EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 12
Year: 2024

"NANOTECHNOLOGY BASED DRUG DELIVERY SYSTEM FOR FUNGAL INFECTIONS OF SKIN"

[1*]Jadhav Swati K., [1]Dr. Ajay Fugate, [1]Sadule Akshay, [1]Punam Londhe and [1]Komal Jadhav

[1]Department of Pharmaceutics, Shivlingeshwar College of Pharmacy, Almala Dist. Latur – 413520, Maharashtra (MH), India.

***Corresponding Author: Jadhav Swati K.**
Department of Pharmaceutics, Shivlingeshwar College of Pharmacy, Almala Dist. Latur – 413520, Maharashtra (MH), India

Article Received on 19/10/2024 **Article Revised on 08/11/2024** **Article Accepted on 28/11/2024**

ABSTRACT
Fungal skin infections, such as ringworm and athlete's foot, are common and often difficult to treat due to challenges like drug resistance and poor skin penetration of conventional treatments. Nanotechnology has emerged as a promising solution to enhance the effectiveness of antifungal therapies. By utilizing nanoparticles and nanoscale carriers, such as liposomes, solid lipid nanoparticles (SLNs), and polymeric micelles, researchers are developing advanced drug delivery systems that improve targeting, bioavailability, and sustained release of antifungal agents. These nanotechnology-based systems can enhance drug penetration through the skin, protect drugs from degradation, and reduce side effects, offering more effective and patient-compliant treatments. Additionally, gels, as versatile drug carriers, are being integrated with nanotechnology to further optimize drug delivery, providing localized and controlled release while improving therapeutic outcomes.

KEYWORDS: Nanoparticles, SLNs, drug delivery, antifungal drug.

1. INTRODUCTION
Fungal infections of the skin, also known as dermatophytosis or tinea, are a common and bothersome health issue affecting millions of people worldwide. These infections can manifest as ringworm, athlete's foot, jock itch, or other forms of fungal skin conditions, causing discomfort, itching, redness, and sometimes even pain. While topical antifungal creams and oral medications are commonly used to treat these infections, the emergence of drug-resistant fungal strains and challenges in drug delivery have prompted the exploration of innovative approaches to improve treatment outcomes.[1]

In recent years, nanotechnology has emerged as a promising field with the potential to revolutionize drug delivery systems for various diseases, including fungal skin infections. Nanotechnology involves the manipulation of materials at the Nano scale level, typically ranging from 1 to 100 nanometers in size. By harnessing the unique properties of nanoparticles and other nanoscale structures, researchers have developed novel drug delivery systems that offer improved targeting, enhanced efficacy, and reduced side effects compared to traditional drug formulations.

Nanotechnology-based drug delivery systems for fungal skin infections leverage the small size and tailored properties of nanoparticles to overcome the limitations of conventional treatments. These systems can encapsulate antifungal drugs within nanoparticles or liposomes, allowing for precise delivery to the site of infection and improved penetration through the skin barrier. By enhancing the bioavailability and retention of antifungal agents in the skin tissue, nanotechnology-based formulations can increase the concentration of the drug at the infection site, leading to better therapeutic outcomes.[2]

One of the key advantages of nanotechnology in drug delivery is its ability to provide sustained release of drugs over an extended period. By controlling the release kinetics of the encapsulated drug, nanoparticles can maintain therapeutic levels in the skin tissue for longer durations, reducing the need for frequent applications and improving patient compliance. This sustained release profile can also help overcome the rapid clearance of drugs from the skin surface, ensuring continuous exposure to the antifungal agent for effective treatment.

Moreover, nanotechnology offers opportunities to enhance the stability and solubility of antifungal drugs, addressing common challenges associated with poor drug formulation properties. By encapsulating drugs in nanoparticles or modifying their surface properties, researchers can protect the drug molecules from

degradation, improve their solubility in skin tissues, and enhance their overall pharmacokinetic profile.

