A SYSTEMATIC REVIEW ON NANO DRUG DELIVERY SYSTEM: SOLID LIPID NANOPARTICLES (SLN)

SWAPNIL D. PHALAK[1*], VISHAL BODKE[2] , REENU YADAV[3], SATISH PANDAV[4], MALOJI RANAWARE[5]

[1]Department of Pharmaceutics, IES Institute of Pharmacy, IES University, Bhopal, Madhya Pradesh, India. [2]Department of Pharmaceutics, Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Maharashtra, India. [3]IES Institute of Pharmacy, IES University, Bhopal, Madhya Pradesh, India. [4,5]Department of Pharmacology, Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Maharashtra, India
*Corresponding author: Swapnil D. Phalak; *Email: sdphalak@gmail.com

ABSTRACT

Nanomedicine along with nano-delivery systems, are a young but fast-emerging science in which tiny materials are used as diagnostic tools or to deliver therapeutic drugs to specific targeted locations in a controlled manner. Nanotechnology has numerous advantages in the treatment of chronic human diseases through the site-specific and target-oriented delivery of precise medications. There have recently been several notable applications of nanomedicine (chemotherapeutic agents, biological agents, immunotherapeutic agents, and so on) in the treatment of various disorders. Efficient use of pricey medications and excipients, as well as cost savings in manufacturing Beneficial to patients, improved therapy, comfort, and the standard of living. Lipids have been proposed as an alternate carrier to circumvent the constraints of polymeric nanoparticles, notably for lipophilic medicines. Such small particles of lipid are known as solid lipid nanoparticles (SLNs), and they are gaining popularity among formulators all over the world. SLNs are colloidal carriers that were developed in the last decade as a replacement for traditional carriers. Lipid nanoparticles have caught the interest of researchers during the last two decades and have shown considerable therapeutic success since the first clinical approval of Doxil in 1995. Simultaneously, lipid nanoparticles have shown significant promise in conveying nucleic acid medications, as proven by the approval of two RNA treatments and an mRNA COVID-19 vaccination.

Keywords: Nanoparticles, Sold lipid nanoparticle, Liposomes, Carriers etc

INTRODUCTION

In nanotechnologies in medicine and nano delivery systems, particles in the nanoscale range are employed as diagnostic tools or to deliver therapeutic substances to specific targeted places in a regulated manner. Nanotechnology offers various benefits in the treatment of long-term human diseases by delivering precise drugs to specific places and objectives. Nanomedicine (including chemotherapeutic medications, biological agents, immunotherapeutic agents, and so on) has recently seen several notable uses in the treatment of various diseases [1]. The current study, through an in-depth examination of the discovery and use of nanomaterials in improving the efficacy of both new and old pharmaceuticals, provides an updated account of recent developments in the field of nanomedicines and nano-based drug delivery systems [2]. The use of nanoparticles (NPs) to deliver medications to cells is causing a surge in interest in improving human health. Such NPs are designed to be drawn directly to damaged cells, allowing for direct therapy of those cells while boosting efficacy, reducing side effects, and thereby enhancing human health. This approach lowers pharmacological adverse effects on the body. Despite the potential of nanomedicine for all diseases, there are still some drawbacks to adopting these nano-drug delivery vehicles that should not be overlooked. those administered using nanoscale entities may act differently than those delivered via conventional means [3, 4].

NDDSs are materials that have at least a single dimension at the nanoscale scale (1-100 nm) or are made of basic units in space with three dimensions. NDDSs have been a research hotspot in the fields of pharmacy and advanced biomedicine due to their effectiveness in optimizing drug delivery. For more than 40 y, researchers have been studying NDDSs, yielding a plethora of nano-drug carriers. The nanomaterials utilized in NDDSs are classified as organic, inorganic, or composite materials based on their composition. The following is a description of some common NDDSs and their distinctive features. Novel medication delivery and drug targeting are novel strategies in pharmaceutical science. Targeted drug delivery, vaccine delivery, gene therapy, and commercial development of novel carriers (liposomes) are all examples of novel drug delivery systems [5]. Efficient utilization of pricey medications, excipients, and production cost reduction Patients benefit from enhanced therapy, comfort, and quality of life [7-9].

Drug design at the nanoscale has received extensive research and is by far the most advanced technology in the field of nanoparticle applications due to potential benefits such as the ability to modify properties such as solubility, drug release characteristics, diffusivity, bioavailability, and immunogenicity. This may result in the creation of more accessible dosing routes, lower toxicity, fewer adverse effects, enhanced biodistribution, and a longer medication life cycle [10, 11]. The tailored drug delivery systems are either directed at a specific place or are designed for a controlled dispensing of therapeutic substances at that location. Their development involves self-assembly, in which well-defined shapes or patterns emerge spontaneously from building blocks [12].

Nanoparticles are colloidal particles with sizes ranging from 10 to 1000 nm. They are made of synthetic/natural polymers and are ideal for optimizing drug distribution and lowering toxicity. They have developed as an alternative substitute for liposomes as drug carriers over the years. The capacity of nanoparticles to overcome many anatomical barriers, the prolonged release of their contents, and their stability in the nanometer size all contribute to the successful deployment of nanoparticles for drug delivery. However, the shortage of safe polymers with regulatory approval, as well as their high cost, have hindered the widespread use of nanoparticles in clinical treatment [13, 14].

Liposomes

Liposomes are small vesicles made of a phospholipid bilayer that can encapsulate an active medication. The medication's properties and the encapsulation procedure determine whether the drug is encapsulated in the core or the bilayer of the liposome. Water-soluble medications are typically enclosed inside the center of the aqueous core, whereas lipid-soluble pharmaceuticals are directly integrated into the lipid membrane [15]. Liposomes are spherical

particles that include hydrophilic and lipophilic compounds. They can have a single, numerous, or multiple concentric membranes [8, 16]. Liposomes can change the drug's tissue distribution and rate of clearance by causing the drug to adopt the pharmacokinetic features of the carrier [17, 18].

Dendrimers

Dendrimers' great level of control over their architecture, size, shape, branching length and density, and surface functioning make them appropriate carriers for drug delivery purposes. The bioactive agents can be encapsulated within the dendrimers or chemically bonded or physically adsorbed onto the dendrimer's surface, with the option of tailoring the carrier properties to the specific needs of the active material and its uses in therapy. A dendrimer particle is a molecule made of polymers composed of several precisely branching monomers that radiate radially from a central core, giving rise to the name. When a dendrimer's core disappears, plenty of identical fragments known as dendrons remain [19].

Nanoparticles

Nanoparticles (NPs) and nanostructured materials (NSMs) are an active area of research as well as a techno-economic industry in multiple application domains. Because of their tenable physicochemical properties such as their melting point, wettability, electrical and thermal conductivity, as well as catalytic activity, light absorption, and scattering, NPs and NSMs have gained prominence in technological advancements, resulting in improved performance over their bulk counterparts [20-22]. A nanometres (nm) is a unit of length in the International System of Units (Système international d'unites, SI). In theory, NMs are materials with lengths ranging from 1 to 1000 nm in at least one dimension; nevertheless, they are most often defined as having diameters ranging from 1 to 100 nm [23-25].

Solid lipid nanoparticle (SLN)

Solid lipid nanoparticles (SLN) were invented in the early 1990s as an alternate colloidal carrier system to emulsions, liposomes, and polymeric nanoparticles for controlled drug delivery. SLN is composed of a matrix of solid lipids that are sustained in an aqueous dispersion by surfactants or polymers, and the dispersion can be spray-dried or lyophilized to form a dry product [26, 27]. Solid lipid nanoparticles can combine particle shape and physical integrity with both physical and chemical stabilization of delicate components. SLN are nanostructures composed of solid lipids such as glyceryl behenate (Compritol), stearic triglyceride (tristearin), cetyl palmitate, and glycerol tripalmitate (tripalmitin) with sizes ranging between 50 and 1,000 nm [28-30].

Lipids have been proposed as an alternate carrier to circumvent the constraints of polymeric nanoparticles, notably for lipophilic medicines. Such small particles of lipid are known as solid lipid nanoparticles (SLNs), and they are gaining popularity among formulators all over the world. SLNs are colloidal carriers that were developed in the last decade as a replacement for traditional carriers (emulsions, liposomes, and polymeric nanoparticles) [31-33].

In fig. 3 gives the Pictorial presentation of the structure of solid lipid nanoparticles they are a new submicron-sized lipid emulsion in which the liquid component of lipid (oil) has been replaced with a solid lipid. SLN has unique qualities such as tiny size, large surface area, high drug loading, and phase interaction at interfaces, and are appealing due to their potential to improve the performance of medicines, "Nutraceuticals" and other materials [34, 35].

