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Review article

Solid lipid nanoparticles: An effective lipid-based technology for cancer treatment

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ABSTRACT

Solid lipid nanoparticles (SLN) are considered at the forefront of nanotechnology's rapidly developing field, with several potential applications in drug delivery and research. SLN possesses promising attributes for reaching the goal of controlled and site-specific drug delivery and hence attracted researchers' wide attention. The present review briefly introduces SLN and discusses the reasoning behind the use of SLN over other colloidal carriers, such as emulsions and liposomes. Techniques to produce SLN, drug incorporation, loading capacity, and drug release mechanisms are reviewed. Aspects of the SLNs route of administration and the in vivo fate of the carriers are also discussed. The potential of SLN in incorporating different anti-cancer drugs and their effectiveness in various cancer therapies is highlighted. The mechanism of action of some commonly used anti-cancer agents with SLN is provided.

1. Introduction

Solid lipid nanoparticles (SLNs) are a colloidal delivery system made from solid (under room temperature) lipids [1–3] with particle sizes varying from 50 to 500 nm. SLNs were first introduced in 1991 as an alternative drug carrier system to other traditional colloidal carriers, namely oil-in-water emulsions, liposomes, and polymeric micro or nanoparticles [4,5]. SLN are attractive as they consist of spherical lipid particles small diameter in the nano-range with high specific area and have favourable zeta potential (Fig. 1). They comprise of crystallised lipid elements combined with emulsifiers and surfactants that are sued for drug encapsulation.

SLNs are used for the controlled and targeted delivery of drugs which are entrapped in the solid lipid matrix. SLNs are stabilized by a layer consisting of a single surfactant or through a mixture of surfactants which result in smaller particle size and improved storage stability [7,8]. In general, SLNs comprise of single lipids or blends such as fatty acids, steroids, waxes, triglycerides, acyl-glycerols, or a combination thereof. Different classes and ratios of emulsifiers have been successfully utilised to stabilise SLNs. Some of the most common emulsifiers are lecithin, bile salts (such as sodium taurocholate), non-ionic emulsifiers such as ethylene oxide/propylene oxide copolymers, sorbitan esters, fatty acid, etc.

SLNs combine the merits of liposomes, emulsions, and polymeric nanoparticles. They provide both stability of the solid matrix and lipid carriers' biological compatibility, avoiding the limitations related to those drug delivery systems [9]. The solid matrix of SLN can preserve encapsulated drugs against chemical instability and provide controlled drug release patterns. SLNs can provide stable nano-suspensions for extended periods compared to liposomal delivery systems. The compositions of SLNs are physically well-tolerated and generally recognized as safe (GRAS), which significantly minimizes cytotoxicity, one of the traits polymeric nanoparticles lack. Their minimal cytotoxicity leads to SLN's broad application range such as dermal, oral, pulmonary and parenteral administration. [10–12]; Alshehri). SLNs do not present disadvantages, such as unpredictable particle growth or unexpected drug expulsion from the lipid core, which are known to be common phenomena [13]. Table 1 shows the advantages and disadvantages of using SLN as a drug delivery system [14,15].

2. SLN production technologies

SLN can be produced using a wide range of technologies, such as high-pressure homogenisation, cold homogenisation, solvent

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emulsification evaporation, ultra-sonication, and multi-emulsion technique [16]. The produced SLNs can be stabilized by using a range of surfactants such as lecithin, Tween 80, Pluronic F68, or combinations thereof [4,17]. General ingredients to produce SLN include solid lipid(s), emulsifiers, and water. The term lipid is used here in a broad sense; these lipids can consist of triglycerides (e.g., tristearin), partial glycerides (e.g., Imwitor), fatty acids (e.g., stearic acid), steroids (e.g., cholesterol), and waxes (e.g., cetyl palmitate). Emulsifiers help to stabilise the lipid nanoparticles where a combination of emulsifiers has been shown to prevent particle agglomeration [13]. Table 2 shows a list of excipients that can be used for the preparation of SLN [13].

Table 1
Advantages and disadvantages of using SLN.