Colloidal Carriers

- Vesicular systems
- Liposomes
- Noisome
- Pharmacosomes
- Virosomes
- Immunoliposomes

2. Nanotechnology

Gels are versatile drug delivery systems that play a vital role in modern pharmaceutical and cosmetic formulations. These semi-solid systems consist of a three-dimensional network structure that can hold a large amount of water or other solvents, providing a suitable environment for incorporating active pharmaceutical ingredients (APIs) or other bioactive compounds. Gels offer several advantages as topical drug delivery systems, including ease of application, localized drug delivery, reduced systemic side effects, and improved patient compliance The choice of gelling agent is crucial in formulating gels, as it determines the rheological properties, drug release kinetics, and overall performance of the formulation. Common gelling agents include synthetic polymers like carbomers and cellulose derivatives, as well as natural polymers such as agar or alginate. Each gelling agent has unique characteristics that influence the gel's viscosity, texture, and drug release mechanisms. For example, carbomers are widely used in topical gels due to their ability to form transparent and stable formulations with good spread ability.[3]

Drug release from gels can occur through various mechanisms, including diffusion through the gel matrix, erosion of the gel structure, or a combination of both. Formulation parameters such as the concentration of the gelling agent, pH, temperature, and presence of other excipients can be optimized to achieve the desired drug release profile. Stability considerations are also important when formulating gels, as factors like pH sensitivity. Temperature stability and compatibility with active ingredients can affect the product's efficacy and shelf-life.

Gels find applications in various fields, including dermatology, cosmetology, and pharmaceuticals. They are suitable for delivering both hydrophobic and hydrophilic drugs and can be formulated for different routes of administration, such as topical, oral, or ocular delivery. In dermatology, gels are commonly used for treating skin conditions like acne, eczema, or psoriasis, providing targeted drug delivery to the affected area while minimizing systemic exposure. Regulatory considerations are essential when developing gel formulations for drug delivery. as health authorities like the FDA or EMA require compliance with Good Manufacturing Practices (GMP) and demonstration of product safety and efficacy. Clinical studies are typically conducted to evaluate the bioavailability, pharmacokinetics, and therapeutic efficacy of gel formulations before seeking regulatory approval for commercialization. Looking ahead, future trends in gel formulations include advancements in nanotechnology and biomaterials, leading to the development of smart gels that respond to external stimuli for controlled drug release. Combination therapies using gels with multiple active ingredients are also being explored for synergistic therapeutic effects. Overall, gels continue to be valuable tools in drug delivery systems, offering a flexible platform for formulating medications with tailored release profiles and improved patient outcomes.[4]

3. Types of NPS as carrier for drug & diagnostic agents

1. Polymeric NPS
2. Nano suspensions and nanocrystals
3. Polymeric micelles
4. Liposomes
5. Fullerenes and dendrimers
6. SLN (Solid lipid nanoparticles)
7. Magnetic nanoparticle

3.1. Solid Lipid Nanoparticle: Solid lipid nanoparticles (SLNs) were introduced in 1991 with the objective to provide biocompatibility, storage stability and to prevent the incorporated drug from degradation. SLNs that is colloidal carriers of nanoscopic size (50-1000 nm) are made up of solid lipids (high melting fat matrix) and are developed to conquer the weaknesses (e.g.. polymer degradation and cytotoxicity, lack of a suitable large scale production method, inferior stability, drug leakage and fusion, phospholipid degradation, high production cost, and sterilization problems) of traditional colloidal carriers, like polymeric nanoparticles and leptosomes.[5] SLNs show various distinctive features such as low toxicity, large surface area, prolonged drug release, superior cellular uptake as compared to traditional colloidal carriers as well as capability to improve solubility and bioavailability of drugs. The release of drug from SLNs depends on matrix type and drug location in the formulation. The SLNs fabricated from biodegradable and biocompatible ingredients are able to incorporate both hydrophilic and lipophilic bioactive and thus turning out to be a viable option for controlled and targeted drug delivery. The solid core of SLNs is hydrophobic with a monolayer coating of phospholipids and the drug is usually dispersed or dissolved in the core.[6]

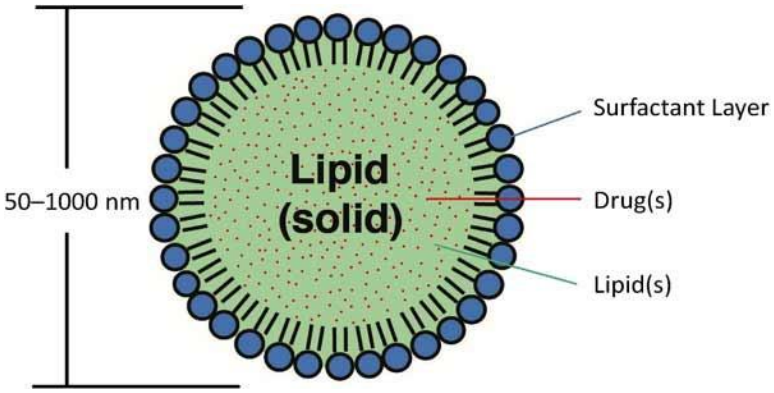

Fig.1: Solid Lipid Nanoparticle.

