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Solid Lipid Nanoparticles as a Promising Strategy for Enhancing Oral Bioavailability of Poorly Absorbed Drugs: A Comprehensive Review

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Abstract

Recent advances in nanotechnology-based oral drug delivery systems have provided promising approaches to address the challenges posed by drugs with poor bioavailability. Ahighly present of newly developed pharmaceutical compounds have low oral bioavailability. Due to their low aqueous solubility, intestinal permeability, and extensive first-pass metabolism. Addressing these challenges continues to be a key priority in pharmaceutical research. Solid lipid nanoparticles (SLNs) have gained considerable attention as lipid-based nanocarriers that can improve drug solubility, protect sensitive compounds from degradation in the gastrointestinal tract, enhance intestinal permeability, and support controlled drug release. They are considered a promising delivery system for oral medications. Because they have several advantageous characteristics, such as their biocompatibility, ability to encapsulate both hydrophilic and lipophilic drugs, and suitability for large-scale production.

This review draws on a wide range of studies published between 1993 and 2025. with a particular focus on research exploring the use of SLNs to enhance oral bioavailability. The use of old references to document the original information.

The reviewed studies consistently show that SLN-based formulations can markedly enhance drug bioavailability, with reported improvements generally ranging from about 2- to 12-fold, depending on the drug's physicochemical characteristics and the formulation conditions.

The review provides a comprehensive overview of SLNs, covering formulation strategies, preparation methods, and key characterization techniques. It also offers a critical evaluation of their main advantages and potential limitations. Particular attention is given to their role in oral drug delivery and their effectiveness in enhancing systemic drug absorption.

When taken as a whole, SLNs offer a reliable and flexible delivery system that has great potential to improve the oral bioavailability of medications that are poorly absorbed and to further the creation of contemporary therapeutic formulations.

الجسيمات الدهنية النانوية الصلبة كاستراتيجية واعدة لتعزيز التوافر الحيوي الفموي للأدوية ضعيفة الامتصاص: مراجعة شاملة

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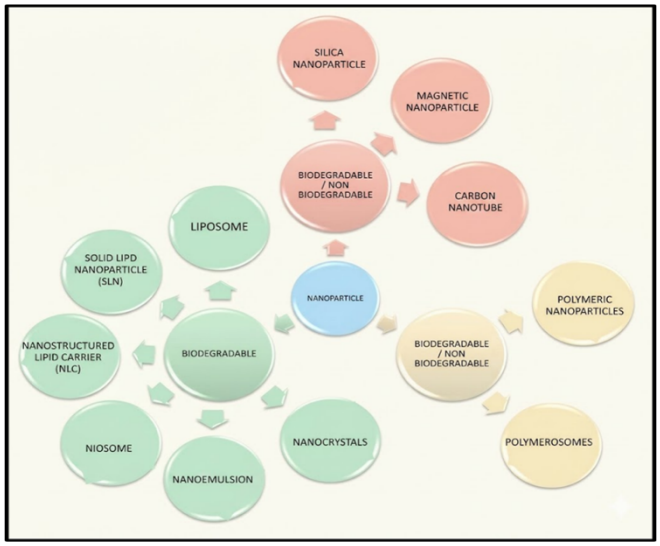
الخلاصة:
وفرت التطورات الحديثة في أنظمة إيصال الأدوية عن طريق الفم القائمة على النانو تقنيات ونهجاً واعدة لمعالجة التحديات التي تفرضها الأدوية ذات التوافر الحيوي الضعيف. حيث تعاني نسبة عالية من المركبات الصيدلانية المطورة حديثاً من انخفاض التوافر الحيوي الشفوي؛ ونظراً لقلة ذوبانيتها المائية، وضعف نفاذيتها المعوية، وتعرضها للأيض العابري الأول المكثف (First-pass metabolism)، تظل معالجة هذه التحديات أولوية رئيسية في البحوث الصيدلانية. حازت الجسيمات الشحمية النانوية الصلبة (SLNs) على اهتمام كبير كحوامل نانوية قائمة على الدهون؛ حيث يمكنها تحسين ذوبانية الدواء، وحماية المركبات الحساسة من التحلل في الجهاز الهضمي، وتعزيز النفاذية المعوية، ودعم التحرر الدوائي المُنظّم. وتُعد هذه الجسيمات نظام إيصال واعد للأدوية الفموية؛ نظراً لتمتعها بالعديد من الخصائص المتميزة، مثل التوافق الحيوي (Biocompatibility)، والقدرة على تغليف الأدوية المحبة للماء والمحبة للدهون على حدٍّ سواء، وملائمتها للإنتاج على نطاق واسع. تستند هذه المراجعة العلمية إلى مجموعة واسعة من الدراسات المنشورة بين عامي 1993 و2025، مع التركيز بشكل خاص على البحوث التي تستكشف استخدام الجسيمات الشحمية النانوية الصلبة لتعزيز التوافر الحيوي الفموي، مع الاستعانة والمحافظة على المراجع القديمة لتوثيق المعلومات الأصلية. أظهرت الدراسات التي تم استعراضها بشكل مستمر أن الصياغات الدوائية القائمة على (SLNs) يمكنها تعزيز التوافر الحيوي للدواء بشكل ملحوظ، حيث تراوحت التحسينات المسجلة عموماً بين 2 إلى 12 ضعفاً، اعتماداً على الخصائص الفيزيوكيميائية للدواء وظروف الصياغة الدوائية. تقدم المراجعة نظرة عامة وشاملة عن الجسيمات الشحمية النانوية الصلبة، متضمنةً استراتيجيات الصياغة، وطرق التحضير، وتقنيات توصيف الخصائص الرئيسية. كما تقدم تقييماً نقدياً لمزاياها الرئيسية والقيود المحتملة لها. وقد أُولي اهتمام خاص لدورها في إيصال الأدوية عن طريق الفم وفعاليتها في تعزيز الامتصاص الدوائي النظامي (الجهازي). وبشكل عام، تقدم (SLNs) نظام إيصال موثوقاً ومَرناً يمتلك إمكانات كبيرة لتحسين التوافر الحيوي الفموي للأدوية ضعيفة الامتصاص، ولدعم تطوير الصياغات العلاجية الحديثة.