Drug release through SLN

The partition coefficient of the medication has an inverse connection with its release. Higher drug release is achieved by increased surface area due to reduced particle size in the nanometer range [36]. When the drug is homogeneously disseminated in the lipid matrix, controlled drug release can be achieved. It is determined by the type and drug entrapment model of SLNs. The lipid's crystalline nature and the drug's high mobility result in rapid drug release. The degree of crystallization and drug mobility has an inverse relationship**.** Fig. 1 gives pictures Structure of different types of Nanocarriers.
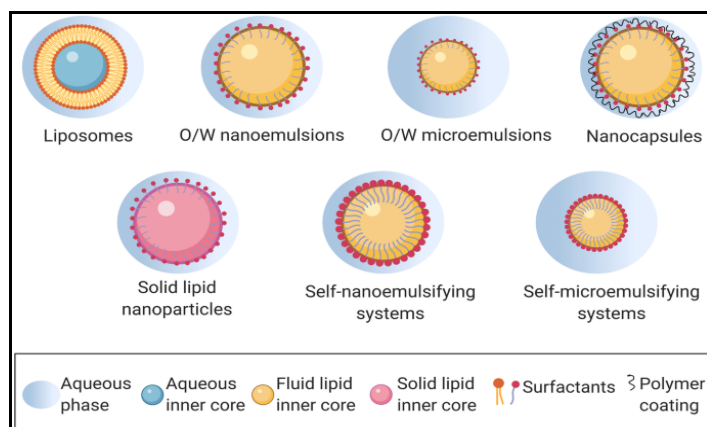

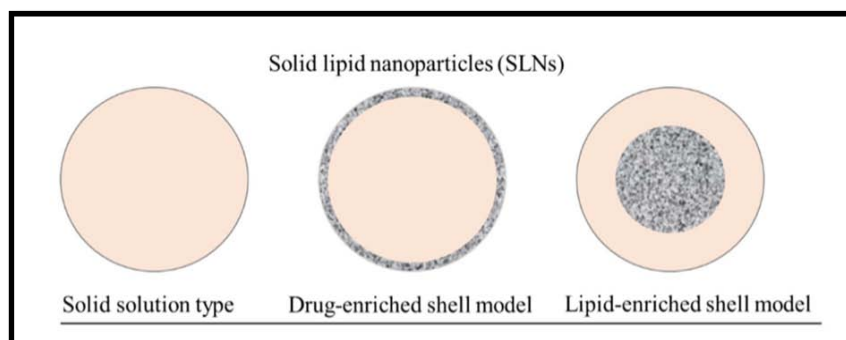**Fig. 1: Structure of various types of nanocarriers [36, 37]**
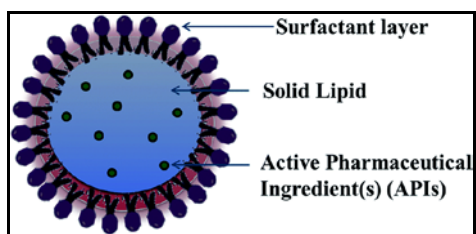

Fig. 2: Models of solid lipid nanoparticles [39-41]

Fig. 3: **Structure solid lipid nanoparticles [42, 43]**

Advantages of SLN

Due to their nano-size range, reticuloendothelial system (RES) cells are unable to take up SLNs, allowing them to avoid spleen and liver filtration [8, 9]. Provide integrated medications with great stability. The ability to include both hydrophilic and lipophilic medicines [47]. Increase the bioavailability of weakly water-soluble compounds. Facilitate sterilization and scale-up. Immobilizing drug molecules into solid lipids protects sensitive pharmaceuticals from photochemical, oxidative, and chemical degradation, with reduced drug leakage. Lyophilization drying is possible. Allow for targeted and regulated

drug release. Compositional components that are biocompatible and biodegradable [4]. No special solvent is required and Easy for Preparations. Application versatility [54].

Disadvantages of SLN

SLNs are densely packed lipid matrix networks (perfect crystalline structure) with little room for drug encapsulation, resulting in low drug loading capacity [10-13]. A variety of factors influence drug loading or encapsulation in SLNs, including drug-lipid melt interaction, the composition or state of the lipid matrix, drug miscibility with the lipid matrix, and the drug being distributed or dissolved in the lipid matrix. Drug release after polymeric transformation during storage [14, 15] The dispersion particles have a high water content (70-90%) [16].

Applications of solid lipid nanoparticles [1, 52-58, 60]

There are various Applications of Solid Lipid Nanoparticles widely used SLN as Listed below

Composition of solid lipid nanoparticle

Solid lipid nanoparticle contains various compositions. Given below table lists the most used compositions in solid lipid nanoparticles.

Fig. 4: Applications of solid lipid nanoparticle [52-58]

Table 1: General compositions of nanoparticles

S. No.	Ingredients	Examples
1	Lipid compound	Beeswax, Stearic acid, Cholesterol, Caprylic/capric triglyceride, Cetyl palmitate, Glyceryl stearate (-mono, and-tri), Glyceryl tri laurate, Glyceryl tri myristate, Glyceryl behenate (Compritol), Glyceryl tripalmitate, Hardened fat (Witepsol E85, H5 and W35), Monostearate mononitrate, Solid paraffin, Behenic acid [98]
2	Emulsifier	Phosphatidylcholine, Soy and Egg lecithin, Poloxamer, Poloxamine, Polysorbate 80
3	Surfactant	Sodium dodecyl sulfate, Tyloxopol, Sodium oleate, Taurocholate sodium salt, Sodium glycocholate, Butanol
4	cryoprotectant	Gelatin, Glucose, Mannose, Maltose, Lactose, Sorbitol, Mannitol, Glycine, Polyvinyl alcohol, Polyvinyl pyrrolidone [99].
5	Charge modifiers	Dipalmitoyl phosphatidylcholine, stearyl amine, Dicetylphosphate, Dimyristoyl phosphatidyl glycerol
6	Preservative	Thiomersal

Methods of preparations [1, 3, 22]

1. High-pressure homogenization technique

2. Hot homogenization technique

3. Cold homogenization technique

4. Emulsification solvent evaporation technique

5. Solvent emulsification-diffusion technique [84]

6. Supercritical fluid technique

7. Microemulsion-based technique Ultrasonication/high Precipitation technique

8. speed homogenization technique

9. Film-ultrasound dispersion technique

10. Double emulsion technique

11. Solvent Injection Technique

12. Membrane Contractor technique

13. Spray Drying Method

High shear homogenization

The high shear homogenization technique was originally used to prepare solid lipids, which was originally used to prepare solid lipid Nano dispersions [47, 48]. Both methods are common and easy to handle. However, the presence of microparticles often reduces the quality of the dispersion. A rapid homogenization method is used to produce SLN by melt emulsification [49]. Olbrich *et al.* investigated the effects of various process parameters, including emulsification time, stirring speed, and cooling conditions, on particle size and zeta potential. A higher mixing speed did not significantly change the particle size but slightly improved the polydispersity index.

Hot homogenization

Hot homogenization is performed at temperatures above the melting point of lipids and is similar to emulsion homogenization. Pre-emulsion of the drug-loaded lipid melt and the aqueous phase of the emulsifier (same temperature) is obtained with a high-shear mixer (for example, a silver-type homogenizer). The quality of the pre-emulsion greatly affects the quality of the final product, and it is desirable to obtain droplets of a few micrometers in size. High-pressure homogenization of the pre-emulsion is carried out above the melting temperature of the lipids. Smaller particle sizes are usually obtained at higher processing temperatures due to the reduced viscosity of the lipid phase [50], although this can also accelerate drug and carrier degradation. Better products are obtained after several passes through the High-Pressure Homogenizer (HPH), usually after 3-5 runs. High-pressure treatment always increases the temperature of the sample (about 10 ° at a pressure of 500 bars) [51]. In most cases, 3-5 homogenous cycles at 500-1500 bar are sufficient. Increasing homogenization leads to an increase in particle size due to particle coalescence due to the high kinetic energy of the particles.

Cold homogenization

The cold homogenization process is carried out on a solid lipid and is, therefore, similar to high-pressure suspension milling. Effective temperature control is necessary to ensure the solid state of lipids during homogenization [52-55]. Cold homogenization was developed to solve the following problems of the heat homogenization technique, such as temperature-mediated accelerated degradation of the drug load, distribution and thus drug loss during aqueous phase homogenization, and unstable lipid polymorphic transitions. the complexity of the drug. nanoemulsion crystallization step leading to multiple modifications and/or supercooled melts. The first preparation step is the same as in the hot homogenization procedure and involves dissolving or dispersing the drug in the lipid melt. However, the next steps are different. The drug-containing melt is rapidly cooled (using dry ice or liquid nitrogen) to promote homogeneous distribution of the drug in the lipid matrix. The solid lipid drug is ground into microparticles by ball/mortar milling. Typical particle sizes achieved are in the range of 50-100 microns. The cold treatment further facilitated particle milling by increasing lipid fragility. SLNs are dispersed in a chilled emulsification solution. The dispersion is homogenized at high pressure at room temperature or at a lower temperature with appropriate temperature control taking into account the normal temperature rise in high pressure processing. However, compared to hot homogenization, cold homogenized samples are characterized by larger particle sizes and a wider size distribution [56, 57]. The

cold homogenization method minimizes heat deposition of the sample, but it does not avoid it due to the melting of the lipid/drug mixture at an early stage.

Solution emulsification-evaporation method

The solvent emulsification-evaporation method involves two steps: (i) preparation of oil/water nanoemulsions and (ii) solvent evaporation. In this method, the lipids and medicine are dissolved in a solvent or a mixture of solvents to form an oil phase, which is then emulsified into an aqueous phase. Solvents are water-immiscible organic solvents such as dichloromethane, chloroform, cyclohexane, and toluene [58, 59]. After oil-in-water-in-water Nanoemulsions are formed, the organic solvent is evaporated. Evaporation of the solvent is usually done using a rotary evaporator or mechanical stirring. As the solvent evaporates, the lipid concentration in the droplets gradually increases, leading to lipid precipitation and the formation of SLNs [60]. This method involves the use of toxic organic solvents; therefore, additional steps are necessary to remove the solvents and evaluate the toxicity of the formulations *in vitro* and *in vivo*. The resulting SLNs usually have a high water content and should be concentrated by ultrafiltration or evaporation. On the other hand, the solvent emulsification-vapor method is well suited for heat-sensitive medicines because it does not require high temperatures and physical stress, such as high-pressure homogenization and rapid mixing. The prepared SLNs generally have a narrow size distribution, with an average particle size of about 100 nm [61].