3.2 Advantages of SLNs

1. The cells of reticule endothelial system (RES) are unable to take up SLNs because of their nano size range, thus enabling them to bypass spleen and liver filtration.
2. Provide high stability to incorporate drugs.
3. Feasibility of incorporating both hydrophilic and lipophilic drugs.
4. Improve bioavailability of poorly water-soluble molecules.
5. Ease in sterilization and scale up.
6. Immobilizing drug molecules within solid lipids provides protection from photochemical, oxidative, and chemical degradation of sensitive drugs, with reduced chances of drug leakage.
7. Drying by lyophilisation is achievable.
8. Provide opportunities for targeted and controlled release of drug.
9. Biocompatible and biodegradable compositional ingredients.

3.4 Disadvantages of SLNs

1. SLNs are compactly packed lipid matrix networks (ideal crystalline structure) having low space for drug encapsulation, leading to poor drug loading capacity.
2. Various factors affect the loading or encapsulation of drugs in SLNs, such as interaction of drug and lipid melt, nature or state of lipid matrix, drug miscibility with lipid matrix, and the drug being dispersed or dissolved in the lipid matrix.
3. Chances of drug expulsion following polymeric transition during storage.
4. The dispersions have high (70-90%) water content.

4. METHOD OF PRODUCTION FOR SOLID LIPID NANOPARTICLES

4.1 High-pressure homogenization technique: HPH is a technique in which the oil/water coarse emulsion obtained after hot homogenization is reconstituted at high pressure above the melting point of the lipid to convert the lipid-rich Drug emulsion into a nanoemulsion. Here, the high homogenization rate increases the temperature of the sample by approximately 10 °C at 5 x 10 Pa. In severe cases, 3-5 homogenization cycles at 5 x 10 Pa to 5 x 10 Pa are sufficient to achieve a good pressure. lipids in the nanometer range.[7]

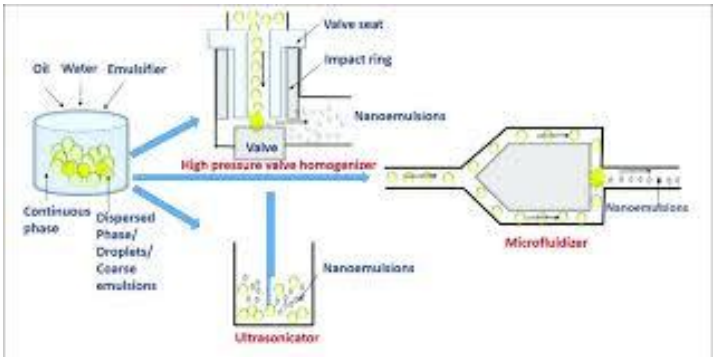

Fig. 2: High-pressure homogenization technique.

4.2 Hot homogenization technique: Hot homogenization is a sample homogenization technique that takes place at a temperature higher than the melting point of the lipids used. In this method, lipids are first absorbed into the soluble and easily soluble lipophilic compounds in the lipids. Another phase containing pure water mixed with surfactant is prepared and heated to seal the lipid phase. The molten phase was dispersed in the hot water mixture of surfactants, which was intelligently stirred and stirred under high pressure to form the initial o/w emulsion". This type of emulsion concentrate has small particle size. This emulsion is further mixed at high pressure above the temperature of the lipid water to convert the lipid-rich drug emulsion

into a nanoemulsion.[8] This hot nanoemulsion is kept aside to cool to room temperature, where the lipids solidify at room temperature and are mixed, and allowing filtration through a filter to obtain lipid nanoparticles.

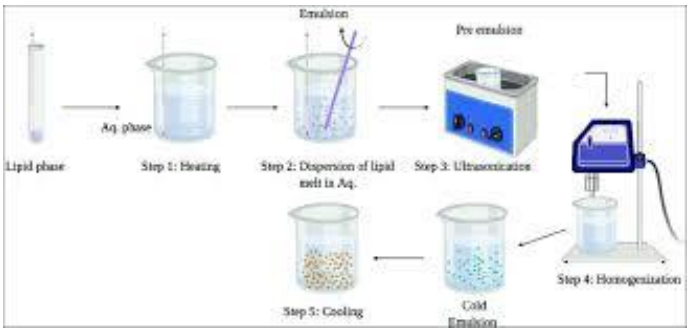

Fig. 3: Hot homogenization technique.

