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Sustained Release Oral Solid-Lipid Nanoparticles (SLNs) for Enhanced Bioavailability: A Comprehensive Review

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Oral drug delivery always remains the most preferred route of drug administration due to its convenience, patient compliance, and importantly the cost-effectiveness. However, many therapeutic agents may suffer from the poor aqueous solubility, extensive first-pass metabolism and also the limited bioavailability, which may restrict their clinical efficacy. Solid-lipid nanoparticles (SLNs) have emerged potently as a most promising nanocarrier system which is capable of addressing these challenges by combining the advantages of the lipid-based formulations with the nanoscale drug delivery system. This review comprehensively explores the potential of SLNs in the sustained release oral delivery system, highlighting their abilities to enhance the bioavailability and to most effective therapeutic outcomes. The paper also focuses on the overview of SLNs fundamentals, including the composition, preparation techniques and the physicochemical properties that governs the drug encapsulation and drug release. Advancement in the formulation strategies, such as lipid selection, surfactant optimization, and scale-up approaches, are critically examined in this paper. Furthermore, the review also emphasizes the pharmacokinetic improvements which are achieved through SLNs, particularly their role in the promotion of the lymphatic transport and bypassing the hepatic metabolism. Applications across diverse the therapeutic domains which includes the anticancer agents, antiretrovirals, anti-inflammatory drugs and nutraceuticals which are presented with the case studies demonstrating the enhanced oral bioavailability. Characterization techniques such as dynamic light scattering, electron microscopy, and differential scanning calorimetry are also outlined to provide a framework for evaluating the SLNs performance. Despite their promises, challenges such as lipid polymorphism, drug leakage, and regulatory hurdles remains the significant barriers to the clinical translation. Finally, future perspectives are discussed, including hybrid lipid-polymer systems, stimuli-responsive carriers and personalized nanomedicine approaches. By consolidating the current available knowledge and identifying the research gaps, this review collectively underscores the transformative potential of the sustained release oral SLNs in the modern drug delivery and encourages the further innovation towards the clinical application.

1. INTRODUCTION

Nanotechnology has revolutionized the drug delivery systems by offering the innovative platforms that are capable to overcome the limitations which are associated with the conventional formulations. Among these, solid lipid nanoparticles (SLNs) have gained the most significant attention as they are versatile carriers for the oral drug delivery [1]. SLNs are the submicron colloidal particles that are composed of the physiologically compatible lipids that may remain solid at both the room and body temperature [2]. Their unique architecture is consisting of the solid lipid core which are stabilized by the surfactants which enables the efficient encapsulation of the lipophilic and hydrophilic drugs, while providing the controlled and sustained release profiles [3]. The development of the SLNs was motivated by the need to combining the advantages of the polymeric nanoparticles and the lipid emulsions, which minimizes their respective and combined drawbacks such as cytotoxicity, instability and scale-up the challenges. SLNs also offers the several benefits such as improved drug stability, protection against the enzymatic degradation, enhanced bioavailability and the potential for the large-scale production using the established pharmaceutical processes [4]. Importantly, their lipid-based composition facilitates the lymphatic uptake, thereby helps in the bypassing the hepatic first-pass metabolism and improving the systemic exposure of the poorly soluble drugs [5]. Over the past two decades, SLNs have been extensively investigated for the oral delivery of diversify the therapeutic agents which may ranging from the anticancer drugs, antiretrovirals to the nutraceuticals [6]. Their ability to modulate the pharmacokinetics and to provide the sustained release makes them particularly attractive for the chronic therapies which are requiring the consistent plasma drug levels. Despite these advantages, several challenges such as lipid polymorphism, drug leakage, and long-term stability remains the areas of active research [7].

This review aims to provide a comprehensive overview of sustained release oral SLNs, focusing on formulation strategies, mechanisms of drug release, pharmacokinetic improvements, and therapeutic applications. By consolidating the current knowledge and highlighting the future directions, this paper underscores the potential of SLNs as a transformative approach in the modern drug delivery.