Solution emulsification-diffusion method

The solvent emulsification-dispersion method is mainly used to prepare polymeric nanocarriers. In 2003, Trotta *et al.* first used this technique to fabricate SLNs and NLCs. Partially water-miscible organic solvents such as methyl acetate, ethyl acetate, isopropyl acetate, benzyl alcohol, and butyl lactate are commonly used to carry out this method. Initially, the organic solvent and water are saturated with each other to achieve an initial thermodynamic equilibrium of both phases. Lipids and drugs are dissolved in a water-saturated solvent, which is then emulsified into an aqueous phase (solvent-saturated water containing a stabilizer) by stirring to form an o/w emulsion. The emulsion is diluted with water (1:5 to 1:10 by volume) to allow diffusion of the solvent into the continuous phase. SLNs and NLCs are formed spontaneously by lipid precipitation and then the solvent is removed by lyophilization or vacuum distillation [65, 66].

Spray drying method

This is an alternative method to lyophilization to convert SLN aqueous dispersion into a medicinal product. It is a cheaper method than freeze drying. This method causes particle aggregation due to high temperature, shear forces, and partial melting of particles. Freitas and Mullera recommend using a lipid with a melting point>700 for spray. The best results were obtained with SLN concentrations of 1% trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v). Double emulsion method: A new method based on solvent emulsification by evaporation was used to prepare hydrophilically charged SLN [67]. Here, the drug is encapsulated with a stabilizer to prevent the drug from partitioning into the external aqueous phase upon evaporation of the solvent in the external aqueous phase of the w/o/w double emulsion.

Solution injection method

The solvent injection method used to prepare SLNs and NLCs was first described by Schubert *et al.* in 2003 [68]. In this method, lipids and drugs are dissolved in a water-miscible solvent (e. g., methanol, ethanol, isopropanol, or acetone) or a water-miscible solvent mixture. The aqueous phase is usually prepared by adding an emulsifier or a mixture of emulsifiers to water or a buffer solution. The organic phase is then rapidly injected into the aqueous phase using continuous mechanical agitation using a needle. This approach and the solvent emulsification-diffusion methodology have similar fundamental ideas. A scheme of the formation of SLNs and NLCs using the solvent injection method is described in After injection, two main mechanisms occur simultaneously and help each other to form SLNs and NLCs. First, the solvent is used from the droplets to

the aqueous phase, which leads to a decrease in droplet size. As a result, the lipid content in the droplets increases, leading to the formation of local supersaturated regions stabilized by emulsifiers in the aqueous phase [69]. Second, emulsifiers reduce the surface tension between water and solvent, which causes the formation of small solvent-lipid droplets at the injection site. Due to interfacial pulsation and turbulence during solution diffusion, these droplets break up into smaller droplets with essentially the same lipid concentration [70]. The free energy released when the solvent is 9/35 redistributed to its equilibrium state provides the energy required for droplet distribution [71]. Therefore, in the solvent injection method, solvent diffusion leads to the formation of small droplets and precipitation of lipids. Emulsifiers play an important role in determining PS and size distribution.

Quick mixing and ultrasonication methods

Rapid mixing (high shear homogenization) is a simple and cost-effective method to prepare SLNs [72]. This method involves three steps: (i) preparation of aqueous and lipid phases, (ii) homogenization, and (iii) cooling. In the first step, the lipids and the drug are homogeneously dispersed at a high temperature (5-10 C higher than the melting point of solid lipids), while an aqueous phase containing surfactants is prepared at the same temperature. In the second step, the two phases are mixed and dispersed homogeneously with a high-shear mixer to form a hot oil/water emulsion. The third step is to cool this emulsion to form SLNs. This method is usually combined with sonication at the end of the second step to reduce the size of the emulsion. The advantages of rapid mixing and ultrasonic methods are the free operation of organic solvents and ease of use. However, these methods are associated with large amounts of surfactant [73], drug exposure at high temperatures, and metal contamination of ultrasound probes [74]. These methods have been successfully used to incorporate various drugs such as linagliptin, quercetin and resveratrol, amphotericin B, buspirone, clozapine, piribedil, primaquine, and astaxanthin into SLNs.

Evaluations of solid lipid nanoparticles

Particle size

The physical stability of SLNs is determined by particle size. The most potent approaches for determining particle size are photon correlation spectroscopy (PCS) and laser diffraction (LD). The fluctuation in the intensity of dispersed light is induced by particle movement. Photon correlation spectroscopy (PCS) detects particle sizes ranging from 3 nm to 3m, and laser diffraction detects particle sizes ranging from 100 nm to 180 m. Although PCS is an excellent technique for characterizing nanoparticles, it is also capable of detecting bigger microparticles. The LD approach is based on the diffraction angle's dependence on particle size. Smaller particles scatter more intensely at high angles than larger ones [75-77].

Zeta potential

A zeta potential analyzer or zeta meter can be used to measure zeta potential. For size characterization and zeta potential measurement, dispersions of SLN are diluted 50-fold with their original dispersion preparation media before measurement In the absence of any complicating elements, such as steric stabilizers or hydrophilic surface appendages, a higher zeta potential value may lead to particle diaggregation. Predictions concerning storage can be made using zeta potential measurements. Colloidal dispersion stability [78]. The zeta potential's significance value is connected to the stability of colloidal dispersions. In the dispersion phase, the ZP represents the degree of repulsion between nearby charged particles. Because the molecules and particles are tiny enough, a high zeta potential will provide stability, implying that the solution or dispersion will resist aggregation [79-81].

Surface morphology

Electron microscopy validated the morphological characterization of solid lipid nanoparticles. The surface morphology of solid lipid nanoparticles was studied using scanning electron microscopy. Scanning electron microscopy (SEM) provides 3D images of the particles and superficial morphology, and TEM (transmission

electron microscopy) provides information on the shape and size of nanoparticles as well as their interior structure [82-87].

Degree of crystallinity

Differential scanning calorimetry (DSC) can be used to evaluate the degree of crystalline structure of lipid particles. It is a thermo-analytical methodology that provides a quick and accurate method for evaluating the degree of crystal structure of lipids based on lipid enthalpy. Powder X-ray diffractometry (PXRD) is an additional non-destructive technology used to describe crystalline materials and examine the crystal structure of SLN [88-90].

Nuclear magnetic resonance (NMR)

NMR can be used to determine the size and qualitative nature of nanoparticles. ^1H NMR spectroscopy was used to examine the prepared Solid Lipid Nanoparticles SLN. The nanoconjugates were dissolved in D2O and measured at 300 MHz using a ^1H NMR Spectrometer model Avance-II (Bruker, Germany). Several shifts and peaks were noted, which were interpreted differently for different groups [91]. Carbonyl proton from an amide bond and nitrogen proton from an ester bond both appeared. Chemical shift selectivity augments sensitivities to molecular movement to offer information regarding the physicochemical condition of nanoparticle components [92].

Atomic force microscopy (AFM)

A probing tip with microscopic sharpness is photographed across a sample to generate a topological map based on forces between the tip and the surface. This method provides ultra-high resolution, which, combined with the capacity to map a sample based on features other than size, such as colloidal attraction or resisting deformation, makes AFM a valuable tool [93, 94].

Entrapment efficiency

The level of concentration of the drug alone in the dispersion medium is used to calculate the drug's entrapment efficiency. Centrisart was used for ultracentrifugation, which consists of a filter membrane (molecular weight cutoff 20,000 Da) at the bottom of the sample recovery chamber. The SLNs and encapsulated medication stay in the outer chamber while the aqueous phase enters the sample-collecting chamber. HPLC or a UV spectrophotometer is used to determine the amount of medication contained in the aqueous phase [95-99].

$$\% \text{ Entrapment efficiency} = \frac{[(\text{Initial drug weight of free drug})}{[\text{ Weight of initial drug}]} \times 100\%$$

In vitro drug release

Dialysis tubing

Dialysis tubing could be used to achieve *in vitro* medication release. The solid lipid dispersion of the nanoparticle is inserted in hermetically sealed dialysis tubing that has been pre-washed. The dialysis sac is then dialyzed at room temperature against a suitable dissolution medium; samples are collected from the dissolution media at appropriate intervals, centrifuged, and tested for the presence of drugs using a suitable analytical method [100, 101].

Reverse dialysis

Several tiny dialysis sacs containing 1 ml of dissolving medium are inserted in SLN dispersion in this procedure. After that, the SLNs are shifted into the medium [102, 103].

Stability testing

Plain SLN and linked SLN formulations held at 41 °C were more stable than those kept at room temperature, according to storage stability testing. The average particle size of nanoparticles has been demonstrated to increase throughout storage, which could be attributed to particle aggregation under varying storage circumstances [104]. This effect was minimal in formulations held at 41 °C, indicating that aggregation can be managed by temperature, with 41 °C being the best storage temperature. The various SLN

formulations were kept at 41 °C and at room temperature, and the amount of leftover drug content was estimated after 30, 60, and 90 d, assuming that the initial drug content was 100% [106-109].