Advantages

1. High temperature reduces the viscosity and leads to smaller particles size
2. Suitable for large scale industrial production
3. High temperature exposure is short, hence no degradation of heat liable drugs
4. No use of organic solvent in this method

Disadvantages

1. Not suitable to encapsulate water soluble drugs
2. High temperature may cause degradation of lipid or drug
3. In-vitro burst release sometimes observed due to drug portioning in water phase
4. Lipid crystallization is retarded due to high temperature
5. High pressure homogenization may lead to aggregation of particles due to high kinetic energy.

Cold homogenization technique

4.3 Cold homogenization technique: The cold homogenization technique used to prepare solid lipid nanoparticles has the advantage of overcoming the problems associated with hot homogenization methods. The hot homogenization method causes degradation of thermolabile drugs, migration of unwanted lipids during reconstitution, and reduction of the drug in the aqueous phase. The first step in cold homogenization was the same as in hot homogenization. In this method, lipid with a boiling point of is hydrolyzed and the drug is dispersed in the lipid. The lipid-carrying phase is frozen to solidity using dry ice or liquid nitrogen. The dropped medicine contained large solid particles. Addition of these particles was done using a mill up to 50 m (100 in). The surfactant was dispersed in the liquid phase and the powder was dispersed in the surfactant mixture. The mixture was synthesized under high pressure at room temperature or below room temperature to obtain solid lipid nanoparticles.[9]

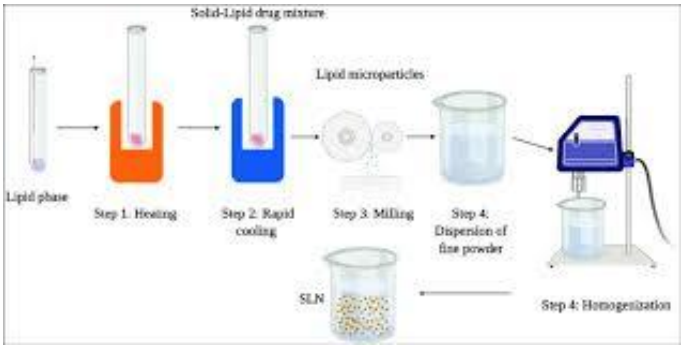

Fig. 4: Cold homogenization technique.

Advantages

1. Lipid and drug degradation due to high temperature is avoided.
2. Suitable for heat liable drugs.
3. Melting of lipid is reduced and prevents the portioning of hydrophilic drug into aqueous phase.

Disadvantages

1. Particle and poly dispersity index are higher than hot homogenization process.
2. Thermal exposure of drug is reduced but not completely removed.
3. Method is expensive and requires special provisions like liquid nitrogen or dry ice.
4. Milling is not appropriate method for reducing the particles size in nanometre range.

4.5 High shear homogenization (Ultra sonication) technique: Solid lipid nanoparticles are also prepared using the ultrasonication method. During rapid ultrasound of the distribution of drugs in vital organs according to lipid pores.[10]

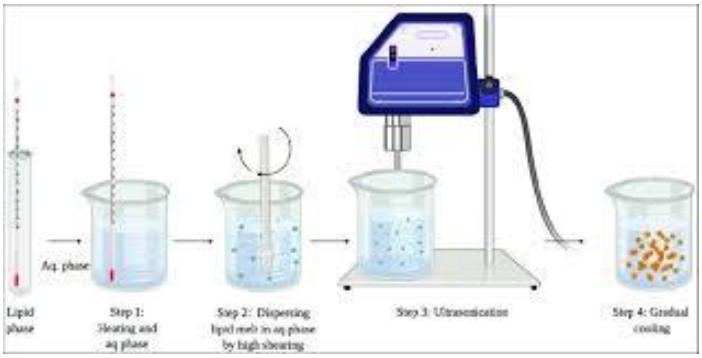

Fig. 5: High shear homogenization (Ultra sonication) technique.

Advantages
1. This method is convenient to use.
2. There is no use of organic solvent.
3. High shear enhances the formulation temperature may degrade the lipid or drug.