الكلمات المفتاحية: الجسيمات الشحمية النانوية الصلبة، التوافر الحيوي، النانو تقنية، إيصال الأدوية، الحوامل الدهنية.

INTRODUCTION

Oral delivery is unequivocally recognized as the most convenient route for medication administration. offering numerous benefits over alternative routes, including painlessness, ease of self-management, and high patient adherence. The vast majority of medications available worldwide are mostly administered orally [(1)]. Despite these benefits, a lot of medications have poor oral bioavailability, mainly because of high first-pass metabolism, restricted intestinal permeability, and low aqueous solubility. As a result, the drug's pharmacological effect is diminished and its bioavailability is suboptimal because not enough of it reaches the target site and the systemic circulation [(2-4)] . To establish a relationship between in-vitro drug solubility and in vivo bioavailability, Gordon L. Amidon and colleagues introduced a systematic approach for evaluating drug behavior. The Biopharmaceutics Classification System (BCS) is a widely used framework for classifying drugs based on their solubility and intestinal permeability. Under this system, drugs are grouped into four classes: Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability)[(2,5-7)] . In addition, many BCS Class IV drugs act as substrates for efflux transporters such as P-glycoprotein, as well as for metabolizing enzymes like cytochrome P450, which further reduces their systemic availability [(8)] . Thus, the development of oral formulations for BCS Class IV drugs has become an important and increasingly active area of research. To overcome these limitations, various formulation strategies have been explored. Including liposomes [(9)] , nano-micelles [(10)] , nano-emulsifying drug delivery systems [(11)] , lipid nano carriers [(12)] , and polymeric nanoparticles [(13)] . Figure (1) shows a variety of nanoscale systems made of different materials that can serve as nanocarriers. These delivery systems have shown promise in improving drug solubility and absorption, but they are frequently linked to drawbacks like low drug loading capacity, physical instability, intricate manufacturing procedures, and possible toxicity issues [(14-16)] . These drawbacks can hinder their large-scale production and clinical translation [(17, 18)]. Nanoparticles in pharmaceutical applications are generally defined as submicron colloidal systems with particle sizes typically ranging from 10 to 1000 nm, designed to improve drug delivery performance [(19, 20)]. With respect to lipid-based nanocarriers, solid lipid nanoparticles (SLNs) are helpful colloidal systems that have emerged as a promising alternative drug delivery system [(21)]. These are prepared from physiologically

compatible lipids that maintain a solid state at both body and ambient temperature. So, in general, they should have a melting point above 40°C. These lipids create a solid core surrounded by surfactants and, sometimes, cosurfactants, which stabilize the nanoparticles in dispersions (Figure 2) [22, 23]. Additionally, SLNs offer better drug stability, controlled release, increased permeability, and protection against gastrointestinal degradation by combining the benefits of lipid-based carriers and nanotechnology [19,24]. Additionally, their biocompatibility, low toxicity, and suitability for large-scale production make them attractive candidates for oral drug delivery applications [25].



Figure(1): Represents several nano-based systems[19].

This article illustrates the different excipients that may be used in formulations of SLNs. offers a detailed overview of SLN characteristics, the different production methods employed, and some applications that improve the enhancement of oral bioavailability by SLNs. This assessment may support the future design and further development of solid lipid nanoparticles for applications aligned with the drug's intended use.

Literature Search Strategy

A comprehensive literature search was performed using major electronic databases, including PubMed, Scopus, and Web of Science. Relevant studies published between 1993 and 2025 were identified using combinations of keywords such as "solid lipid nanoparticles," "oral bioavailability," "poorly absorbed drugs," and "lipid-based drug delivery systems." The inclusion criteria covered original research articles published in English that examined the use of solid lipid nanoparticles to enhance oral bioavailability. Studies focusing on formulation development, physicochemical characterization, and in vitro and in vivo evaluations were included.

In contrast, review papers, conference abstracts, duplicate publications, and studies lacking adequate experimental data or clear relevance to the topic were excluded. The selection process included an initial screening of titles and abstracts, followed by full-text assessment to ensure the inclusion of relevant and high-quality studies.

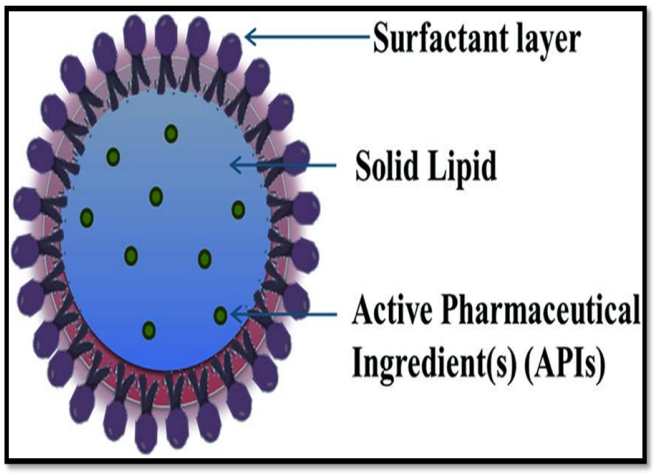


Figure (2): The main compositions of SLN[19].