Advantages of SLN	Disadvantages of SLN
1. Target-based drug delivery system. 2. Drugs are released for a prolonged time. 3. Less expensive. 4. Used for poorly water-soluble drugs. 5. Long-term stability 6. It can be administered via different routes. 7. No bio-toxicity of the carrier.	1. Particle growth. 2. High pressure-induced drug degradation. 3. Unpredictable gelation tendency. 4. Drug expulsion after polymeric transition during storage

Table 2
An overview of ingredients that are commonly used for the preparation of SLNs.

Triglycerides (lipids)	Free fatty acids & alcohols	Hard fat types	Surfactants
Tricapin Trilaurin Trimyristin Tripalmitin Tristearin Tristeain	Behenic acid Myristic acid Oleic acid Stearyl alcohol Cetyl alcohol Myristil alcohol Lauril alcohol	Glyceryl monostearate Glyceryl behenate Glyceryl palmitostearate Cetyl palmitate Stearic acid Palmitic acid Decanoic acid Witepsol grades	Soybean lecithin Egg lecithin Phosphatidylcholine PEG-35 castor oil PEG-40 hydrogenated castor oil Poloxamer 188 Poloxamer 182 Poloxamer 407 Polyoxyethylene (20) oleyl ether Polyoxyethylene (20) stearyl ether Poloxamine 908 Polysorbate 20 Polysorbate 60 Polysorbate 80 Sodium dehydrocholate Sodium taurocholate Sodium glycocholate Sodium cholate Sodium lauryl sulpha

2.1. Methods of preparing solid lipid nanoparticles

2.1.1. High-pressure homogenisation

High-pressure homogenisation (HPH has been shown to be an effective dispersing technique in the preparation of SLN. The implementation of HPH results in the reduction of the SLN particle size in a controllable manner. The technology is preferred due to the easiness of scale-up, low production times and the possibility to avoid the usage of organic solvents [17,18]. Hover, the technology encounters the same issues related to drug degradation, supercooled melts and gelation phenomena.

2.1.2. Hot homogenisation

For hot homogenisation the temperature is kept above the melting point of the lipid(s) where the drug is dissolved in the melted lipid(s), and the mixture is dispersed in a hot surfactant solution. The pre-emulsion is produced by mixing the drug, lipid(s), and surfactants, which is then pre-homogenized using an ultra Turrax homogenizer for 3 min. The crude dispersion is then passed through a homogenizer for by applying elevated temperatures and pressure for up to three cycles [19]. Fig. 2 shows a schematic diagram of the hot homogenisation technique to produce SLN.

2.1.3. Cold homogenisation

In the cold HPH technique, the lipid is melted above its melting point, and the drug is dissolved or dispersed in the melted material. The mixture is cooled down using dry ice or liquid nitrogen. After solidification, the lipid mass is grounded using ball or mortar milling to yield lipid microparticles between 50 and 100 μm. Then a microemulsion is formed by adding these micro-particles into a cold surfactant solution with stirring and subsequently suspension is passed through a high-pressure homogenizer at/or below room temperature, and the micro-particles are broken down into nanoparticles. SLNs prepared using cold HPH possess a slightly higher (polydispersity index) PI and mean particle size than those obtained by the hot HPH technique [21].

2.1.4. Solvent emulsification evaporation

In this approach the lipid is dissolved in water-immiscible organic solvents, e.g., chloroform, which is then emulsified in an aqueous phase before evaporation of the solvent under reduced pressure. This method is suitable for incorporating highly thermolabile drugs due to the avoidance of heat during the preparation. Still, the presence of solvent residues in the final dispersion may create problems due to regulatory concerns [21].

2.1.5. Micro-emulsion technique

A warm micro-emulsion is prepared containing molten lipid, surfactant, and co-surfactant added with stirring. This solution is then dispersed in cold water while stirring. Excess water can be removed by

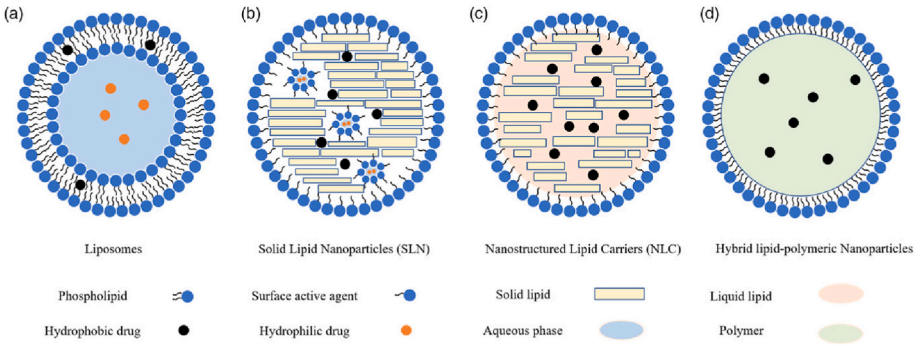

Fig. 1. A diagrammatic representation of lipid nanoparticles [6].