Disadvantages
1. Use of filtration is required for removal of impurities if any.
2. Particle obtained are larger in size in micrometer range.
3. Physical stability is poor due to larger size.

4.6 Solvent emulsification-evaporation technique: This method is widely used in the synthesis of solid lipid nanoparticles. This technique facilitates the creation of a lipid phase in a drug that disperses the drug into pure lipids. Emulsification of lipids is facilitated by surfactants in the aqueous phase. Emulsification of the two phases is carried out using a machine operating at a speed of 1000 rpm. The organic phase is removed by suction under high pressure at room temperature. Lipid nanoparticles separated by precipitation.[11]

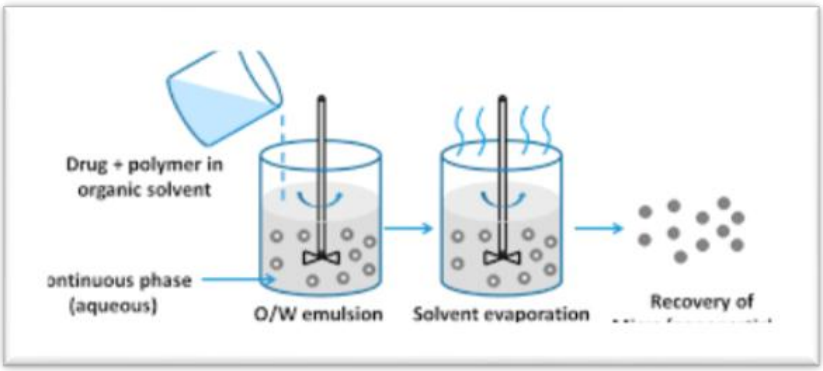

Fig.6: Solvent emulsification-evaporation technique.

Advantages
1. Small particles size is produced.
2. Suitable to encapsulate heat sensitive drugs.
3. Temperature caused degradation is avoided.

Disadvantages
1. Organic solvent may lead to toxicity in the final product2. Loss of solvent due tom evaporation.

4.7 Solvent in water diffusion technique: The distinguishing feature of diffusion techniques compared to direct ventilation is the selection of results for the process. While it is selected to be processed by transferring layers of volatile and organic solvents, the water is not clear enough in the diffusion method. This technique is used for both liquid and organic phases. [12]

Advantages
1. Water miscible solvent reduces the toxicity.
2. Less size particles are obtained.
3. Method is simple and easy to conduct.
4. Also suitable for heat sensitive drugs.

Disadvantages
1. Drug diffusion in water phase lead to reduction in drug loading.
2. Toxicity is reduced but not removed completely due to use of organic solvent.
3. Drug dispersion in lipid matrix is essential therefore suitable for lipophilic drugs.
4. Use of freeze drying require sophisticated instruments.

4.8 Microemulsion technique: The concept of microemulsion formation was a unique evolution in NDDS research. In this method, the drug is separated into water and oil phase depending on the distribution coefficient of the drug. The reduction of

lipids in this method leads to a lower coverage in the final form compared to the homogenization technique.[13]

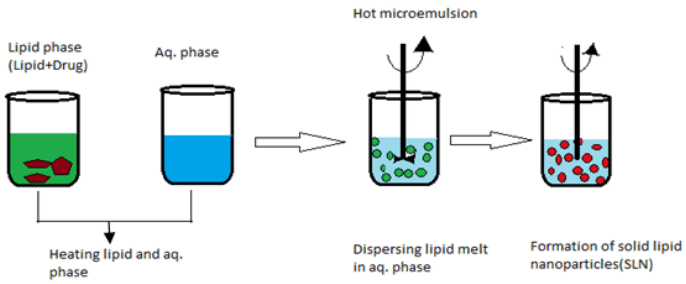

Fig.7: Microemulsion technique.

4.8 Hot microemulsion induced SLNs: This is another microemulsion method in which the emulsion is made by dispersing dissolved lipids in a liquid phase at a temperature between 60 and 80 °C. Using this method, lipid droplets in the nanometer range are produced after washing and filtering.[14]

Advantages

1. Emulsion obtained shows thermodynamic stability.
2. No excess energy is required for the formulation
3. Rapid lipid crystallization takes place due to high temperature.

Disadvantages

1. The concentration of nano droplets formed are less.
2. Highly sensitive to stability during storage.
3. High labour cost is involved.