Challenges in Oral Drug Delivery

Following oral administration, medications must pass through several anatomical and physiological barriers within the gastrointestinal tract before reaching the systemic circulation. Initially, the drug encounters the acidic environment of the stomach and then travels through the intestinal lumen. Subsequently, it must cross the mucosal barrier lining the intestinal epithelium to be absorbed [26, 27]. Anatomically, the stomach wall is composed of four principal layers arranged from the inner surface outward: the mucosa, submucosa, muscularis externa, and serosa. The mucosal layer contains numerous gastric glands, which include specialized cells that secrete gastric juice. Within the small intestine, the epithelial lining forms finger-like projections known as villi. These structures greatly increase the surface area available for nutrient and drug absorption [26]. The villi are covered mainly by absorptive enterocytes together with mucus-producing goblet cells, and they are sprinkled with areas of follicle-associated epithelium. Various physiological characteristics of the gastrointestinal tract can influence drug absorption and ultimately affect bioavailability. Limited permeability of the mucosal barrier, together with enzymatic degradation of drugs before they are absorbed, may significantly reduce the amount of active compound that reaches systemic circulation [28].

Multidrug efflux proteins, including P-glycoprotein, located on the epithelial cell membrane, constitute an additional blockade to orally taken pharmaceuticals [27]. Certain medications or substances with a substantial hepatic first-pass effect accordingly limit gastrointestinal absorption. The supplementary oral absorption problems include chemical instability, a short half-life, and food interactions [29]. Some medications have poor solubility, which adversely impacts oral bioavailability and complicates the development of effective delivery systems.

Figure 3 illustrates the obstacles and problems associated with the effective oral administration of the drugs. Nonetheless, oral formulations are being developed based on fundamental biological and pharmacological principles of oral drug administration [30].

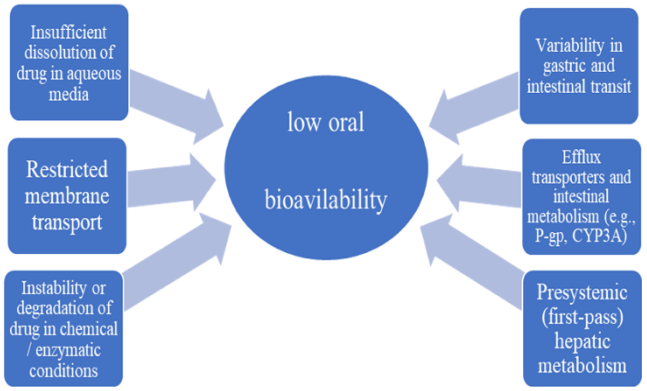


Figure (3): illustrates the obstacles and problems associated with the effective oral administration of the drugs.

Advancement of SLNs in enhancing the oral bioavailability of pharmaceuticals

Alongside significant advancements in nanomedicine, solid lipid nanoparticles (SLNs) for active-component administration have proliferated rapidly owing to their nanoscale size (50−1000 nm) (35), thereby facilitating evasion of physiological obstacles more easily. The reduction in particle size significantly increases the surface area of insoluble drug particles, hence enhancing absorption by the monolayer cells of the gastrointestinal tract [31]. Furthermore, the lipid degradation products of solid lipid nanoparticles in bowel fluid, including glycerides and fatty acids, can facilitate intestinal transit by forming mixed micelles, hence increasing medication absorption into enterocytes [32]. Furthermore, in lipid-based systems utilising self-emulsifying excipients, absorption is augmented not only through M cell and paracellular uptake but also through lipase-mediated chylomicron formation in the lymphatic system, similar to the absorption of long-chain fatty acids via facilitated chylomicron formation [33]. Transporting of Drugs to systemic circulation can be efficiently achieved through M cell uptake in intestinal lymphatics by the thoracic lymph duct, thereby enhancing oral drug delivery by providing direct delivery to the immune system while circumventing first-pass metabolism [34]. Solid lipid nanoparticles (SLNs) have shown considerable promise in enhancing gastrointestinal absorption and bioavailability of several medications. Also, these carriers are crucial for regulated drug delivery. SLNs are respected for their adaptability as a drug-delivery method, employed in the management of many conditions impacting the heart, blood vessels, brain, central nervous system, as well as malignancies and infectious disorders. This approach is recognized as the most promising for the oral delivery of peptide-based medicines, and hence requires advancing this Essential carrier mechanism to protect against proteolytic conditions in the stomach [35].

Composition of SLN

Solid lipid nanoparticles are colloidal systems composed of a hydrophobic, biocompatible central matrix, comprised of lipids, or a blend of lipids that keep on solid at both body and ambient temperatures. Lipids are the principal element of the matrix, profoundly affecting the properties of the colloidal system that utilises them. Incorporating Compritol 888 ATO, Precirol ATO 5, glyceryl monostearate, palmitic acid, stearic acid, among others, and stabilised by surfactants in the outer shell, with active pharmaceutical substances including medications, genes, DNA, plasmids, and proteins [36,37]. However, the physicochemical characteristics of lipids and emulsifiers also affect the behaviour of the corresponding solid lipid nanoparticles in both in vivo and in vitro release contexts. The synthesis of colloidal nanoparticles is contingent upon the interfacial and surface tension between two liquids. The primary mechanism regulating the formation of solid lipid nanoparticles is the adhesive forces between two liquids. The interfacial tension between two liquids is frequently lower than their surface tension owing to weaker adhesive forces related to those between a liquid and a gas. Materials at the interface generate interfacial tension, while agitation creates a spherical configuration to minimise surface free energy [38].
Surfactants aggregate at the interface, creating a coating around the particles, so as to maintain the physical stability of the dispersion system throughout storage [39]. It is imperative to consider the surfactant's toxicity. Not all surfactants are suitable for each form of solid lipid nanoparticle (SLN). The production of solid lipid

nanoparticles typically requires the use of different types of surfactants, such as anionic and nonionic surfactants, with sporadic inclusion of cationic surfactants [40].

As illustrated in Figure (4), stearic acid, glyceryl behenate, tripalmitin, acetyl palmitate, glyceryl monostearate, and tristearin collectively constitute approximately 70% of the most utilised solid lipids.