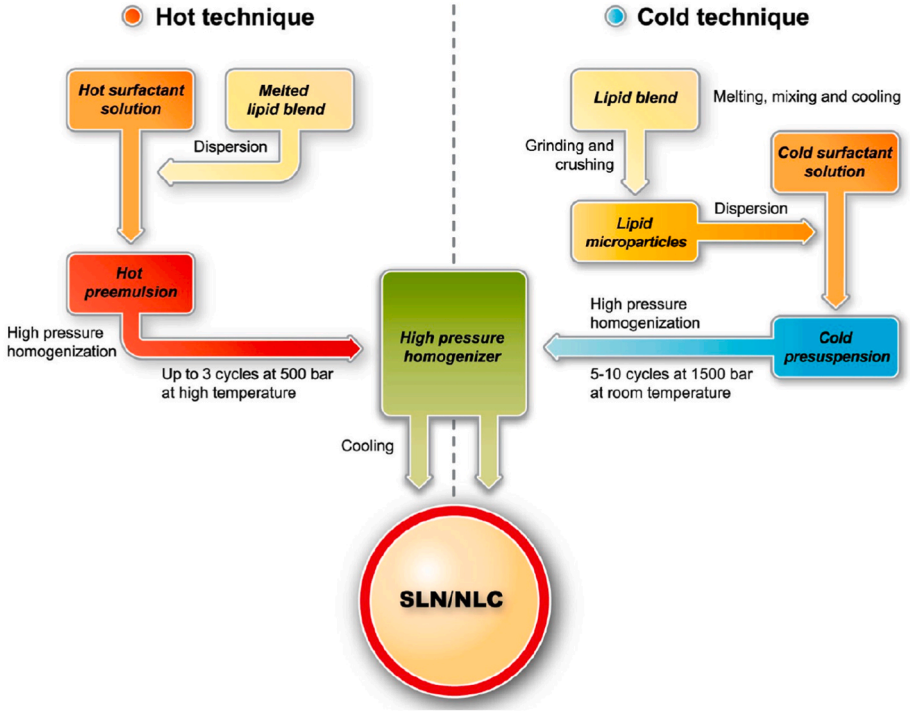

Fig. 2. Flow chart for preparing SLN using hot and cold high-homogenisation pressure [20].

freeze-drying. This method has certain advantages, including no need for specialized equipment, energy for production is not required, and scale-up production of lipid nanoparticles is possible. The disadvantage of the microemulsion technique is the dilution of the particle suspension with water; thus, removal of excess water needs additional efforts. Also, high concentrations of surfactants and co-surfactants in the formulation raise regulatory concerns [21].

2.1.6. Ultra-sonication

SLN can be obtained by high-speed stirring using ultra-sonication. This method is used to produce an oil-in-water emulsion in which high-speed stirring is applied to the melted lipid phase and the hot aqueous dispersion of surfactant. After cooling the resulting emulsion, solid particles of lipid are obtained. The main drawback of this method is the use of a high amount of surfactant, which is necessary to produce nanometer-size particles. The physical instability and a micro-sized range of particles are some of the other disadvantages of this approach [2].

2.1.7. Supercritical fluid method

Supercritical fluids have been used broadly for the SLN production. There are several variations in this platform of technology for powder and nanoparticle preparation. This method uses a gas such as carbon dioxide or nitrogen as supercritical fluids because of their non-toxicity, low critical temperature, and pressure. By modifying the temperature and pressure conditions, it is simple to vary the properties of viscosity, density, and diffusivity. Some of the advantages of this technique include no usage of organic solvents and the ability to produce nanoparticles and micro-particles in the form of dry powders [22]. Additional benefits of SCF technologies for creating SLNs is that relatively minor pressure changes can result in a considerable change in a drug's solubility in the lipid components. In a typical SCF procedure, supersaturation of dissolved chemicals and their subsequent precipitation can be quickly take place by carefully controlling the depressurization of a SCF. There are many ways to prepare SLNs using this mechanism, including Supercritical Fluid Extraction of Emulsions, Particles from Gas Saturated Solution, Rapid Expansion of Supercritical Solutions, and Gas Antisolvent procedures [23].