2. COMPOSITION OF THE SOLID LIPID NANOPARTICLES (SLNS)

Solid lipid nanoparticles (SLNs) are the submicron colloidal carriers which are composed of the biocompatible and biodegradable lipids that always remains solid at both room and body temperature. Their composition is relatively simple but highly versatile, allowing the perfect encapsulation to provide a wider range of the therapeutic agents [8]. The core component is the solid lipid matrix which may include the triglycerides, partial glycerides, fatty acids, waxes, or sterols. This lipid core serves as the reservoir for drug molecules and plays a critical role in controlling release kinetics and stability [Figure 1] [9].

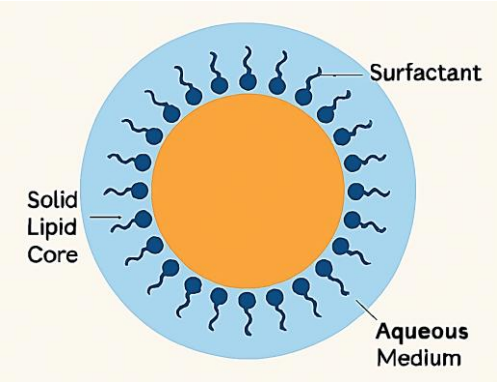

Figure 1: Solid Lipid Nanoparticles (SLNs)

To stabilizes the lipid dispersion, surfactants or emulsifiers are also incorporated in them. Common examples of the surfactants include the phospholipids, poloxamers, bile salts and the Tween derivatives which reduces the interfacial tension and also prevents the particle aggregation. The choice and concentration of this surfactant significantly influences the particle size, surface charge, and long-term stability [10, 11]. In certain formulations, co-surfactants or stabilizers such as lecithin or polyethylene glycol (PEG) are also added to enhance the steric stabilization and to improve the bioavailability. Additionally, these aqueous dispersion media are the purified water or buffer solutions which provides the continuous phase for nanoparticle suspension [12, 13]. These simple but adaptable composition enables the SLNs to combine their advantages of the traditional lipid carriers with the nanoscale properties as result of which they are capable for offering a controlled drug release system and also provides the protection against the degradation and improves the oral bioavailability [14].

3. METHODS OF PREPARATION OF SOLID LIPID NANOPARTICLES (SLNS)

Solid Lipid Nanoparticles (SLNs) can be prepared by using the various methods, which can be broadly categorized into high-energy methods (requiring specialized equipment and high power input) and low-energy/solvent-based methods (15,16).

3.1 High-pressure homogenization

High-pressure homogenization (HPH) is a reliable method for preparing SLN. Several manufacturers provide affordable homogenizers of various sizes. Submicron particles are produced with high shear stress and cavitation compulsion. Nanoemulsions for parenteral feeding are made by HPH. HPH forces liquid through a limited area (a few microns) at high pressures (100-2,000 bar). A short distance with high velocity propels the fluid quickly. High lipid concentrations may be homogenized into nanodispersions (17, 18). Hot and cold homogenization methods are used to produce SLN. Both scenarios require a preliminary step. This approach uses lipid matrix derived from physiological lipids, reducing the risk of acute and longterm toxicity.

3.1.1 Hot homogenization

To produce Solid Lipid Nanoparticles (SLNs), the process begins by selecting temperatures that exceed the melting point of the lipids, followed by homogenization of an emulsion. An aqueous surfactant is integrated with the lipid and drug at uniform temperature. This mixture is then subjected to high shear mixing, leading to the formation of a pre-emulsion characterized by oil in water. Following this, the product is allowed to cool, which triggers the crystallization of lipids and subsequently forms SLNs. It is essential to conduct 3 to 5 cycles of homogenization at pressures ranging from 500 to 1,500 bar to achieve optimal SLN characteristics (19). Additionally, it is important to note that high-pressure homogenization (HPH) results in temperature increases, and a higher number of cycles or increased pressure may lead to larger particle sizes due to the attractive forces generated by the kinetic energy of the particles (20). Finally, the nanoemulsion is cooled to room temperature, wherein recrystallization of the lipids occurs, resulting in the formation of nanoparticles.

3.1.2 Cold homogenization

The initial step closely resembles the hot homogenization process, where the drug is solubilized in the lipid melt. However, the subsequent processes differ significantly: the drug-laden melt is quickly cooled using solid carbon dioxide or liquid nitrogen to achieve a uniform distribution within the lipid matrix. Following this, the solidified material undergoes levigation via a ball mill to create a fine powder, typically sized between 50 and 100 μm (21). This powder is then dispersed in a chilled aqueous surfactant solution, and the resulting dispersion is processed through high-pressure homogenization (HPH) to produce solid lipid nanoparticles (SLNs). Notably, compared to hot homogenization, the cold homogenization method tends to yield larger particle sizes and exhibits a broader size distribution. While cold homogenization mitigates heat sensitivity, some degree of heat exposure remains due to the softening of the lipid mixture in the initial step (22).