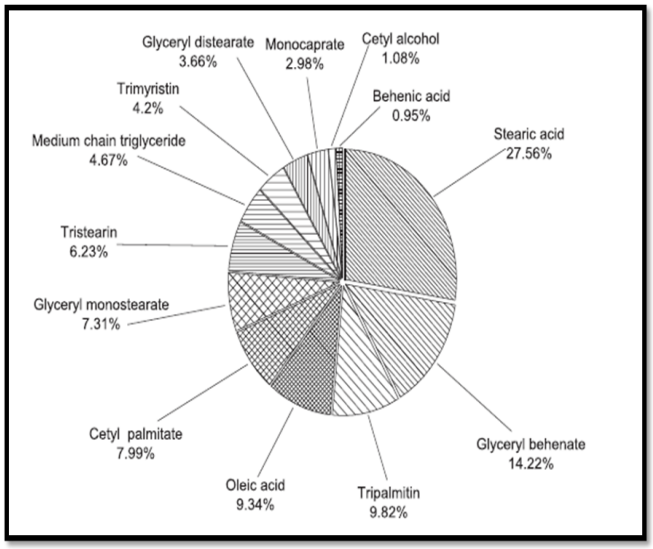


Figure (4): Estimated distribution of the predominant lipids utilised in the formulation of lipid nanoparticles[39].

Poloxamer® 188, Tween® 20, and Tyloxapol are the predominant non-ionic stabilising mediators, but soy or egg lecithin are typically the preferred amphoteric stabilising mediators in numerous investigations, as illustrated in Figure (5).

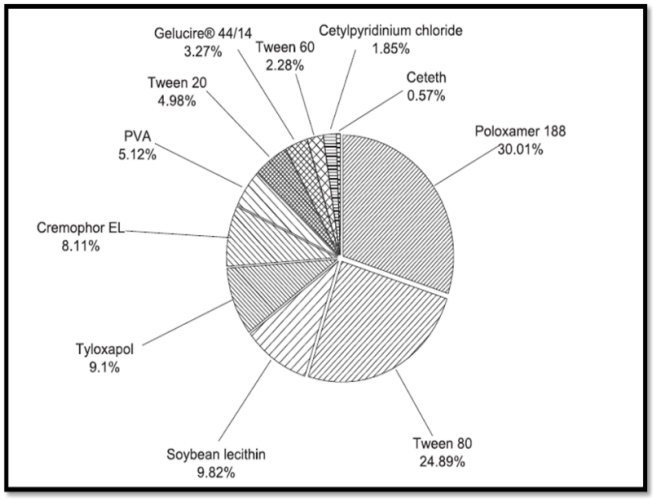


Figure (5): Estimated dispersal of the most often utilized stabilising agents for the formulation of lipid nanoparticles [39].

Advantages of SLN

Solid lipid nanoparticles (SLNs) offer several advantages that make them promising carriers for oral drug delivery, for example: (a) prevent the degradation of photosensitive, moisture-sensitive, and chemically labile pharmaceutical compounds. in both physiological (post-oral administration), and external environments (during storage) (b)) It is feasible to make highly lipophilic substances more bioavailable, and the viability of incorporating both hydrophilic and lipophilic medications and peptides [41] (c) utilization of biodegradable and physiological lipids are in formulation of solid lipid nanoparticles [42], (d) a low cost and in a relatively straightforward manner, for achieving of the scaling up of the formulation technique to an industrial production level (e) the use of organic solvents can be avoided in the creation of SLNs [43].

Limitations of SLNs

SLNs have a number of drawbacks that could impair their effectiveness despite their benefits [44-46].

Drug expulsion during storage, which results from lipid crystallization and polymorphic changes from less stable to more stable forms, is one of the most important problems. A highly ordered lipid matrix is created as a result of this process, which eventually reduces drug loading and may cause drug leakage. Long-term storage or high temperatures, which hasten lipid recrystallization, cause drug expulsion to be more noticeable. Furthermore, drug incorporation may be restricted by the high crystallinity of solid lipids, especially for hydrophilic drugs.

Particle size expansion, dispersion gelation, and fluctuations in drug release characteristics while being stored. Formulation techniques like the use of lipid mixtures, the addition of surfactants, and the creation of nanostructured lipid carriers (NLCs) have been suggested to improve drug loading capacity and stability in order to address these issues.

Preparation Methods for Fabrication of SLN

The preparation approaches of SLNs can be categorized into three groups [47, 48], as illustrated in Figure (6).

High-energy methods often involve the employment of equipment that may produce high shear forces, pressure distortions, or any other approaches to reduce particle size.

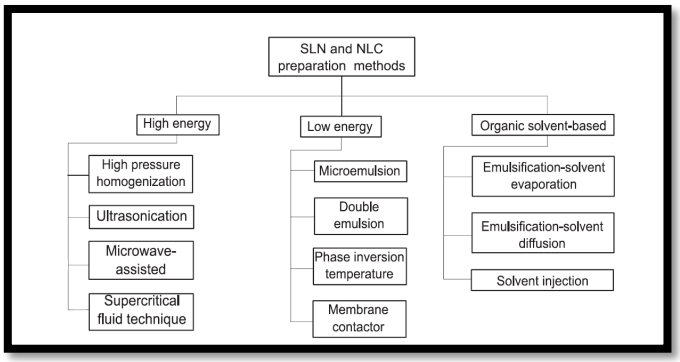
Approaches based on low energy, that do not need substantial energy consumption to produce particle size reduction, with certain processes occurring spontaneously. Microemulsion techniques, double emulsion generation, temperature-induced phase inversion, membrane contactors, and coacervation are among the most extensively researched methods.

Methods utilising organic solvents can be categorised as either low-energy or high-energy, as relevant.

Nevertheless, they are classified distinctly due to the incorporation of organic solvents in the system, which underlies the mechanism for particle size diminution. This encompasses emulsification-evaporation of

solvent, emulsification-diffusion of solvent, and solvent injection procedures.

Figure (6): A comprehensive categorisation of preparation techniques for solid lipid nanoparticles (SLN) [47].