2.1.8. Double emulsion-based method

Warm w/o/w double micro-emulsions can be prepared in two steps. Firstly, w/o microemulsion is prepared by adding an aqueous solution containing a drug to a mixture of melted lipid, surfactant, and co-surfactant at a temperature slightly above the melting point of lipid to obtain a transparent system. In the second step, w/o prepared micro-emulsion is added to a mixture of water, surfactant, and co-surfactant to get a transparent w/o/w system. SLN can be obtained by dispersing the warm micro double emulsions in the cold and then washed with dispersion medium by an ultra-filtration system. Multiple emulsions have inherent instabilities due to the coalescence of the internal aqueous droplets within the oil phase, the coalescence of the oil droplets, and the layer's rupture on the surface of the inner droplets [22].

2.1.9. Solvent emulsification diffusion method

This method can obtain an average diameter of particle sizes between 50 and 100 nm. One of the advantages of this technique is the avoidance of high temperatures during preparation. Here the lipid is generally dissolved in the organic phase in a water bath at 50 °C and used as an acidic aqueous phase to adjust the zeta potential to form coacervation of SLN. The easy separation can be done by centrifugation. The SLN suspension was quickly produced. The entire dispersed system can then be centrifuged and re-suspended in distilled water [24].

2.1.10. Use of microfluidics

Microfluidic arrays have been successfully used to prepare lipid nanoparticles [25–29] for the delivery of various biomolecules. Dattani et al. compared the release kinetics of paclitaxel from SLNs, liposomes and micelles prepared by microfluidic arrays and found that SLNs provide much slower release rates with the highest stability in biological media. SLNs also demonstrated significantly slower delays in tumour growth in mice compared to the other drug delivery systems [30]. Arduino et al [29,30] developed microfluidic-assisted SLNs for the encapsulation of a paclitaxel and their functionalisation with a tumour homing peptide (iRGD). The SLNs presented particle sizes below 150 nm

and −20 to −34 mV zeta potential. The functionalisation demonstrated better cellular uptake in glioblastoma cell lines. The same group developed cetyl-palmitate SLNS for the loading of paclitaxel and sorafenib to demonstrate the effectiveness in cellular uptake in various cell lines. Recently Anderluzzi et al., developed SLNs comprising of Tristearin and 1,2-Distearoyl-phosphatidylethanolamine-methyl-polyethyleneglycol conjugate-2000 manufactured using a M − 110P Microfluidizer® processor (see Fig. 3). The particle size of SLNs could be monitored in-line while nanoparticles were filtered through tangential flow filtration. The technology was used successfully for the scale-up of the nanoparticles.

2.2. Secondary production steps

2.2.1. Stability of the drug and solid lipid nanoparticles

Stability considerations relevant to SLNs are the chemical stability of the drug and the physical stability of SLN. Prevention of degradation reactions such as hydrolysis is a vital chemical stability parameter, and examples of physical stability issues include the prevention of particle size growth and polymorphic changes of the solid lipid. Lipids and surfactants must be chosen carefully and mutually compatible with improving chemical stability [31].

Particle size distribution determines the biodistribution, shelf-life, and route of administration of SLN formulation. The SLN dispersions should have a narrow particle size distribution to avoid particle size growth due to Ostwald ripening. Ostwald ripening is a thermodynamically driven process in which smaller particles dissolve and redeposit onto larger particles' surfaces. This process occurs because smaller particles have a larger surface area, higher surface energy, and hence higher Gibbs free energy than larger particles. All systems tend to attain the lowest Gibbs free energy. In other words, larger particles are more energetically stable and favoured over smaller particles. Ostwald ripening can be reduced by minimizing polydispersity in the particle size, but it cannot be prevented [22].