3.2 Ultrasonication

SLN (Solid Lipid Nanoparticles) can be produced through techniques such as high-speed

stirring or sonication, which are commonly utilized in laboratory settings (23). However, these methods exhibit a significant drawback: they result in a wider particle size distribution, extending into the micrometer range. This broad size range is a primary factor contributing to physical instability issues of the nanoparticles (24). Additionally, challenges such as particle gain during storage and potential metal decay are critical concerns associated with these techniques. Nevertheless, extensive studies and research have demonstrated that when high-speed stirring is combined with ultrasonication at elevated temperatures, it leads to a more stable formulation of SLNS.

3.3 Solvent Emulsification–Evaporation (SEE)

In this method, lipophilic materials and hydrophobic drugs are first dissolved in organic solvents that do not mix with water, such as cyclohexane, toluene, and chloroform. Subsequently, through high-speed homogenization, the resultant mixture is emulsified into an aqueous phase (25). The coarse emulsion produced is then processed using a microfluidizer to achieve finer emulsification. Following this, a rotary evaporator equipped with mechanical agitation operates at room temperature and reduced pressure to evaporate the organic solvent. This method is noteworthy for its ability to avoid thermal stress, thereby allowing for the incorporation of highly thermolabile drugs. However, a significant drawback to this technique is the potential for the organic solvent to react with the drug molecules, as emphasized by other studies in the field (26).

3.4 Microemulsion

SLN (Solid Lipid Nanoparticles) preparations were advanced by Gasco and colleagues through methods aimed at decreasing the concentration of microemulsions, which are biphasic systems comprising both external and internal phases. These microemulsions typically consist of a low melting fatty acid, such as stearic acid, an emulsifier like polysorbate 20, polysorbate 60, or soy phosphatidylcholine, as well as coemulsifiers such as butanol and sodium mono cetyl phosphate, combined with water (27). In a controlled process, the hot microemulsion is introduced into cold water at temperatures between 2°C and 3°C, allowing for a fixed dilution process based on the specific microemulsion formulation used. Essential to the formation of nanoparticles is the choice of solvent; certain solvents are necessary for effective dispersion into an aqueous phase, while more lipophilic solvents are employed to yield larger particle sizes. The primary advantage of this approach lies in its low requirement for mechanical energy input, which is adequate for the production process (28).

4. CHARACTERIZATION OF SOLID LIPID NANOPARTICLES (SLNS)

Characterization of SLNs is essential to ensure their stability, efficacy, and suitability for drug delivery. Key parameters include particle size, zeta potential, morphology, drug encapsulation efficiency, and crystallinity (29, 30). Together, these techniques provide a comprehensive understanding of SLN behavior, guiding formulation optimization for targeted therapeutic applications.

4.1 Particle size and distribution are typically measured using dynamic light scattering (DLS). Smaller particles (<200 nm) enhance bioavailability and cellular uptake. **Zeta potential** indicates surface charge and predicts colloidal stability; values above ±30 mV suggest good stability due to electrostatic repulsion.

4.2 Morphological analysis using transmission electron microscopy (TEM) or scanning electron microscopy (SEM) reveals shape and surface features. SLNs generally exhibit spherical morphology with smooth surfaces.

4.3 Encapsulation efficiency (EE%) and **drug loading capacity** are determined via centrifugation and spectrophotometric or chromatographic methods. High EE% ensures effective drug delivery.

4.4 Differential scanning calorimetry (DSC) and **X-ray diffraction (XRD)** assess lipid crystallinity and polymorphic transitions. Reduced crystallinity may enhance drug incorporation but affect long-term stability.

4.5 In vitro release studies using dialysis methods evaluate drug release kinetics, often showing sustained release profiles. Additionally, **stability studies** under various conditions (temperature, pH) help predict shelf-life.