High-energy approaches

High-Pressure Homogenization (HPH)

This technique has been employed as a viable, robust approach for the large-scale production of NLCs, LDCs, SLNs, and parenteral emulsions. The approach involves the high-pressure (100-200 bars) pumping of lipids by a small aperture of some microns. Shear stress and cavitation are the principal forces that fragment particles to the submicron scale, with lipid content often between 5% and 10%. In contrast to other production methods, HPH does not provide a scaling-up challenge [21,49].

Advantages: Highly efficient dispersion technology

Disadvantages: Highly energy-demanding procedure.

There are two main HPH production techniques: hot and cold homogenization. There is a similarity between the two approaches, where the drug is solubilized in the melted lipid matrix at a temperature exceeding the melting point of the lipid by approximately 5-10º C [50].

A - Hot Homogenization Technique

This procedure involves dispersing the medication and molten lipid through continuous agitation in a high-shear mixer in an aqueous surfactant solution maintained at a constant temperature. The generated preemulsion is homogenised with a piston-gap homogeniser, and the resulting nanoemulsion is cooled to room temperature, promoting lipid recrystallisation and the formation of lipid nanoparticles, as shown in Figure 7 (A).

Advantages: commercially available, Scalable.

Disadvantages: Distribution of the drug into the aqueous phase during homogenisation, Thermal degradation of pharmaceuticals, and the intricacy of the crystallisation phase of nanoemulsion result in several alterations and supercooled melts [50].

B -Cold Homogenization Technique

Cold homogenisation has been established to address the problems of hot homogenization, including degradation of drug payloads induced by the high temperature and the partitioning of drug into the aqueous phase during the homogenisation. The initial stage is the same in both cold and hot procedures. In the subsequent phase, the liquefied lipid-based pharmaceutical is rapidly chilled using ice or liquid nitrogen to facilitate dispersion of the drug within the lipid matrix, as shown in Figure 7A. This cold homogenisation method minimises sample exposure to heat.

Advantages: No drug degradation induced by temperature and no crystalline modification

Disadvantages: have not reported one [50]

High Shear Homogenization and Ultrasound

This technique involves particles or liquids experiencing shear between two contiguous solid surfaces. The standard process involves heating the drug-lipid blend to a temperature exceeding the lipid's melting point. Prepare the aqueous phase by dissolving the surfactants in water and heating it to match the oil phase temperature. The hot aqueous phase was added to the lipid phase, followed by high-speed homogenisation for a specified duration. After the formation of a coarse hot oil-in-water emulsion, it was ultrasonicated using a probe sonicator, as shown in Figure 7c. The resultant SLN dispersions were ultimately acquired by cooling the heated nanoemulsion to ambient temperature or more swiftly in a refrigerator [51].

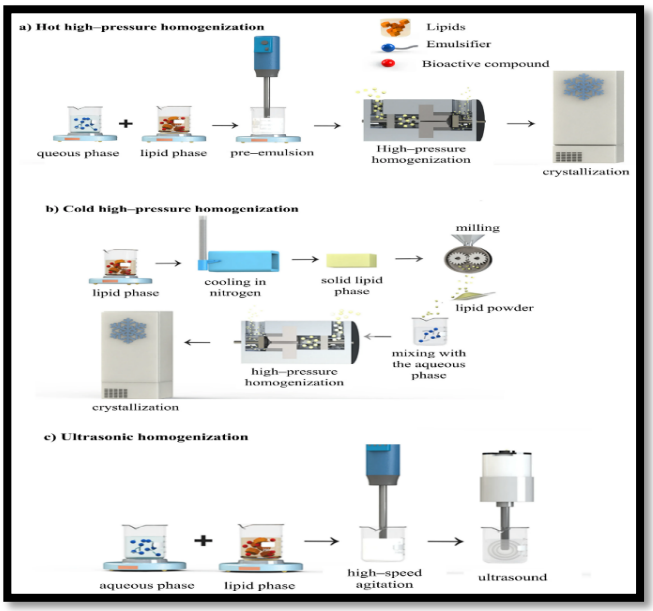


Figure (7): Methods of SLN preparation, high-energy methods [47].

Low-energy approaches

Microemulsion Method

The first development of this method was in the early 1990s [52] and has since been investigated by several researchers. The SLNs will be produced in two phases, as illustrated in the image. The initial phase will include dissolving the medication in the lipid, which has been heated above its melting point. The second phase will be formulated by dissolving the surfactant in the aqueous medium and heating it to the lipid's melting point. The aqueous phase will be combined with the oil phase to create a stable microemulsion. The microemulsion will thereafter disperse in cold water (2–10 °C). This phase will result in the solidification of nanolipids. This will scatter in the cooled water, forming solid lipid nanoparticles, as illustrated in Figure (8).

Advantages: its appropriateness for large-scale production, its solvent-free characteristic, and its classification as a straightforward approach.

Disadvantages: encompass excessive water consumption and elevated surfactant concentration requirements. Freeze-drying can eliminate moisture [53].

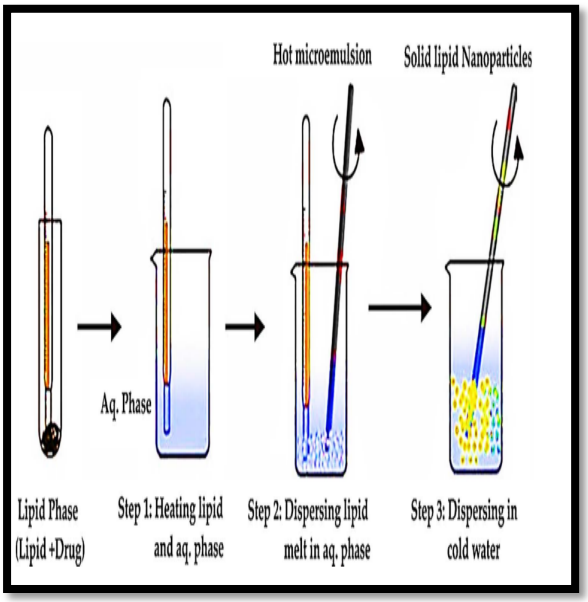


Figure (8): steps of the microemulsion method [50].