In SLN dispersions, there are three types of instabilities. These are creaming, flocculation, and coalescence. In the creaming process, the less dense phase migrates to the top of the dispersion under the influence of buoyancy or centripetal force. Creaming causes the SLN particles to come close to each other, which in turn also initiates Ostwald ripening, flocculation, and coalescence. It has been reported that the creaming phenomenon can be prevented by matching the lipid density and the aqueous phase. Flocculation is a process in which weak van der Waals forces hold the nanoparticles together in loose associations. Coalescence is a process in which the nanoparticles fuse to form larger particles. The electrostatic repulsion and steric hindrance between particles produced in the presence of surfactants have been found to inhibit flocculation [32].

Electrostatic repulsion produces an electrical double layer around each nanoparticle in SLN dispersion. The electrical double layer comprises two parts: an inner region (stern layer), in which the ions are tightly bound, and an outer diffuse region, in which the ions are less firmly attached. A notional boundary forms between particles and ions within this diffuse layer. Ions within the boundary move with the particle, and the ions outside the boundary do not proceed with the particle. This notional boundary is called a slipping plane. The potential at the slipping plane is known as zeta potential [33]. The magnitude of the zeta potential is an essential determinant of the stability of SLN dispersions. As the zeta potential increases, the importance of electrostatic repulsion between the particles also increases; hence the particles will tend to repel each other, and there is no tendency to flocculate. Colloidal dispersions with a more positive zeta potential than +30 mV and negative than −30 mV are considered stable. Steric effects also play an essential role in the stability of SLN dispersion by hindering the particles from coming close to each other and thus preventing flocculation and coalescence. The polyoxyethylene chain present in non-ionic surfactants extends in the aqueous medium in the form of a coil and provides a steric hindrance. Optimum surfactant concentration and sufficient chain length (≥20 ethylene oxide units) will impart steric effect-mediated formulation stability. For long-term stability, a balance between electrostatic repulsion and steric effect must be obtained [32].

2.2.2. Lyophilisation

Lyophilisation can play an essential part in increasing the chemical and physical stability of SLN over an extended period. Lyophilisation was required to achieve long-term stability for a product containing hydrolysable drugs or a suitable oral administration product. Transformation into the solid state would prevent Ostwald ripening and avoid hydrolytic reactions. In the case of freeze-drying of the product, all the lipid matrices used can form larger solid lipid nanoparticles with a broader size distribution due to the presence of aggregates between the nanoparticles. The conditions of the freeze-drying process and the removal of water promote aggregation among SLNs. An adequate amount of cryo-protectant (such as sucrose, lactose, mannitol, polyethylene glycol, etc.) can protect against the aggregation of solid lipid nanoparticles during the freeze-drying process [34].

2.2.3. Spray drying

Compared to lyophilisation, spray drying is a cost-effective approach [35]. The usage of spray drying is particularly encouraged when the lipid's melting point is more than 70 °C. According to Ref. [13]; the best results with spray drying were obtained with an SLN concentration of 1% in a trehalose solution in water or 20% trehalose in the ethanol-water mixture. The addition of carbohydrates and low lipid content favoured the preservation of the colloidal particle size in spray drying.

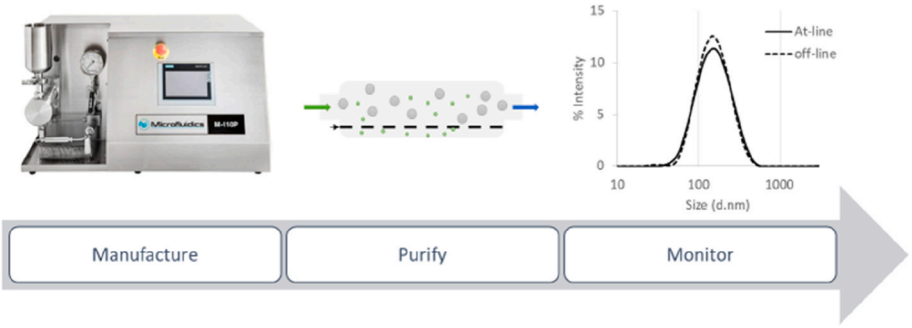

Fig. 3. Production and at-line monitoring of SLNs after production via Microfluidizer processor. SLNs were produced, purified via TFF and the particle size measured by circulation between the mixing tank and the homogenizer, until complete detection. Data obtained with al-line and off-line dynamic light scattering were compared.