Solid lipid nanoparticles delivery by various routes of administration

Solid lipid nanoparticles are given by various routes in which Parenteral administration is the most often suggested route of administration for lipid-based nanosystems, with oral administration coming in second. Although the trend described is at odds with how pharmaceutical products are currently distributed in the market, where oral drug administration is the most popular and preferred method, both administration routes aim to achieve systemic effects of the encapsulated drugs [110-113]. Contrarily, parenteral methods, including intramuscular and/or subcutaneous routes, allow the transport of medications straight to the systemic circulation with little to no limits and no need to overcome absorptive obstacles. In the therapeutic field of anticancer drugs, the IV route remains predominant despite its non-negligible negative aspects, including invasiveness, associated risks, inability to self-manage, and higher technological requirements to be manufactured with appropriate microbiological quality. Of the lipid nanosystems assayed by parenteral routes, 46 out of 81 correspond to anticancer drugs [114, 115].
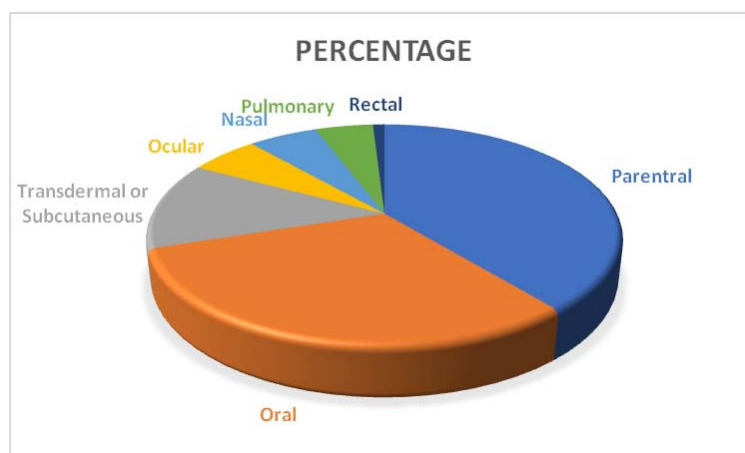

Fig. 5: Various routes that can be deliver solid lipid nanoparticles [100, 114, 115]

There are various tremendous works on solid lipid nanoparticles. This study listed some works done on solid lipid nanoparticles by researchers throughout the world. The listed works are shown in table 2 given below.

Table 2: SLN formulations research done by some listed researchers in the last 5-7 y

Therapeutic agent	Formulation types or components	Preparation methods	References
Tomatine (α-TM) and tomatidine (TD)	Lipid Nanoparticles Loading Steroidal Alkaloids	Solvent-diffusion technique	[104]
Phyllanthus emblica	Phyllanthi Tannin Loaded Solid Lipid Nanoparticles	Thin film hydration method and then homogenized by probe sonication	[105, 108]
Gefitinib	Gefitinib-Loaded Solid Lipid Nanoparticles for the Treatment of Breast Cancer for (MCF-7) Cells	Single emulsification–evaporation technique using glyceryl Tri stearate	[106]
Fluoxetine	Solid Lipid Nanoparticles Loaded Topical Gels: Repurpose of Fluoxetine in Diabetic Wound Healing	Emulsion solvent evaporation technique using stearic acid as a lipid,	[107]
Alprazolam	Compritol-Based Alprazolam Solid Lipid Nanoparticles for Sustained Release of Alprazolam	Hot melt encapsulation	[107]
Simvastatin	Hydrogel Containing Solid Lipid Nanoparticles Loaded with Argan Oil and Simvastatin	High-pressure homogenization (HPH)	[108]
Fluvastatin	Fluvastatin Loaded Solid Lipid Nanoparticles	Hot homogenization approach and an ultra-sonication method. In a combination of methanol and chloroform	[109]
Insulin	Solid Lipid and PLGA Nanoparticles Designed to Facilitate Nose-to-Brain Delivery of Insulin	Double-emulsion solvent-evaporation technique	[110]
Favipiravir	Characteristics and *In vitro* Toxicity/Anti-SARS-CoV-2 Activity of Favipiravir Solid Lipid Nanoparticles	Hot-evaporation method.	[111]
Clarithromycin	Clarithromycin Solid Lipid Nanoparticles for Topical Ocular Therapy	Ultra-sonication method	[117]
Fenofibrate and nabumetone SLN	Hypromellose, Polyethylene glycol, Polysorbate 80, SLS, Microcrystalline cellulose, Titanium dioxide.	Hotmelt homogenization.	[118]
SLNs loaded with Simvastatin (SIM-SLNs)	Solid lipids glyceryl behenate, Glyceryl palmitostearate containing Tween 80 as surfactant	Nanotemplate engineering	(Rizvi *et al.*, 2019)
Chitosan-Shea butter SLNs(C-SLNs)	Curcumin, Phospholipids/Tween 80 stabilized shea butter SLNs, Chitosan microparticles (CS-C-SLNs), Sodium tripolyphosphate (TPP)	Highshearhomogenization–ultrasonication	[119]
Piroxicam loaded SLNs	Piroxicam, Tripamitinlipid, Polyvinyl alcohol (PVAL) stabilizer, Ethylacetate solvent	Solvent emulsification/Evaporation method	[120]

Therapeutic agent	Formulation types or components	Preparation methods	References
Itraconazole (ITZ) (Intravenous formulation)	ITZ, Tristearin, Triolein, Egg PC, Tween 80, DSPE-PEG2000	HPH	[121]
Pterodon pubescents fruit oil NLCs	Precirol®ATO5,0.5%Phospholipon®80H, PEG-40hydrogenated castor oil/sorbitan oleate	Melt emulsification	(Outuki *et al.*, 2018)
Trehalose monooleate SLNs for Cyclosporin-Atopic release	Dichloromethane (DCM), chloroform, n-hexane, concentrated sulfuric acid, 1-butanol and methanol, trehalose, Oleic acid, Dicyclohexylcarbodiimide, DCC, DMAP, Dimethyl aminopyridine, Polyoxymethylene sorbitol monolaurate (Tween 20), Biliary acid, Coumarin-6, Cyclosporin-A, Methylparaben, Propylparaben	Microemulsion	[122]
Glutathione-loaded SLNs (GSH-SLNs)	Gelucire®50/13, L-Glutathione reduced (GSH), Tween85, aceticacid,2,2-diphenyl-1-picrylhydrazyl (DPPH), cetyl trimethylammonium bromide,3,3 ′,5,5′ tetramethylbenzidinehydrochloride (TMB) phorbol myristate acetate (PMA), fluorescein isothiocyanate (FITC) and luminol, Penicillin, and streptomycin, RPMI-1640 culture medium and fetal calf serum (FCS)	X-ray photoelectron spectroscopy analysis (XPS)	[123]
Clarithromycin	Liquid matrix, Glyceryl behenate, Tripalmitin, and stearic acid.	High-speed homogenization technique.	[124]
Sea buckthorn	Probiotic, Lactobacillus acidophitus, Bifidobacterium lactis, TTA.	Microwave extraction.	(Aynur *et al.*, 2016)
Clotrimazole loaded SLN and NLC	Cetostearyl alcohol, Cetyl esters wax, 2-octyl dodecanol, polysorbate 60, Sorbitan monostearate, Benzyl alcohol, purified water.	Hot high-pressure homogenization technique.	[124]
Doxorubicin	Adriomycin	Small angle neutron scattering (SANS), and small angle X-ray scattering (SAXS).	[125]
Lopinavir (Lo) SLN	Lopinavir and ritonavir	Hot homogenization, ultrasonication.	[126]
Fenofibrate And Nabumetone SLN	Hypromellose, Polyethylene glycol, Polysorbate80, SLS, Microcrystalline cellulose, Titanium dioxide.	Hotmelt homogenization.	[127]
Ascorbic acid	Vitamin C complex, Ascorbic acid, Volatile acid	Hot homogenization	[128]
Trans-Ferulic acid (TFA)	Ethyl oleate, Glyceryl behenate.	Microemulsion	[129]
Rivastigmine (RHT)SLN	Hydroxypropyl methylcellulose, Magnesium state, Microcrystalline cellulose, Silicon dioxide, Compritol 888ATO, Poloxamer188	Ultrasonication, Homogenization.	[130]
α Bisabolol SLN	Sterols, Triterpenes, Volatiles, Polar, and other constituents.	Hot homogenization	[131]

CONCLUSION

With their outstanding characteristics and benefits over other traditional forms of administration, SLNs have radically captured the attention of several researchers, and other colloidal equivalents of SLN have proven to be an important development in nanotechnology due to their efficacy and as a secured vehicle in pharmaceutical administration. Both hydrophilic and lipophilic medicines can be carried by lipid nanoparticles. They can be delivered by a variety of methods, including topical, oral, parenteral, ophthalmic, pulmonary, and brain drug administration. These nanoparticles offer advantages and disadvantages for each method of administration that should be evaluated. Using surface modification, the system demonstrates a robust and safe pharmaceutical platform for the future management of several awful disorders such as cancer, HIV, tuberculosis, Malaria, and others. SLN as a colloidal drug carrier, combines the benefits of polymeric nanoparticles and liposomes, such as better physical stability, the feasibility of incorporating lipophilic and hydrophilic medicines, economics, and ease of scale-up and production. SLNs can achieve site-specific and sustained drug release. SLNs are created using a variety of advanced approaches. SLNs have been widely used in drug discovery applications. Medication distribution, diagnostics, and many other applications in the medical field.