Double - Emulsion Method

This procedure is intended to incorporate hydrophilic pharmaceuticals into SLNs. By solubilising the medication in the aqueous phase and subsequently incorporating this phase into the molten oil (the oil phase), a water/oil emulsion will be generated. The emulsion will then disintegrate in the secondary aqueous phase, aided by the surfactant, forming a water/oil/water double emulsion. The SLNP will thereafter separate by cooling and precipitation, as illustrated in Figure (9)[54].

Advantages: Minimal energy consumption, Conceptual stability

Disadvantages: Highly susceptible to alterations, time-consuming formulation processes, and low quantity of nanoparticles[51].

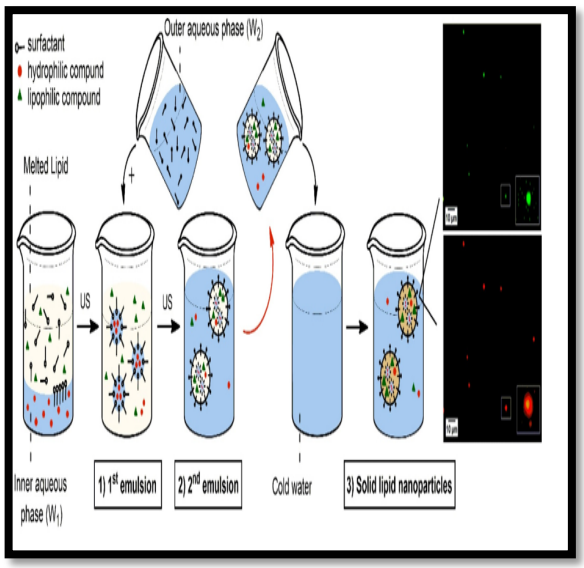


Figure (9): double - emulsion technique [54].

Approaches with organic solvents

Solvent Emulsification Evaporation

This approach involved dissolving lipophilic compounds in a water-immiscible organic solvent (e.g., cyclohexane) and emulsifying them in an aqueous phase to create an oil-in-water (o/w) emulsion. A solid lipid nanoparticle dispersion is produced by evaporating the solvent at low pressure [55]. The mean particle size depends on the lipid concentration in the organic phase. Minuscule particles could be obtained only with low fat loading associated with the organic solvent. The efficacy of homogenisation diminishes as lipid content rises, attributable to the increased viscosity of the dispersed phase. A significant disadvantage of this method is the [56].

Advantages: low particle size ≤ 24 nm, Circumvention of heat, low viscous system formed, Minimal energy consumption.

Disadvantages: Low dispersion degree, emulsion instability, lipid insolubility in organic solvents. Supplementary solvent extraction process, Toxicological concern (remaining solvent).

Both solvent emulsification-evaporation and microemulsion procedures are regarded as advanced methods aimed at overcoming the substantial mechanical energy requirements linked to high-shear and high-pressure homogenisation, as illustrated in Figure (10)[57].

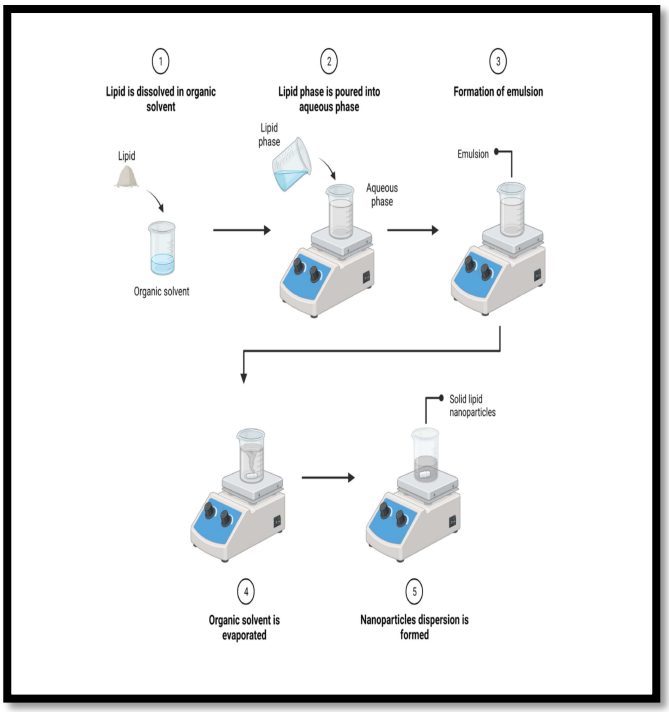


Figure 10:Schematic representation of the solvent emulsification method[44].

Solvent Emulsification Diffusion Method

This approach employed a solvent partially miscible with water, such as ethyl acetate, as shown in Fig. 11. The initial step in the preparation entails saturating the two phases to attain thermodynamic equilibrium. The medication and lipid will dissolve in the solvent phase saturated with water, and the resultant solution will disperse in the water phase saturated with solvent, which also contains the emulsifier, forming an oil-in-water emulsion. Subsequently, a dilution procedure will incorporate distilled water into the emulsion, helping the solvent diffusion into the aqueous phase. The solvent may be eliminated using freeze-drying or vacuum distillation [58].

Advantages: Minimise heat exposure throughout the manufacturing process; lipids are solubilised in partly miscible solvents such as benzyl alcohol and tetrahydrofuran.

Disadvantages: low dispersion degree, emulsion instability, lipid insolubility in organic solvents, and additional requirement for solvent removal, Toxicological issue (residual solvent), as illustrated in Figure (11)[47].