3. Influence of ingredient composition on product quality

3.1. Influence of lipid

According to Ref. [13]; the critical parameters for forming nanoparticles are related to using different lipids. Some examples are the velocity of lipid crystallization, the lipid hydrophilicity (influence on several self-emulsifying properties), and the shape of the lipid crystals, which also influence the surface area [36]. Moreover, most of the lipids are used to represent a mixture of several chemical compounds. The quality of these chemical compounds can vary from different suppliers or batches from the same supplier. These slight differences in the lipid composition can have a considerable impact on the quality of SLN dispersion (e.g., changing the zeta potential, retarding crystallization processes, etc.). According to Ref. [37]; lipid composition can influence the particle size of SLN that is produced by high-shear homogenisation. Increasing the lipid content over 5–10% in most cases results in larger particles (including micro-particles) and broader particle size distributions [38].

3.2. Influence of emulsifiers

The choice of the emulsifiers and their concentration significantly impact the quality of the SLN dispersion [13]. Either surfactant or surfactant mixture affects the particle size of the lipid nanoparticles. According to Ref. [13]; SLN exhibited a much smaller particle size when the surfactant amount was increased. The decrease in surfactant concentration increased particle size during storage. One of the most common characteristics of surfactant is that it decreases the surface tension between the particles' interface, causing portioning of the particles and thereby increasing the surface area [22].

4. Drug incorporation and drug release from SLN

4.1. Drug incorporation

[17] have extensively studied three different models to incorporate active ingredients into SLN. These are the homogeneous matrix model, drug-enriched shell model, and drug-enriched core model (Fig. 4). The structure obtained is a function of formulation composition, such as lipid, the active compound, surfactant, and the production conditions (hot vs. cold homogenisation). A homogeneous matrix with a molecularly dispersed drug or drug present in amorphous clusters is thought to be mainly obtained when applying the cold homogenisation method and incorporating very lipophilic drugs in SLN with the hot homogenisation method [39].

During the cold homogenisation method, the bulk lipid matrix contains the dissolved drug in a molecularly dispersed form, which is mechanically broken down by high-pressure homogenisation leading to nanoparticle formation. In the hot homogenisation method, the oil droplet is cooled and crystallised. It is to note that no phase separation between lipids and drug occurs during the cooling process [39].

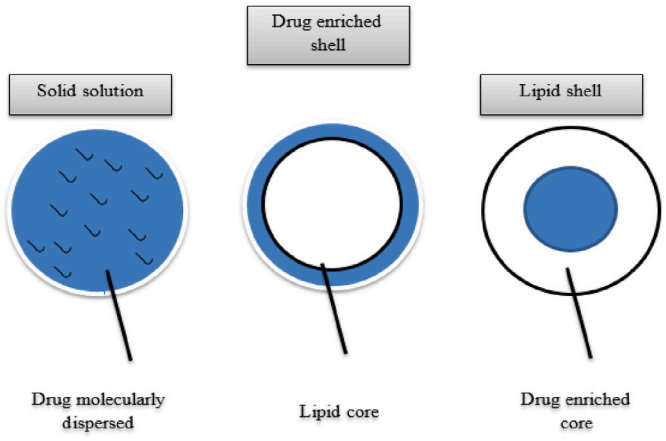

Fig. 4. Illustration of different drug incorporation models.

Drug-enriched outer shell can be obtained when phase separation occurs during the cooling process from liquid oil droplet to the formation of solid lipid nanoparticles [17]. state that the lipid can precipitate first, forming a practically compound-free lipid core. Also, during the forming process of the lipid core, the concentration of the active compound in the remaining liquid lipid increases continuously. Finally, the compound-enriched shell crystallises; this model is assumed to give away a speedy release, which is highly desired in various SLN applications. Core enriched with the active compound can be formed when the opposite occurs, which means the active compound starts precipitating first, and the shell will have distinctly less drug. This leads to a membrane-controlled release governed by Fick's law of diffusion. The structure of SLN formed depends on the chemical nature of the active compound and excipients and the interaction thereof. Also, the structure can be influenced or determined by the production conditions [17].