4.9 Double emulsion technique: This technique involves the formation of o/w/o type emulsion. Firstly, the hydrophilic drug is dissolved into purified water to prepare the primary emulsion. The aqueous phase is then dispersed into melted lipid phase, and with the help of a surfactant, the immiscible phases are emulsified to create the primary emulsion. The primary emulsion is then dispersed into an aqueous phase containing surfactant to produce a double emulsion. The process involves solvent evaporation, where the drug is entrapped in the lipid matrix after the solvent is removed.[15]

4.10 Reverse micelle-double emulsion technique: The double emulsion technique provided micrometer size and low drug loading. It is caused by the transition of chemicals into the outer liquid phase during emulsification. These problems have motivated researchers to develop two-phase micelle technology. In this method, mixed micelles containing phosphatidylcholine cholate are prepared and the drug is incorporated into the lipid matrix by inhalation. Stabilizers are used to provide adequate stability to nanodroplets using o/w/o emulsions.[16]

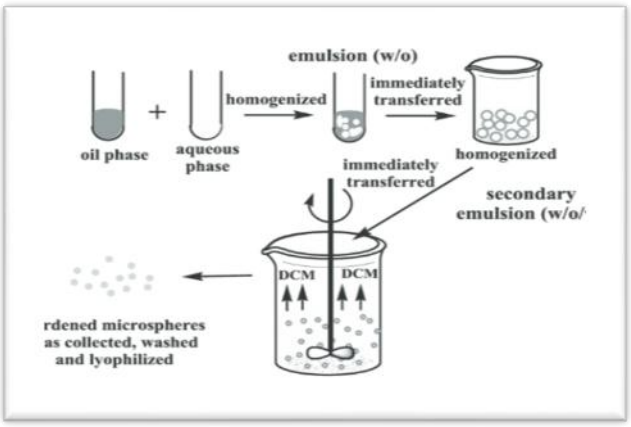

Fig. 8: Reverse micelle-double emulsion technique.

Advantages

1. The lipid content is decreased
2. Ability to encapsulate therapeutic and nutritional compounds in aqueous phase
3. Incompatible components can be easily separated

Disadvantages

1. High yield of the product is obtained.

4.11 Melting dispersion method: In this way, lipids met at temperatures above their melting points. The drug is dispersed in dissolved lipids to prepare the oil phase. The liquid phase is prepared by dissolving the surfactant in

pure water, and the liquid phase is heated to mox and duperse the oil. Dispension of the oil phase occurs slowly and continuously throughout the liquid plase. The mistare in cooled to room temperature to obtain the expected SLNs. Finally, excess solvent is removed by solvem emulsification.[17]

Advantages
2. This is reproducible method for development of SLNs
3. Size distribution is uniform.

Disadvantages
1. The final product may have toxicity as organic solvent is utilized
2. Thermos sensitive drugs could not be processed

4.12 Solvent injection method
This technique involves precipitating solid lipid nanoparticles from an aqueous organic phase. The process starts by melting the lipid and converting it into a dispersion with a water-miscible organic solvent. A hydrophilic surfactant is then dissolved in purified water to create an aqueous phase. Next, the organic lipid phase is rapidly injected into a miscible phase containing water. with regular agitation. The organic solvent mixes with the water and the drug-loaded lipid matrix separates to form lipid nanoparticles. The resulting nanoparticles are then filtered to separate them and the surfactant present in the formulation provides stabilization for the developed nanoparticles.[18]

Fig.9: Solvent injection method.

Advantages
1. Non-toxic organic solvent is used
2. Easy and fast process
3. No use of specific equipments
4. Uniform size distribution with small size
5. Temperature induced loss of drug is avoided

Disadvantages
1. Additional operation of filtration is required
2. Toxicity is not completely removed

4.13. Precipitation method: In this method, the organic solvent facilitates the dispersion of lipids and emulsifies them in the aqueous phase in the presence of the emulsifier under continuous active. Because of the constant stirring, the temperature of the dispersion rises, and the volatility of the solvent makes it better for it to dissolve. As a result of the evaporation of organic solvents, it is dissolved in liquid in which precipitates and come out in the form of solid liquid nanoparticles.[19]

Advantages
1. Ease of preparation
2. No use of specific equipment
3. Suitable for heat sensitive drugs

Disadvantages
1. Huge size particles formed
2. Solvent toxicity problem
3. Not compatible for large scale production

5. Applications of Solid Lipid Nanoparticles: SLNs enhance the bioavailability of entrapped drugs via modification of the dissolution rate, and can be used to improve tissue distribution and targeting of drugs.