ABBREVIATIONS

Solid Lipid Nanoparticle (SLN), Intravenous Route (IV Route), Scanning Electron Microscopy (SEM).

FUNDING

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

REFERENCES

1. Nguyen TTL, Duong VA. Solid lipid nanoparticles. Encyclopedia. 2020;2(2):952-73. doi: 10.3390/encyclopedia2020063.
2. Madkhali OA. Perspectives and prospective on solid lipid nanoparticles as drug delivery systems. Molecules. 2022;27(5):1543. doi: 10.3390/molecules27051543, PMID 35268643.
3. Scioli Montoto S, Muraca G, Ruiz ME. Solid lipid nanoparticles for drug delivery: pharmacological and biopharmaceutical aspects. Front Mol Biosci. 2020;7(Oct):587997. doi: 10.3389/fmolb.2020.587997, PMID 33195435.
4. Basha SK, Dhandayuthabani R, Muzammil MS, Kumari VS. Solid lipid nanoparticles for oral drug delivery. Mater Today Proc. 2021;36:313-24. doi: 10.1016/j.matpr.2020.04.109.
5. Garud A, Singh D, Garud N. Solid lipid nanoparticles (SLN): method, characterization and applications. Int Curr Pharm J. 2012;1(11, Oct):384-93. doi: 10.3329/icpj.v1i11.12065.
6. Rastegari E, Hsiao YJ, Lai WY, Lai YH, Yang TC, Chen SJ. An update on mesoporous silica nanoparticle applications in nanomedicine. Pharmaceutics. 2021;13(7):1067. doi: 10.3390/pharmaceutics13071067, PMID 34371758.
7. Mishra V, Bansal KK, Verma A, Yadav N, Thakur S, Sudhakar K. Solid lipid nanoparticles: emerging colloidal Nano drug delivery systems. Pharmaceutics. 2018;10(4):191. doi: 10.3390/pharmaceutics10040191, PMID 30340327.
8. De Jong. "Drug delivery and nanoparticles: applications and hazards. Int J Nanomedicine. 2008 Jun;S596:133. doi: 10.2147/IJN.
9. Perez Herrero E, Fernandez Medarde A. Advanced targeted therapies in cancer: drug nanocarriers, the future of chemotherapy. Eur J Pharm Biopharm. 2015;93(Jun):52-79. doi: 10.1016/j.ejpb.2015.03.018, PMID 25813885.
10. Garg NK, Tandel N, Jadon RS, Tyagi RK, Katare OP. Lipid–polymer hybrid nanocarrier-mediated cancer therapeutics: current status and future directions. Drug Discov Today. 2018;23(9):1610-21. doi: 10.1016/j.drudis.2018.05.033, PMID 29857164.

11. Garud A, Singh D, Garud N. Solid lipid nanoparticles (SLN): method, characterization and applications. Int Curr Pharm J 2023;1(11):384-93. doi: 10.3329/icpj.v1i11.12065.

12. Raut ID, Doijad RC, Mohite SK. Solid lipid nanoparticles: a promising drug delivery system. Int J Pharm Sci Res. 2018;9(3):862-71. doi: 10.13040/IJPSR.0975-8232.9(3).862-71.

13. Deng Y, Zhang X, Shen H, He Q, Wu Z, Liao W. Application of the nano-drug delivery system in the treatment of cardiovascular diseases. Front Bioeng Biotechnol. 2019;7:489. doi: 10.3389/fbioe.2019.00489, PMID 32083068.

14. Naseri N, Valizadeh H, Zakeri Milani P. Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application. Adv Pharm Bull. 2015 Sep;5(3):305-13. doi: 10.15171/apb.2015.043, PMID 26504751.

15. Jeevanandam J, Barhoum A, Chan YS, Dufresne A, Danquah MK. Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein J Nanotechnol. 2018;9:1050-74. doi: 10.3762/bjnano.9.98, PMID 29719757.

16. Wesselinova D. Current major cancer targets for nanoparticle systems. Curr Cancer Drug Targets. 2011 Feb;11(2):164-83. doi: 10.2174/156800911794328484, PMID 21158716.

17. Kushwaha AK, Vuddanda PR, Karunanidhi P, Singh SK, Singh S. Development and evaluation of solid lipid nanoparticles of raloxifene hydrochloride for enhanced bioavailability. BioMed Res Int. 2013. doi: 10.1155/2013/584549, PMID 24228255.

18. Altammar KA. A review on nanoparticles: characteristics, synthesis, applications, and challenges. Front Microbiol. 2023;14:1155622. doi: 10.3389/fmicb.2023.1155622, PMID 37180257.

19. Jeevanandam J, Barhoum A, Chan YS, Dufresne A, Danquah MK. Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein J Nanotechnol. 2018 Apr 3;9:1050-74. doi: 10.3762/bjnano.9.98, PMID 29719757, PMCID PMC5905289.

20. Buzea C, Pacheco II, Robbie K, Robbie K. Nanomaterials and nanoparticles: sources and toxicity. Biointerphases. 2007 Dec;2(4):MR17-71. doi: 10.1116/1.2815690, PMID 20419892.

21. Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez Torres MDP, Acosta Torres LS. Nano-based drug delivery systems: recent developments and future prospects. J Nanobiotechnology. 2018;16(1):71. doi: 10.1186/s12951-018-0392-8, PMID 30231877.

22. Khater D, Nsairat H, Odeh F, Saleh M, Jaber A, Alshaer W. Design, preparation, and characterization of effective dermal and transdermal lipid nanoparticles: a review. Cosmetics. 2021;8(2). doi: 10.3390/cosmetics8020039.

23. Noble GT, Stefanick JF, Ashley JD, Kiziltepe T, Bilgicer B. Ligand-targeted liposome design: challenges and fundamental considerations. Trends Biotechnol. 2014;32(1):32-45. doi: 10.1016/j.tibtech.2013.09.007, PMID 24210498.

24. Akbarzadeh A, Rezaei Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y. Liposome: classification, preparation, and applications. Nanoscale Res Lett. 2013 Feb 22;8(1):102. doi: 10.1186/1556-276X-8-102, PMID 23432972, PMCID PMC3599573.

25. Liu P, Chen G, Zhang J. A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives. Molecules. 2022 Feb 17;27(4):1372. doi: 10.3390/molecules27041372, PMID 35209162, PMCID PMC8879473.

26. Genç L, Dikmen G, Guney Eskiler G. Formulation of nano drug delivery systems. J Mater Sci Eng A. 2011;1:132-7.

27. Blasi P, Giovagnoli S, Schoubben A, Ricci M, Rossi C. Solid lipid nanoparticles for targeted brain drug delivery. Adv Drug Deliv Rev. 2007 Jul 10;59(6):454-77. doi: 10.1016/j.addr.2007.04.011. PMID: 17570559.

28. De Jong WH, Borm PJ. Drug delivery and nanoparticles: applications and hazards. Int J Nanomedicine. 2008;3(2):133-49. doi: 10.2147/ijn.s596, PMID 18686775, PMCID PMC2527668.

29. Khan I, Saeed K, Khan I. Nanoparticles: properties, applications and toxicities. Arabian Journal of Chemistry. 2019;12(7):908-31. doi: 10.1016/j.arabjc.2017.05.011.

30. Mo K, Kim A, Choe S, Shin M, Yoon H. Overview of solid lipid nanoparticles in breast cancer therapy. Pharmaceutics. 2023;15(8):2065. doi: 10.3390/pharmaceutics15082065, PMID 37631279.

31. Geszke Moritz M, Moritz M. Solid lipid nanoparticles as attractive drug vehicles: composition, properties and therapeutic strategies. Mater Sci Eng C Mater Biol Appl. 2016 Nov 1;68:982-94. doi: 10.1016/j.msec.2016.05.119, PMID: 27524099.

32. Manjunath K, Reddy JS, Venkateswarlu V. Solid lipid nanoparticles as drug delivery systems. Methods Find Exp Clin Pharmacol. 2005 Mar;27(2):127-44. doi: 10.1358/mf.2005.27.2.876286, PMID: 15834465.

33. Mehnert W, Mader K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev. 2001 Apr 25;47(2-3):165-96. doi: 10.1016/s0169-409x(01)00105-3, PMID: 11311991.

34. Zur Muhlen A, Schwarz C, Mehnert W. Solid lipid nanoparticles (SLN) for controlled drug delivery–drug release and release mechanism. Eur J Pharm Biopharm. 1998;45(2):149-55. doi: 10.1016/s0939-6411(97)00150-1, PMID 9704911.

35. Sastri KT, Radha GV, Pidikiti S, Vajjhala P. Solid lipid nanoparticles: preparation techniques, their characterization, and an update on recent studies. J Appl Pharm Sci. 2020;10(6):126-41. doi: 10.7324/JAPS.2020.10617.

36. Xu L, Wang X, Liu Y, Yang G, Falconer RJ, Zhao C. Lipid nanoparticles for drug delivery. Advanced NanoBiomed Research. 2022;2(2):2100109. doi: 10.1002/anbr.202100109.