4.2. Drug release from SLN

[40]; intensively investigated the effect of formulation parameters and production conditions on the release profile of SLN. For example, they examined the release profile as a function of the production temperature. In most cases, a biphasic process is observed where an initial burst release occurs followed by a prolonged release. It has also been noticed that the burst release phenomenon only occurs when hot homogenisation is used and very high temperatures are applied [41]. investigated the encapsulation of Doxurobicin and found that the loading was dependent to the drug:lipid ratio and DMSO:lipid ratio where higher lipid amounts resulted in increased encapsulation efficiency while the addition of DMSO resulted in the same effect. The Doxorubicin release rate was pH dependent and faster at pH 5 in comparison to pH 7.4.

Enrofloxacin -loaded SLNs were fabricated through hot homogenizationusing tetradecanoic acid, palmitic acid, and stearic acid, showed an effect of the lipid type on the encapsulation efficiency drug loading [42]. In addition, the hot process affected the particle size (stearic acid produced larger particles), polydispersity and zeta potential. Animal trials showed increased bioavailability of 6.79, 3.56 and 2.39 folds for tetradecanoic acid-SLN, palmitic acid-SLN, and stearic acid-SLN respectively. On the other hand, biphasic release patterns are completely non-existent when cold homogenisation is used. The release kinetics can also depend on the release conditions (sink or non-sink conditions, release medium, etc.) Surfactant concentration can also play a vital role in burst release. Different studies have suggested high surfactant concentration can lead to high burst release. This was explained by the redistribution effects of the active compound between the lipid and the water phase during the heating-up process and, subsequently the cooling-down process after the production of the hot oil in water emulsion during the hot homogenisation process [13]. The solubility of the active compound in the water phase increases due to heating the lipid/water mixture, and the compound partitions from the melted lipid droplet to the water phase. After the homogenisation procedure is done, the lipid core starts to crystallize with still a relatively high amount of active compounds in the water phase. Further cooling leads to supersaturation of the compound in the water phase, then the compound partitions back into the lipid phase; a solid core has already started forming, leaving only the liquid outer shell for compound accumulation. So, it can be observed that as the solubility in the water phase goes higher, so does the burst effect. Solubility increases drastically when increased temperature and increased surfactant concentrations are used [13,43].

5. Biological and pharmaceutical aspects of SLN

SLNs are considered to be suitable for parenteral drug delivery because of their small particle size. Drug-loaded SLN may be injected intravenously, subcutaneously, intramuscularly, and used to directly target particular organs [14].

Upon administration into the systemic circulation, several colloidal carriers, such as liposomes and polymeric nanoparticles, are rapidly cleared by cells of the reticuloendothelial system (RES). RES usually resides in the spleen, and liver, and in the form of Kupffer cells in the liver consisting of phagocytic cells, considered the central part of the immune system. RES is known to remove drug carriers within minutes identified as foreign objects [44]. Clearance by RES is beneficial only when the spleen (or) liver, and lymph nodes are the target tumour site; for other types of cancers, RES is known to be the primary barrier. When the colloidal carrier surface is modified with a hydrophilic polymer, it increases the blood circulation time and resistance to clearance by RES. This type of surface modification of drug delivery systems by polymers is called long-circulating drug carriers. Polyethylene glycols (PEG) coating have been employed widely in SLN to get the stearic stabilization of colloidal carriers. PEG-coated SLN enabled longer circulation time by avoiding RES. A more prolonged presence in systemic circulation improves bioavailability and is especially interesting for the delivery of chemotherapeutic drugs that relies on enhanced permeation and retention (EPR) effect. Polyethylene glycol having electrical neutrality, chain flexibility, lack of functional group, and high hydrophilicity, which prevents it from interacting with biological components unnecessarily [45].

Other surfactants that have been investigated are Brij 68, Brij 78, and Pluronic F188 [46]. To facilitate drug targeting a reticuloendothelial system avoidance facility, these block polyoxyethylene polypropylene copolymers like Pluronic F188 can be used, in which the hydrophobic portion of the molecule forms the nanoparticle matrix. In contrast, the water-soluble polyoxyethylene block forms a hydrophilic coating on the SLN, increasing the tumour accumulation and anti-cancer activity of drugs [47,48]. The administered particles are cleared from the circulation by the liver and spleen. Because of the small size of SLN (below 1 μm), these lipid nanoparticle formulations can be used for systemic body distribution with a minimal risk of blood clotting and aggregation, which can lead to embolism. SLN can also provide a sustained release of drugs when administered intravenously. The drug encapsulated inside the lipid core can be released gradually on erosion (e.g., degradation by enzymes) or by diffusion from the particles [3].

