zur topischen Applikation, Ph.D. thesis, Free University of Berlin (2001).
53. Sznitowska, M., Gajewska, M., Janicki, S., Radwanska, A., Lukowski, G. Bioavailability of diazepam from aqueous organic solution, submicron emulsion and solid lipid nanoparti cles after rectal administration in rabbits. Eur J Pharm Bio pharm 2001, 52: 159-63.
54. Alvarez-Roman R, Naik A, Kalia YN, Guy RH, Fessi H. Skin penetration and distribution of polymeric nanoparticles. J. Control. Release. 2004;99:53–62.
55. Cavalli, R., Gasco, M.R., Chetoni, P., Burgalassi, S., Saet tone, M.F. Solid lipid nanoparticles (SLN) as ocular delivery systems for tobramycin. Int J Pharm 2002, 238: 241-5
56. V R Charan Teja et al, JGTPS, 2014, Vol. 5(2): 1649 – 1657.