37. Plaza Oliver M, Santander Ortega MJ, Lozano MV. Current approaches in lipid-based nanocarriers for oral drug delivery. Drug Deliv Transl Res. 2021;11(2):471-97. doi: 10.1007/s13346-021-00908-7, PMID 33528830.

38. Viegas C, Patrício AB, Prata JM, Nadhman A, Chintamaneni PK, Fonte P. Solid lipid nanoparticles vs. nanostructured lipid carriers: a comparative review. Pharmaceutics. 2023;15(6):1593. doi: 10.3390/pharmaceutics15061593, PMID 37376042.

39. Montasser I, Shahgaldian P, Perret F, Coleman AW. Solid lipid nanoparticle-based calix[n]arenes and Calix-resorcin arenes as building blocks: synthesis, formulation and characterization. Int J Mol Sci. 2013 Nov 5;14(11):21899-942. doi: 10.3390/ijms141121899, PMID: 24196356.

40. Parhi R, Suresh P. Preparation and characterization of solid lipid nanoparticles-a review. Curr Drug Discov Technol. 2012 Mar;9(1):2-16. doi: 10.2174/157016312799304552, PMID: 22235925.

41. Marcato PD, Duran N. New aspects of nanopharmaceutical delivery systems. J Nanosci Nanotechnol. 2008 May;8(5):2216-29. doi: 10.1166/jnn.2008.274, PMID: 18572633.

42. Patil P, Harak K, Saudagar R. THE solid lipid nanoparticles a review. JDDT. 2019 May 15;9(3):525-30.

43. Duan Y, Dhar A, Patel C, Khimani M, Neogi S, Sharma P. A brief review on solid lipid nanoparticles: part and parcel of contemporary drug delivery systems. RSC Adv. 2020;10(45):26777-91. doi: 10.1039/D0RA03491F, PMID 35515778.

44. Radtke M, Muller RH. Comparison of structural properties of solid lipid nanoparticles (SLN) versus other lipid particles. Proceedings of the International Symposium Control Rel Bioact Mater. 2000;27:309-10.

45. Ekambaram P, Abdul HS. Formulation and evaluation of solid lipid nanoparticles of ramipril. J Young Pharm. 2011 Jul;3(3):216-20. doi: 10.4103/0975-1483.83765, PMID 21897661, PMCID PMC3159275.

46. Soma D, Attari Z, Reddy MS, Damodaram A, Koteshwara KBG. Solid lipid nanoparticles of irbesartan: preparation, characterization, optimization and pharmacokinetic studies. Braz J Pharm Sci. 2017;53(1):e15012. doi: 10.1590/s2175-97902017000115012.

47. Suresh G, Manjunath K, Venkateswarlu V, Satyanarayana V. Preparation, characterization, and *in vitro* and *in vivo* evaluation of lovastatin solid lipid nanoparticles. AAPS PharmSciTech. 2007 Mar 23;8(1):24. doi: 10.1208/pt0801024, PMID 17408223.

48. Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez Torres MDP, Acosta Torres LS. Nano based drug delivery systems: recent developments and future prospects. J

Nanobiotechnology. 2018;16(1):71. doi: 10.1186/s12951-018-0392-8, PMID 30231877.

49. Prabhakaran E, Hasan A, Karunanidhi P. Solid lipid nanoparticles: a review. Vol. 2; 2011.

50. Katare OP, Raza K, Singh B, Dogra S. Novel drug delivery systems in topical treatment of psoriasis: rigors and vigors. Indian J Dermatol Venereol Leprol. 2010 Nov-Dec;76(6):612-21. doi: 10.4103/0378-6323.72451, PMID: 21079304.

51. Sivadasan D, Ramakrishnan K, Mahendran J, Ranganathan H, Karuppaiah A, Rahman H. Solid lipid nanoparticles: applications and prospects in cancer treatment. Int J Mol Sci. 2023;24(7):6199. doi: 10.3390/ijms24076199, PMID 37047172.

52. Bayon Cordero L, Alkorta I, Arana L. Application of solid lipid nanoparticles to improve the efficiency of anticancer drugs. Nanomaterials (Basel). 2019 Mar 22;9(3):474. doi: 10.3390/nano9030474, PMID 30909401, PMCID PMC6474076.

53. Shah MK, Madan P, Lin S. Preparation, *in vitro* evaluation and statistical optimization of carvedilol-loaded solid lipid nanoparticles for lymphatic absorption via oral administration. Pharm Dev Technol. 2014;19(4):475-85. doi: 10.3109/10837450.2013.795169, PMID 23697916.

54. Kristl J, Teskac K, Grabnar PA. Current view on nanosized solid lipid carriers for drug delivery to the skin. J Biomed Nanotechnol. 2010 Oct;6(5):529-42. PMID: 21329046.

55. Krishnatreyya H, Dey S, Pal P, Das PJ, Sharma VK, Mazumder B. Piroxicam loaded solid lipid nanoparticles (SLNs): potential for topical delivery. Indian J Pharm Educ Res. 2019;53(2S):s82-92. doi: 10.5530/ijper.53.2s.52.

56. Mahajan A, Kaur S, Kaur S. Design, formulation, and characterization of stearic acid-based solid lipid nanoparticles of candesartan cilexetil to augment its oral bioavailability. Asian J Pharm Clin Res. 2018;11(4):344-50. doi: 10.22159/ajpcr.2018.v11i4.23849.

57. Wissing SA, Müller RH. Cosmetic applications for solid lipid nanoparticles (SLN). Int J Pharm. 2003;254(1):65-8. doi: 10.1016/s0378-5173(02)00684-1, PMID 12615411.

58. Abdelgawad NM, Hamza MY, Awad GAS. Topical and systemic dermal carriers for psoriasis. Int J Curr Pharm Res. 2016;8:4-9.

59. AKS, PA, PC. Formulation of solid lipid nanoparticles and their applications. JCPR. 2011;1(2):197-203. doi: 10.33786/JCPR.2011.v01i02.019.

60. Singh R. Preparation of solid lipid nanoparticles through various methods using different precursors. J Drug Delivery Ther. 2019;9(2):415-9. doi: 10.22270/jddt.v9i2.2461.

61. Ekambaram P, Abdul HS. Formulation and evaluation of solid lipid nanoparticles of ramipril. J Young Pharm. 2011 Jul;3(3):216-20. doi: 10.4103/0975-1483.83765, PMID 21897661, PMCID PMC3159275.

62. Sanzhakov MA, Ipatova OM, Torkhovskaia TI, Prozorovskii VN, Tikhonova EG, Druzhilovskaia OS, Medvedeva NV. Nanoparticles as drug delivery system for antituberculous drugs. Vestn Ross Akad Med Nauk. 2013;(8):37-44. PMID: 24340644.

63. Shinde AS, Lala RR. Mannose-anchored solid lipid nanoparticles loaded with atorvastatin calcium and vinpocetine as targeted therapy for breast cancer. Futur J Pharm Sci. 2023;9(1):81. doi: 10.1186/s43094-023-00531-y.

64. Abou Taleb HA, Fathalla Z, Naguib DM, Fatease AA, Abdelkader H. Chitosan/solid-lipid nanoparticles hybrid gels for vaginal delivery of estradiol for management of vaginal menopausal symptoms. Pharmaceuticals (Basel). 2023;16(9):1284. doi: 10.3390/ph16091284, PMID 37765092.

65. Jenning V, Mader K, Gohla SH. Solid lipid nanoparticles (SLN) based on binary mixtures of liquid and solid lipids: a ^{1}H-NMR study. Int J Pharm. 2000 Sep 15;205(1-2):15-21. doi: 10.1016/s0378-5173(00)00462-2, PMID 11000538.

66. Kushwaha AK, Vuddanda PR, Karunanidhi P, Singh SK, Singh S. Development and evaluation of solid lipid nanoparticles of raloxifene hydrochloride for enhanced bioavailability. BioMed Res Int. 2013. doi: 10.1155/2013/584549, PMID 24228255.

67. Parvez S, Yadagiri G, Gedda MR, Singh A, Singh OP, Verma A. Modified solid lipid nanoparticles encapsulated with amphotericin B and paromomycin: an effective oral combination against experimental murine visceral leishmaniasis. Sci Rep. 2020;10(1):12243. doi: 10.1038/s41598-020-69276-5, PMID 32699361.

68. Singh S, Dobhal AK, Jain A, Pandit JK, Chakraborty S. Formulation and evaluation of solid lipid nanoparticles of a water soluble drug: zidovudine. Chem Pharm Bull (Tokyo). 2010;58(5):650-5. doi: 10.1248/cpb.58.650, PMID 20460791.

69. Kumar R, Singh A, Garg N. Acoustic cavitation-assisted formulation of solid lipid nanoparticles using different stabilizers. ACS Omega. 2019;4(8):13360-70. doi: 10.1021/acsomega.9b01532, PMID 31460464.

70. Qushawy M, Nasr A. Solid lipid nanoparticles (slns) as nano drug delivery carriers: preparation, characterization and application. Int J App Pharm. 2020;12(1):1-9. doi: 10.22159/ijap.2020v12i1.35312.

71. Aljaeid BM, Hosny KM. Miconazole-loaded solid lipid nanoparticles: formulation and evaluation of a novel formula with high bioavailability and antifungal activity. Int J Nanomedicine. 2016;11:441-7. doi: 10.2147/IJN.S100625, PMID 26869787.