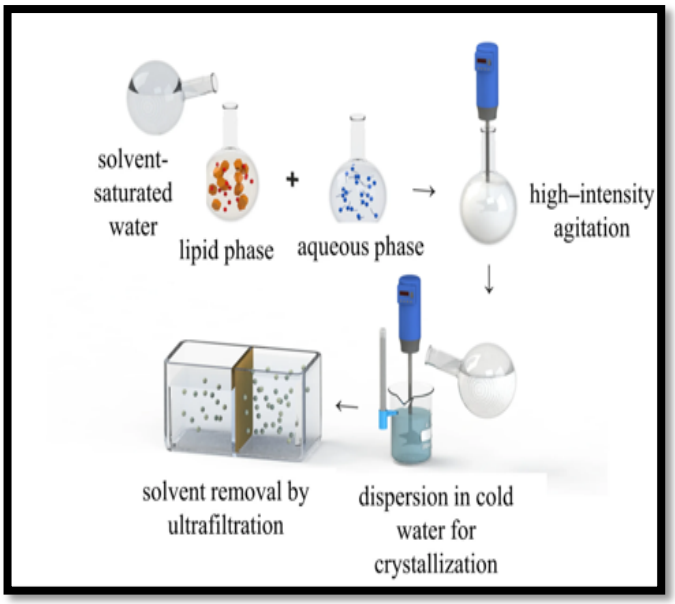


Figure 11: Solvent diffusion methods to produce lipid nanoparticles[47].

Solvent Injection Technique

This method resembles the emulsification-solvent diffusion technique; however, the organic solvents employed are selected from the group that is strongly water-miscible (e.g., DMSO, ethanol), thereby preventing emulsion formation. Primarily, the lipids and the medication are dissolved in an organic solvent and subsequently injected into an aqueous surfactant solution while stirring, resulting in rapid diffusion of the organic solvent into the water and precipitation of the lipids. The particle size formed is highly dependent on the extraction velocity and, correspondingly, on the solvent's lipophilicity. A more hydrophilic solvent yields smaller particles but has a reduced capacity for lipid solubilisation as illustrated in Figure (12)[50].

Advantages: Simple control and expedited manufacturing procedure. Lipids are soluble in water-miscible solvents. For instance, ethanol, methanol, and acetone can be utilised without the need for an advanced instrument, such as a high-pressure homogeniser.

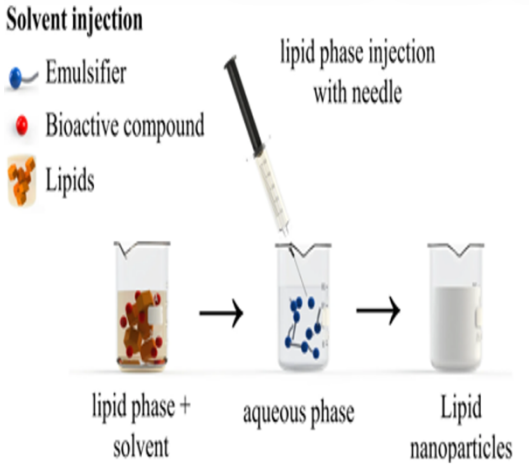


Figure 12: solvent injection method to produce lipid nanoparticles [47].

Characterization methods of SLN

Various methodologies for characterizing solid lipid nanoparticles (SLNs) are presented in tabular form (Table 1).

Stability of Solid Lipid Nanoparticles: Storage and Gastrointestinal Considerations

The stability of SLN is one important factor affecting their performance during storage and following oral administration. SLNs can undergo polymorphic transitions over time because they are made of solid lipids that can exist in metastable supercooled states. Drug expulsion and changes in drug release behavior may result from these transitions from less ordered to more stable crystalline forms [19, 39]. SLN stability is greatly impacted by storage conditions like temperature, light exposure, and mechanical stress (such as shear forces). While low stabilizer concentration can lead to particle aggregation or the formation of gel-like systems, which ultimately shortens shelf life, elevated temperatures speed up the processes of lipid recrystallization and gelation [24, 44]. After being taken orally, SLNs are subjected to a variety of complex gastrointestinal (GIT) conditions, such as bile salts, acidic pH, and digestive enzymes like lipases and colipases. Drug release profiles and nanoparticle integrity may be impacted by these physiological factors that partially degrade the lipid matrix. Lipid digestion may improve drug solubilization, according to studies, but depending on the composition of the formulation [66, 67]. Zeta potential is another important factor influencing the colloidal stability of SLNs. Particles with high absolute zeta potential values (typically ±30 mV or higher) show sufficient electrostatic repulsion to remain well-dispersed, whereas lower values increase the risk of particle aggregation and reduced stability [68]. Various formulation approaches have been explored to enhance the stability of SLNs. These include the use of lipid blends to reduce drug expulsion and limit crystallinity, careful selection of appropriate lipid matrices, and optimization of surfactant concentration. In addition, surface modification strategies can further improve nanoparticle performance and enhance their stability within the gastrointestinal environment [69, 70].

Application of SLN for improving oral bioavailability

A comparison of the summarized studies reveals several significant formulation patterns of SLNs for oral drug delivery. Most formulations had particle sizes ranging from 30 to 400 nm. The reduction in particle size leads to Increased surface area, and intestinal permeability usually goes along with improved absorption. With respect to the Zeta potential, the colloidal system demonstrated better physical stability, with values (>|30| mV). The results varied widely from −34.8 mV to +33.2 mV, indicating differences in colloidal stability depending on formulation composition. The better physical stability, as observed in rifampicin and griseofulvin SLNs.