5. FUTURE PROSPECTUS OF SUSTAINED RELEASE SOLID LIPID NANOPARTICLES (SLNS)

The future prospectus of the sustained release SLNs lies in their abilities to overcome the limitations of their conventional dosage forms by ensuring their prolonged drug release, reduced dosing frequency and enhanced the patient compliance. SLNs are also biocompatible and biodegradable carriers that can encapsulate both the hydrophilic and lipophilic drugs, thus making them versatile platforms for the diverse therapeutic applications.

In oncology, sustained release SLNs can also deliver the chemotherapeutic agents such as paclitaxel or doxorubicin with its reduced systemic toxicity and improved tumor targeting efficiency. Similarly, in neurodegenerative disorders like Alzheimer's and Parkinson's disease, SLNs shows a potential way to cross the blood–brain barrier and provide a continuous drug release, thereby maintaining the therapeutic concentrations in the brain (31). Their applications in infectious diseases is also noteworthy; for example, sustained release SLNs loaded with antitubercular drugs can reduce the dosing frequency and improve the adherence in the long-term treatment regimens (32).

Beyond pharmaceutical applications, SLNs are also being explored in the gene therapy and the vaccine delivery, where sustained release can enhance the immune responses by providing them a controlled antigen exposures. Nutraceuticals such as curcumin, resveratrol, and omega-3 fatty acids also gets the benefit from SLN encapsulation, ensuring their stability and a prolonged bioavailability in the functional foods (33). Advancement in the surface modification and ligand attachments are also expected to enable the site-specific sustained release, thus minimizing the off-target effects. Moreover, these integrations with the nanotechnology innovations such as stimuli-responsive lipids and hybrid nanocarriers could allow the SLNs to release drugs in proper response to the physiological triggers like pH or temperature, further refining the precision medicine approaches (34, 35).

From a regulatory and industrial perspective, the scalability of SLN production using high-pressure homogenization and microemulsion techniques supports their transition from laboratory to commercial formulations. Future research will likely focus on optimizing lipid matrices, improving encapsulation efficiency, and conducting long-term stability studies to meet stringent pharmaceutical standards. With increasing emphasis on patient-centric therapies and personalized medicine, sustained release SLNs are poised to become a cornerstone in modern drug delivery systems. Their adaptability across therapeutic areas, combined with technological advancements, positions them as a transformative tool for healthcare innovation in the coming decades.

6. CONCLUSIONS

The comprehensive review on the Sustained Release Oral Solid-Lipid Nanoparticles (SLNs) presents their transformative potential as advanced drug delivery systems. Oral administration, known for its convenience and patient-friendliness, often encounters challenges such as poor solubility, low permeability, and rapid metabolism of therapeutic agents. SLNs, leveraging a lipid-based matrix, address these issues through sustained release mechanisms that enhance drug stability and bioavailability via controlled gastrointestinal absorption. The review articulates how SLNs merge the advantages of traditional lipid carriers with nanotechnology benefits, allowing for the encapsulation of both hydrophilic and lipophilic drugs, protection against degradation, and provision of extended the drug release profiles. This versatility not only reduces the dosing frequency but also enhances the patient compliance and maintains therapeutic plasma concentrations, which is crucial in chronic treatments for cardiovascular diseases, diabetes, neurodegenerative disorders, and cancer. Formulation strategies play a vital role in the effectiveness of SLNs; this includes considerations for lipid selection, surfactant optimization, and homogenization techniques, which affect particle size, zeta potential, and drug loading capacity. The review also discusses advancements in characterization methods, such as Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), and Transmission Electron Microscopy (TEM), that enhance understanding of SLN structure and stability, contributing to the rational design of oral sustained release

formulations. Successful case studies highlight how SLNs have improved the oral delivery of drugs including curcumin, paclitaxel, and antiretrovirals, underscoring their clinical relevance. Looking forward, the integration of SLNs with targeted delivery, surface modifications, and stimuli-responsive systems may further broaden their therapeutic applications. Achieving these regulatory acceptance and establishing scalable production techniques will be essential for the conversion of laboratory achievements into commercially viable products. In summary, sustained release oral SLNs mark a significant leap in nanomedicine, creating a robust platform for overcoming bioavailability challenges and heralding a new era in oral drug delivery that aligns with patient-centric pharmaceutical innovation across various therapeutic domains.

7. CONFLICT OF INTEREST

None

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