Controlled Release of Drug: SLNs offer an advantage to modulate release of loaded drug either by varying drug loading approach or by altering surface properties or composition.[20]

SLNs for Targeted Brain Drug Delivery: SLNs can improve the ability of the drug to penetrate through the blood-brain barrier (BBB).[21]

SLNs for Anticancer Drug Delivery: Recently, SLNs bearing anti-neoplastic drug have been investigated for breast cancer treatment, and results showed a sustained release of tamoxifen with good therapeutic activity.[22]

SLNs for Antimicrobial Drug Delivery: SLNs release antimicrobial payloads for the effective elimination of infectious microbes harbored at lymphatic sites. Nanoparticles and the nanostructured surfaces oppose the growth of bacteria and infections, which is an effective solution regarding difficulties related to biofilm and antibiotic resistance.[23]

SLNs as Gene Carrier: Several studies have been carried out on SLN bearing genetic materials such as plasmid deoxyribonucleic acid (p-DNA), DNA, and other nucleic acids. SLN based vectors could act as a beneficial system of gene delivery for management of corneal diseases and inflammation.[24]

SLNs for Topical Use SLNs are used topically to deliver: various drugs such as vitamin A, isotretinoin, and flurbiprofen. The flurbiprofen-loaded SLNs gel can be applied directly to the site of action, to induce higher tissue concentrations of the drug in controlled fashion. SN loaded diflunisal (DIF), a non-steroidal anti-inflammatory drug, has also been developed for effective management of rheumatoid arthritis.[25]

CONCLUSION

Nanotechnology-based drug delivery systems represent a transformative approach in the treatment of fungal skin infections. By utilizing nanoparticles, liposomes, solid lipid nanoparticles (SLNs), and other nanocarriers, these advanced systems significantly enhance the efficacy of antifungal therapies. Nanotechnology offers improved drug targeting, better skin penetration, and sustained drug release, overcoming the limitations of traditional treatments. Additionally, the ability to encapsulate drugs within nanocarriers helps protect them from degradation and improves their bioavailability, leading to better therapeutic outcomes. As the field continues to evolve, the integration of nanotechnology with topical formulations, such as gels, holds great potential for further optimizing drug delivery, reducing side effects, and enhancing patient compliance. Ultimately, nanotechnology-based solutions could revolutionize the management of fungal skin infections, providing more effective, targeted, and patient-friendly treatments.