72. Rawat PK, Tyagi CK, Shah SK, Pandey AK. Formulation, characterization and *in vitro* evaluation of famciclovir loaded solid lipid nanoparticles for improved oral absorption. J Pharm Res Int. 2020;32(29):1-17. doi: 10.9734/jpri/2020/v32i2930879.

73. Bhalekar M, Upadhaya P, Madgulkar A. Formulation and characterization of solid lipid nanoparticles for an anti-retroviral drug Darunavir. Appl Nanosci. 2017;7(1-2):47-57. doi: 10.1007/s13204-017-0547-1.

74. Mishra SK, Bhardwaj P, Tripathi A, Gupta R, Dudhe R, Patil PR. Development and characterization of solid lipid nanoparticles of aceclofenac by microemulsion technique using lecithin, pleuronic F-68, and sodium glycocholate. Journal of Advanced Scientific Research. 2022;3Suppl 7:207-12.

75. Shah J, Patel S, Bhairy S, Hirlekar R. Formulation optimization, characterization and *in vitro* anti-cancer activity of curcumin loaded nanostructured lipid carriers. Int J Curr Pharm Sci. 2022;14:31-43. doi: 10.22159/ijcpr.2022v14i1.44110.

76. Shrivastava S, Kaur CD. Fabrication of mebendazole loaded solid lipid nanoparticles: formulation, optimization, characterization, stabilization, and *in vitro* evaluation. IJPSDR. 2022;14:262-8. doi: 10.25004/IJPSDR.2022.140217.

77. Yallavula J, Mandava K, Madhav V. Design and evaluation of topical gel containing solid-lipid nanoparticles loaded with luliconazole. Int J Pharm Res Technol (IJPRT). 2023;13(2):52-64. doi: 10.31838/ijprt/13.02.07.

78. Shinde AS, Lala RR. Mannose-anchored solid lipid nanoparticles loaded with atorvastatin calcium and vinpocetine as targeted therapy for breast cancer. Futur J Pharm Sci. 2023;9(1):81. doi: 10.1186/s43094-023-00531-y.

79. Chen YJ, Jin RX, Zhou YQ, Zeng J, Zhang H, Feng QR. Preparation of solid lipid nanoparticles loaded with Xionggui powder-supercritical carbon dioxide fluid extraction and their evaluation *in vitro* release. Zhongguo Zhong Yao Za Zhi. 2006;31(5):376-9. PMID 16711418.

80. Jenning V, Gysler A, Schafer Korting M, Gohla SH. Vitamin a loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. Eur J Pharm Biopharm. 2000;49(3):211-8. doi: 10.1016/s0939-6411(99)00075-2, PMID 10799811.

81. Pandey R, Sharma S, Khuller GK. Oral solid lipid nanoparticle-based antitubercular chemotherapy. Tuberculosis (Edinb). 2005;85(5-6):415-20. doi: 10.1016/j.tube.2005.08.009, PMID 16256437.

82. Carbone C, Cupri S, Leonardi A, Puglisi G, Pignatello R. Lipid-based nanocarriers for drug delivery and targeting: a patent survey of methods of production and characterization. Pharm Pat Anal. 2013 Sep;2(5):665-77. doi: 10.4155/ppa.13.43, PMID: 24237173.

83. Santos Magalhaes NS, Mosqueira VC. Nanotechnology applied to the treatment of malaria. Adv Drug Deliv Rev. 2010 Mar 18;62(4-5):560-75. doi: 10.1016/j.addr.2009.11.024, PMID: 19914313.

84. Singh S, Chaturvedi P, Jain SK. Development and performance evaluation of tumor targeting potential of folate spacer functionalized solid lipid nanoparticles. Asian J Pharm Clin Res. 2021;14(6):141-7. doi: 10.22159/ajpcr.2021.v14i6.40968.

85. Shenoy VS, Vijay IK, Murthy RS. Tumour targeting: biological factors and formulation advances in injectable lipid nanoparticles. J Pharm Pharmacol. 2005 Apr;57(4):411-22. doi: 10.1211/0022357055894, PMID: 15831200.

86. Bhosale RR, Janugade BU, Chavan DD, Thorat VM. Current perspectives on applications of nanoparticles for cancer management. Int J Pharm Pharm Sci. 2023;15(11):1-10. doi: 10.22159/ijpps.2023v15i11.49319.

87. Attama AA. SLN, NLC, LDC: state of the art in drug and active delivery. Recent Pat Drug Deliv Formul. 2011 Sep;5(3):178-87. doi: 10.2174/187221111797200524, PMID: 21834777.

88. Estella Hermoso de Mendoza A, Campanero MA, Mollinedo F, Blanco Prieto MJ. Lipid nanomedicines for anticancer drug therapy. J Biomed Nanotechnol. 2009 Aug;5(4):323-43. doi: 10.1166/jbn.2009.1042, PMID: 20055079.

89. Chidambaram M, Manavalan R, Kathiresan K. Nanotherapeutics to overcome conventional cancer chemotherapy limitations. J Pharm Pharm Sci. 2011;14(1):67-77. doi: 10.18433/j30c7d, PMID: 21501554.

90. Plaza Oliver M, Santander Ortega MJ, Lozano MV. Current approaches in lipid-based nanocarriers for oral drug delivery. Drug Deliv Transl Res. 2021;11(2):471-97. doi: 10.1007/s13346-021-00908-7, PMID 33528830.

91. Mishra V, Bansal KK, Verma A, Yadav N, Thakur S, Sudhakar K. Solid lipid nanoparticles: emerging colloidal nano drug delivery systems. Pharmaceutics. 2018 Oct 18;10(4):191. doi: 10.3390/pharmaceutics10040191, PMID 30340327, PMCID PMC6321253.

92. Sharma S, Goel V, Kaur P, Gadhave K, Garg N, Das Singla L. Targeted drug delivery using beeswax-derived albendazole-loaded solid lipid nanoparticles in Haemonchus contortus, an albendazole-tolerant nematode. Exp Parasitol. 2023 Oct;253:108593. doi: 10.1016/j.exppara.2023.108593, PMID 37595879.

93. Maiti D, Naseeruddin Inamdar M, Almuqbil M, Suresh S, Mohammed Basheeruddin Asdaq S, Alshehri S. Evaluation of solid-lipid nanoparticles formulation of methotrexate for anti-psoriatic activity. Saudi Pharm J. 2023;31(6):834-44. doi: 10.1016/j.jsps.2023.04.007, PMID 37228325.

94. Granja A, Lima Sousa R, Alves CG, de Melo Diogo D, Nunes C, Sousa CT. Multifunctional targeted solid lipid nanoparticles for combined photothermal therapy and chemotherapy of breast cancer. Biomater Adv. 2023 Aug;151:213443. doi: 10.1016/j.bioadv.2023.213443, PMID 37146526.

95. Liang Z, Zhang Z, Lu P, Yang J, Han L, Liu S. The effect of charges on the corneal penetration of solid lipid nanoparticles loaded econazole after topical administration in rabbits. Eur J Pharm Sci. 2023 Aug 1;187:106494. doi: 10.1016/j.ejps.2023.106494, PMID 37315870.

96. Fogolari O, Leimann FV, Ineu RP, Rudy M, Ludwig AF, Salles FM. Progesterone-loaded solid lipid nanoparticles for use in the regulation of the estrous cycle in female rats. J Drug Deliv Sci Technol. 2023 Oct;88:104954. doi: 10.1016/j.jddst.2023.104954.

97. Abou Taleb Hala HA, Fathalla Z, Naguib DM, Fatease AA, Abdelkader H. Chitosan/solid-lipid nanoparticles hybrid gels for vaginal delivery of estradiol for management of vaginal menopausal symptoms. Pharmaceuticals (Basel). 2023;16(9):1284. doi: 10.3390/ph16091284, PMID 37765092.

98. Mo K, Kim A, Choe S, Shin M, Yoon H. Overview of solid lipid nanoparticles in breast cancer therapy. Pharmaceutics. 2023;15(8):2065. doi: 10.3390/pharmaceutics15082065, PMID 37631279.

99. Satyanarayana SD, Abu Lila AS, Moin A, Moglad EH, Khafagy ES, Alotaibi HF. Ocular delivery of bimatoprost-loaded solid lipid nanoparticles for effective management of glaucoma. Pharmaceuticals (Basel). 2023;16(7):1001. doi: 10.3390/ph16071001, PMID 37513913.

100. Subhan MA, Filipczak N, Torchilin VP. Advances with lipid-based nanosystems for siRNA delivery to breast cancers.

Pharmaceuticals (Basel). 2023;16(7):970. doi: 10.3390/ph16070970, PMID 37513882.

101. Viegas C, Patricio AB, Prata JM, Nadhman A, Chintamaneni PK, Fonte P. Solid lipid nanoparticles vs. nanostructured lipid carriers: a comparative review. Pharmaceutics. 2023;15(6):1593. doi: 10.3390/pharmaceutics15061593, PMID 37376042.

102. Li S, Chen J, Liu Y, Zheng Q, Tan W, Feng X. Application of cinnamaldehyde solid lipid nanoparticles in strawberry preservation. Horticulturae. 2023;9(5):607. doi: 10.3390/horticulturae9050607.