Encapsulation efficiency (EE%) was generally high (>90%) across most lipid systems, particularly those based on across most lipid systems, particularly those based on glyceryl behenate and glyceryl monostearate, highlighting their suitability for incorporating lipophilic drugs. However, lower EE values (e.g., domperidone ~66.3%) indicate that efficiency can vary depending on the formulation, especially due to differences in drug–lipid compatibility. In terms of bioavailability, all studies found significant improvements, with some formulations increasing up to 12-fold (curcumin). This demonstrates the effectiveness of SLNs in improving the oral absorption of poorly soluble drugs. The analysis of the included studies indicates that glyceryl monostearate (GMS) and glyceryl behenate are among the most effective lipid matrices, consistently achieving high encapsulation efficiency (EE%), particularly for lipophilic drugs. This finding is consistent with the properties of Biopharmaceutics Classification System (BCS) Class II and Class IV drugs, where poor aqueous solubility is a major barrier to effective oral absorption. In this context, surfactants such as Tween 80 and Poloxamer 188 play a key role not only in stabilizing SLN dispersions but also in improving drug solubilization and enhancing intestinal permeability, thereby helping to overcome major limitations associated with BCS Class II and IV compounds. Among the reviewed formulations, curcumin-loaded SLNs showed the greatest improvement in bioavailability (approximately 12-fold). This finding is in line with its classification as a BCS Class IV compound and further highlights the ability of SLNs to enhance both solubility and permeability simultaneously. Some applications of SLNs were illustrated in Table 2.

Table (1): Different Techniques, Instruments, and Procedures Used for The Characterization of SLNs.

Characterization Parameter	Analytical Technique / Instrument	Purpose / Significance
Particle size & PDI	Dynamic Light Scattering (DLS)	Determines size distribution, influencing stability, absorption, and bioavailability
Zeta potential	Electrophoretic Light Scattering (ELS)[59]	Indicates surface charge and predicts colloidal stability (±30 mV suggests stable systems)
Morphology & surface characteristics	TEM, SEM, AFM, Freeze-fracture microscopy (58,59)	Provides information on particle shape and surface structure
Encapsulation efficiency (EE%)	Ultrafiltration/centrifugation [60]	Evaluates drug loading capacity and formulation efficiency
Surface pH	pH-sensitive probes [61]	Assesses compatibility with biological environments
Thermal behavior	Differential Scanning Calorimetry (DSC) [62]	Evaluates lipid crystallinity and drug–lipid interactions
Crystallinity & polymorphism	Powder X-ray Diffraction (PXRD) [63]	Determines crystalline structure and polymorphic transitions
Drug–excipient interaction	Fourier Transform Infrared Spectroscopy (FTIR) [64]	Identifies chemical interactions and confirms drug integrity
In vitro drug release	Dialysis membrane method [65]	Evaluates drug release profile and controlled release behavior

Table (2): Application of SLNs.

Drug	Lipid	Surfactant	Method	Size (nm)	ZP (mv)	EE (%)	Bioavailability (AUC fold)	Study Type	Ref
Praziquantel	Labrafil: Plurol Oleique	Labrasol	High shear homogenizatio n	87.32–302.3 nm	−14.5−38.3-	100.23—5.46	Significant enhancement of Bioavailability and efficacy	In vivo	(71)
Simvastatin	Glyceryl behenate and glyceryl palmitostearate	Tween 80	Hot melt emulsification	Below 200	_	Above 96%	Increase efficacy	In vivo	(72)
Curcumin	GMS	TPGS and Brij78	Emulsification	~135.3	−24.7	~91.09%	↑12.27-folds	In vivo	(73)
Domperidone	Dynasan 118	Tween 80 Sodium deoxycholate	Hot homogenizatio n Followed by the ultrasonication method	201.4 nm	− 6.2 mv	66.3%	Significant enhancement in the oral absorption of DOP from optimized SLN	In vivo	(74)
Carvedilol	Precirol	Gelucire	Homogenizati on-ultrasonication technique	31.3 nm	24.25 mv	91.43%	↑2 fold	In vivo	(75)
Tamoxifen	Glycerol behenate	Sodium Tauro glycocholate	Emulsification and high pressure homogenizatio n	~235	-	98.64%	↑ 3.5-fold	In vivo	(76)

Clozapine	Triglycerides (trimyristin, tripalmitin, and tristearin)	Soy lecithin 95%, poloxamer 188, and stearyl amine	Hot homogenization followed by the ultrasonication method	96.7 ± 3.8 to 163.3 ± 0.7 nm	21.3 ± 1.3 to 33.2 ± 0.6 mv	-	↑3.1- to 4.5-fol	In vivo	(77)
Olanzapine	Stearic acid and Glyceryl monostearate	Soy lecithin, poloxamer 188 and charge modifier stearyl amine	Microemulsion	354.7-404.6 nm	2.1 to 33.2	~63.4	↑4-fold	In vivo	(78)
Rifampicin	Stearic acid	Tween 80	A one-pot microwave microemulsion method	150 to 200 nm	-30	≈55%	↑2–4 fold	In vivo	(79)
Griseofulvin	Stearic acid	Chitosan	Two-step hot melt sonication process	56.87 nm	-34.8 mv	_	↑2.0 fold	In vivo	(80)

CONCLUSION

Solid lipid nanoparticles (SLNs) have gained attention as a promising lipid-based nanocarrier system for overcoming key challenges in oral drug delivery, particularly for drugs with poor solubility and limited permeability. This review has outlined the main barriers to oral absorption, including physicochemical constraints and biological factors, and has highlighted how SLNs can help address these limitations effectively. It has been demonstrated that the formulation of SLNs, including lipid composition and surfactant selection, is critical to the performance of nanoparticles. Furthermore, it was discovered that preparation methods and physicochemical characterization parameters such as particle size, zeta potential, and encapsulation efficiency had a significant impact on stability, drug release behavior, and overall bioavailability. Multiple studies summarized in the applications section show that SLNs can significantly improve oral bioavailability, with several formulations achieving notable improvements in drug absorption via enhanced solubilization, protection from gastrointestinal degradation, and potential lymphatic transport. Several studies summarized in the applications section indicate that SLNs can markedly enhance oral bioavailability. Many formulations have shown notable improvements in drug absorption, mainly through enhanced solubilization, protection against gastrointestinal degradation, and the potential for lymphatic transport. To successfully translate SLNs into clinically viable oral drug delivery systems, future research should focus on large-scale manufacturing, long-term stability assessment, and regulatory considerations.

CONFLICT OF INTEREST

The author(s) declare no conflict of interest, financial or otherwise.

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