REFERENCE

1. Hay RJ, Ashbee HR, Tosti A, et al. Dermatophytosis. *Clin Dermatol*, 2006; 24(2): 157-163. doi: 10.1016/j.clindermatol.2005.11.011.
2. Gupton SL, Gunning PW. Cytoskeletal control of cell migration in development and disease. *Nat Rev Immunol*, 2010; 10(5): 293-303. doi: 10.1038/nri2939.
3. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg*; 2008; 121(5): e26-e32. doi: 10.1186/1745-6673-2-16.
4. Shukla R, Prabhakar A, Chuttani K, et al. Novel lipid-core micelles for targeting drug delivery to the lungs. *J Control Release*, 2007; 120(1-2): 87-97. doi: 10.1016/j.jconrel.2007.05.003.
5. Yang G, Li Y, Wang X, et al. The role of neurogenesis in neurodegenerative diseases. *NeuroSci Res*; 2016; 4(2): 65-72. doi: 10.12691/nnr-4-2-5.
6. Yadav N, Khatak S, Singh S. Solid lipid nanoparticles - A review. *J Control Release*, 2021; 330: 1-12. doi: 10.1016/j.jconrel.2021.03.023.
7. Bhattacharya D, Ghosh D, Saha S, et al. Solid lipid nanoparticles: A review on recent developments, and future potential. *Indian J Pharmacol*, 2009; 41(6): 375-382. doi: 10.4103/0250-474X.57282.
8. Kaul A, Dou J, Kolla V, et al. Solid lipid nanoparticles: A versatile carrier for novel drug delivery. *Int J Pharm*, 2000; 195(1): 1-8. doi: 10.1016/S0939-6411(00)00087-4.
9. Yadav V, Mahor A, Prajapati S, et al. Solid lipid nanoparticles (SLN): Formulation by high pressure homogenization. *J Pharm Sci Res*; 2020; 12(1): 33-40.
10. Adav V, Prajapati S, Mahor A, et al. Solid lipid nanoparticles: Recent advances and future perspectives in drug delivery. *J Appl Pharm Sci*; 2021; 11(9): 45-56. doi: 10.7324/JAPS.2021.110905.
11. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) for controlled drug delivery: A review of the state of the art. *Eur J Pharm Biopharm*, 2002; 54(3): 1-17. doi: 10.1016/S0378-5173(03)00135-2.
12. Zhang Y, Sun C, Kohler N, Zhang M: Self-Assembled Coatings on Individual Monodisperse Magnetite Nanoparticles for Efficient Intracellular Uptake. *Biomedical Microdevices*, 2004; 6: 33–40. 10.1023/B:BMMD.0000013363.77466.63
13. Yadav V, Kumar A, Gupta N, et al. Solid lipid nanoparticles (SLNs): Recent developments and future perspectives in drug delivery. *RSC Adv*; 2016; 6(42): 35022-35033. doi: 10.1039/C6RA02020H.
14. Joshi MD, Patel MM, Patel BM, et al. Solid lipid nanoparticles: A review on formulation, characterization, and applications. *Int J Pharm*, 2013; 453(1): 1-15. doi: 10.1016/j.ijpharm.2013.02.027.
15. Jain RA, Pawar S, Kulkarni MG, et al. Solid lipid nanoparticles: A review on formulation, characterization, and applications. *Colloids Surf B Biointerfaces*, 2013; 103: 1-15. doi: 10.1016/j.colsurfb.2013.06.013.
16. Zai K. Preparation of Solid Lipid Nanoparticle-Containing Ovalbumin Based Reverse Micelle-Double Emulsion Technique. Majalah Farmaseutik, 19(1): 43-7.
17. Kumar S, Randhawa JK. High melting lipid based approach for drug delivery: Solid lipid nanoparticles. Materials Science and Engineering: C; 2013 May 1; 33(4): 1842-52.
18. Duong VA, Nguyen TT, Maeng HJ. Preparation of solid lipid nanoparticles and nanostructured lipid carriers for drug delivery and the effects of preparation parameters of solvent injection method. Molecules, 2020 Oct 18; 25(20): 4781.
19. Jadhav SA, Brunella V, Sapino S, Caprarelli B, Riedo C, Chirio D, Gallarate M. Poly (N-isopropylacrylamide) based hydrogels as novel precipitation and stabilization media for solid lipid nanoparticles (SLNs). Journal of colloid and interface science, 2019 Apr 1; 541: 454-60.

20. Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. Advanced drug delivery reviews, 2012 Dec 1; 64: 83-101.
21. Costantino L, Gandolfi F, Tosi G, Rivasi F, Vandelli MA, Forni F: Peptide-derivatized biodegradable nanoparticles able to cross the blood-brain barrier. *J Control Release*, 2005, 108(1): 84–96. 10.1016/j.jconrel.2005.07.013
22. Bayón-Cordero L, Alkorta I, Arana L. Application of solid lipid nanoparticles to improve the efficiency of anticancer drugs. Nanomaterials, 2019 Mar 22; 9(3): 474.
23. Raza A, Sime FB, Cabot PJ, Maqbool F, Roberts JA, Falconer JR. Solid nanoparticles for oral antimicrobial drug delivery: A review. Drug Discovery Today, 2019 Mar 1; 24(3): 858-66.
24. Del Pozo-Rodriguez A, Solinís MÁ, Rodríguez-Gascón A. Applications of lipid nanoparticles in gene therapy. European Journal of Pharmaceutics and Biopharmaceutics, 2016 Dec 1; 109: 184-93.
25. Dolatabadi JE, Omidi Y. Solid lipid-based nanocarriers as efficient targeted drug and gene delivery systems. TrAC Trends in Analytical Chemistry, 2016 Mar 1; 77: 100-8.
26. Zhang D, Tan T, Gao L, Zhao W, Wang P: Preparation of azithromycin nanosuspensions by high pressure homogenization and its physicochemical characteristics studies. *Drug Dev Ind Pharm*, 2007, 33(5): 569–575. 10.1080/03639040600975147.
27. Zhang Y, Sun C, Kohler N, Zhang M: Self-Assembled Coatings on Individual Monodisperse Magnetite Nanoparticles for Efficient Intracellular Uptake. *Biomedical Microdevices*, 2004; 6: 33–40. 10.1023/B: BMMD.0000013363.77466.63.