103. Guven E. Lipid-based nanoparticles in the treatment of erectile dysfunction. Int J Impot Res. 2020;32(6):578-86. doi: 10.1038/s41443-020-0235-7, PMID 32005938.

104. Abd El-Halim SM, Abdelbary GA, Amin MM, Zakaria MY, Shamsel Din HA, Ibrahim AB. Stabilized oral nanostructured lipid carriers of adefovir dipivoxil as a potential liver targeting: estimation of liver function panel and uptake following intravenous injection of radioiodinated indicator. Daru. 2020;28(2):517-32. doi: 10.1007/s40199-020-00355-8, PMID 32564282.

105. Dudhipala N, Veerabrahma Kishan. Candesartan cilexetil loaded solid lipid nanoparticles for oral delivery: characterization, pharmacokinetic and pharmacodynamic evaluation. Drug Deliv. 2016;23(2):395-404. doi: 10.3109/10717544.2014.914986, PMID 24865287.

106. Tzanova MM, Hagesaether E, Tho I. Solid lipid nanoparticle-loaded mucoadhesive buccal films–critical quality attributes and *in vitro* safety & efficacy. Int J Pharm. 2021 Jan;592:120100. doi: 10.1016/j.ijpharm.2020.120100, PMID 33227374.

107. Santonocito D, Campisi A, Pellitteri R, Sposito G, Basilicata MG, Aquino G. Lipid nanoparticles loading steroidal alkaloids of tomatoes affect neuroblastoma cell viability in an *in vitro* model. Pharmaceutics. 2023;15(11):2573. doi: 10.3390/pharmaceutics15112573, PMID 38004552.

108. Wang B, Wu K, Liu R, Huang Y, Chang Z, Gao Y. Phyllanthi tannin loaded solid lipid nanoparticles for lung cancer therapy: preparation, characterization, pharmacodynamics and safety evaluation. Molecules. 2023;28(21):7399. doi: 10.3390/molecules28217399, PMID 37959818.

109. Aljuffali IA, Anwer MK, Ahmed MM, Alalaiwe A, Aldawsari MF, Fatima F. Development of gefitinib-loaded solid lipid nanoparticles for the treatment of breast cancer: physicochemical evaluation, stability, and anticancer activity in breast cancer (MCF-7) cells. Pharmaceuticals (Basel). 2023;16(11):1549. doi: 10.3390/ph16111549, PMID 38004415.

110. Fatima F, Aleemuddin M, Ahmed MM, Anwer MK, Aldawsari MF, Soliman GA. Design and evaluation of solid lipid nanoparticles loaded topical gels: repurpose of fluoxetine in diabetic wound healing. Gels. 2022;9(1):21. doi: 10.3390/gels9010021, PMID 36661789.

111. Asif AH, Desu PK, Alavala RR, Rao GSNK, Sreeharsha N, Meravanige G. Development, statistical optimization and characterization of fluvastatin loaded solid lipid nanoparticles: a 32 factorial design approach. Pharmaceutics. 2022;14(3):584. doi: 10.3390/pharmaceutics14030584, PMID 35335960.

112. Akel H, Csoka I, Ambrus R, Bocsik A, Grof I, Meszaros M. *In vitro* comparative study of solid lipid and PLGA nanoparticles designed to facilitate nose-to-brain delivery of insulin. Int J Mol Sci. 2021;22(24):13258. doi: 10.3390/ijms222413258, PMID 34948054.

113. Tulbah AS, Lee WH. Physicochemical characteristics and *in vitro* toxicity/anti-SARS-CoV-2 activity of favipiravir solid lipid nanoparticles (SLNs). Pharmaceuticals (Basel). 2021;14(10):1059. doi: 10.3390/ph14101059, PMID 34681283.

114. Nair AB, Shah J, Al-Dhubiab BE, Jacob S, Patel SS, Venugopala KN. Clarithromycin solid lipid nanoparticles for topical ocular therapy: optimization, evaluation and *in vivo* studies. Pharmaceutics. 2021;13(4):523. doi: 10.3390/pharmaceutics13040523, PMID 33918870.

115. Uner M, Yener G. Importance of solid lipid nanoparticles (SLN) in various administration routes and future perspectives. Int J

Nanomedicine. 2007;2(3):289-300. PMID 18019829, PMCID PMC2676658.

116. Almeida AJ, Souto E. Solid lipid nanoparticles as a drug delivery system for peptides and proteins. Adv Drug Deliv Rev. 2007 Jul 10;59(6):478-90. doi: 10.1016/j.addr.2007.04.007, PMID: 17543416.

117. Nair AB, Shah J, Al-Dhubiab BE, Jacob S, Patel SS, Venugopala KN. Clarithromycin solid lipid nanoparticles for topical ocular therapy: optimization, evaluation and *in vivo* studies. Pharmaceutics. 2021;13(4):523. doi: 10.3390/pharmaceutics13040523, PMID 33918870.

118. Pathak K, Keshri L, Shah M. Lipid nanocarriers: influence of lipids on product development and pharmacokinetics. Crit Rev Ther Drug Carrier Syst. 2011;28(4):357-93. doi: 10.1615/critrevtherdrugcarriersyst.v28.i4.20, PMID: 21967401.

119. Hajj Ali H, Michaux F, Khanji AN, Jasniewski J, Linder M. Chitosan-shea butter solid nanoparticles assemblies for the preparation of a novel nanoparticles in microparticles system containing curcumin. Colloids Surf A Physicochem Eng Aspects. 2018;553:359-67. doi: 10.1016/j.colsurfa.2018.05.075.

120. Mohammadi Samani S, Zojaji S, Entezar Almahdi E. Piroxicam loaded solid lipid nanoparticles for topical delivery: preparation, characterization and *in vitro* permeation assessment. J Drug Deliv Sci Technol. 2018;47(Oct):427-33. doi: 10.1016/j.jddst.2018.07.015.

121. Kim JK, Park JS, Kim CK. Development of a binary lipid nanoparticles formulation of itraconazole for parenteral administration and controlled release. Int J Pharm. 2010;383(1-2, Jan):209-15. doi: 10.1016/j.ijpharm.2009.09.008, PMID 19747966.

122. Trombino S, Russo R, Mellace S, Varano GP, Lagana AS, Marcucci F. Solid lipid nanoparticles made of trehalose monooleate for cyclosporin-a topic release. J Drug Deliv Sci Technol. 2019;49:563-9. doi: 10.1016/j.jddst.2018.12.026.

123. Jaafar Maalej C, Elaissari A, Fessi H. Lipid-based carriers: manufacturing and applications for pulmonary route. Expert Opin Drug Deliv. 2012 Sep;9(9):1111-27. doi: 10.1517/17425247.2012.702751, PMID: 22724618.

124. Souto EB, Wissing SA, Barbosa CM, Muller RH. Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. Int J Pharm. 2004 Jun 18;278(1):71-7. doi: 10.1016/j.ijpharm.2004.02.032, PMID 15158950.

125. Kang KW, Chun MK, Kim O, Subedi RK, Ahn SG, Yoon JH. Doxorubicin-loaded solid lipid nanoparticles to overcome multidrug resistance in cancer therapy. Nanomedicine. 2010 Apr;6(2):210-3. doi: 10.1016/j.nano.2009.12.006, PMID 20060074.

126. Aji Alex MR, Chacko AJ, Jose S, Souto EB. Lopinavir loaded solid lipid nanoparticles (SLN) for intestinal lymphatic targeting. Eur J Pharm Sci. 2011 Jan 18;42(1-2):11-8. doi: 10.1016/j.ejps.2010.10.002, PMID 20971188.

127. Moutinho CG, Matos CM, Teixeira JA, Balcao VM. Nanocarrier possibilities for functional targeting of bioactive peptides and proteins: state-of-the-art. J Drug Target. 2012 Feb;20(2):114-41. doi: 10.3109/1061186X.2011.628397, PMID: 22023555.

128. Guney G, Kutlu HM, Genç L. Preparation and characterization of ascorbic acid loaded solid lipid nanoparticles and investigation of their apoptotic effects. Colloids Surf B Biointerfaces. 2014 Sep 1;121:270-80. doi: 10.1016/j.colsurfb.2014.05.008, PMID 24985762.

129. Zhang Y, Li Z, Zhang K, Yang G, Wang Z, Zhao J. Ethyl oleate-containing nanostructured lipid carriers improve oral bioavailability of trans-ferulic acid ascompared with conventional solid lipid nanoparticles. Int J Pharm. 2016 Sep 10;511(1):57-64. doi: 10.1016/j.ijpharm.2016.06.131, PMID 27374194.

130. Shah B, Khunt D, Bhatt H, Misra M, Padh H. Application of quality by design approach for intranasal delivery of rivastigmine loaded solid lipid nanoparticles: effect on formulation and characterization parameters. Eur J Pharm Sci. 2015;78:54-66. doi: 10.1016/j.ejps.2015.07.002, PMID 26143262.

131. Sathya S, Shanmuganathan B, Manirathinam G, Ruckmani K, Devi KP. α-Bisabolol loaded solid lipid nanoparticles attenuates Aβ aggregation and protects Neuro-2a cells from Aβ induced neurotoxicity. J Mol Liq. 2018;264:431-41. doi: 10.1016/j.molliq.2018.05.075.

132. Imam SS. Nanoparticles: the future of drug delivery. Int J Curr Pharm Sci. 2023;15(6):8-15. doi: 10.22159/ijcpr.2023v15i6.3076.