[49] investigated the oral bioavailability of tacrolimus by developing thiomer-coated SLNs with biswax as solid lipid. The conjugated TC-SLNs-Tac showed enhanced permeability (P-app) by 4.35-fold while the in-vivo oral bioavailability increased by 4.73-fold improved in comparison to the drug solution. SLNs loaded with meloxicam with high entrapment efficiency (89–98%) were incorporated in chitosan gels and studied for their ex vivo skin permeation capacity [50]. Stearylamine – SLNs were investigated for monosodium iodoacetate-induced osteoarthritis in Wistar rats and demonstrated significantly lower IL-1β and TNF-α levels.

[51] investigated the bioavailability of cilostazol, a water insoluble drug in SLNs comprising of palmityl alcohol, Tween 80, Span 40, and Myrj as a steric stabiliser. The drugs were found in an amorphous state in the lipidic core with high stability over three months while

Histopathological evaluation showed no toxicity, while the pharmacokinetic study in Sprague-Dawley rats revealed high bioavailability (Fig. 5).

In a recent work [52], developed SLNs by HPH for the delivery of Raloxifene HCl in a chitosan gel formulation. The high drug encapsulation (95%) enhanced drug bioavailability by three and 6-fold compared to conventional gel and drug suspension, resulting in reduced levels of alkaline phosphate and calcium, suggesting that the developed nano gel was suitable for osteoporosis treatment. Similarly [53], produced chitosan modified SLNs loaded with thymoquinone to improve oral bioavailability in Wistar albino rats (Fig. 6). The SLNs showed high retention times in the GIT and excellent mucoadhesion due to the presence of chitosan with a Cmax of 61.72 μg/mL.

5.1. Use of SLN in various cancer therapies

Cancer is a condition where cells in a specific body part grow and reproduce uncontrollably. The cancerous cells are known to invade and destroy surrounding healthy tissues, including organs. Apart from a few cancer types (e.g., breast cancer) for which hormonal therapy or immunotherapy is used, cytotoxic drugs are used as the primary form of chemotherapy for cancer [54]. Particulate drug carrier systems can promise to improve the therapeutic effectiveness and safety profile of

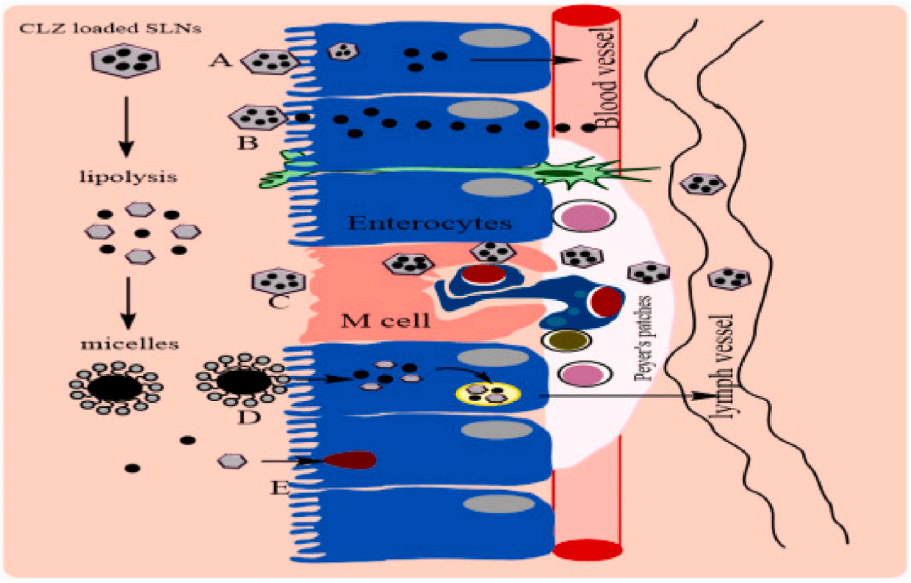

Fig. 5. Graphical presentation of the pathways for enhancing oral drug bioavailability using SLNs. Intestinal absorption of SLNs (A); Endocytosis (B); Adhesion of SLNs leading to drug uptake through the Peyer's patches via M cells (C); Passive diffusion via micellar solubilisation and chylomicron formation (D); Inhibition of efflux transporters by excipients (E).

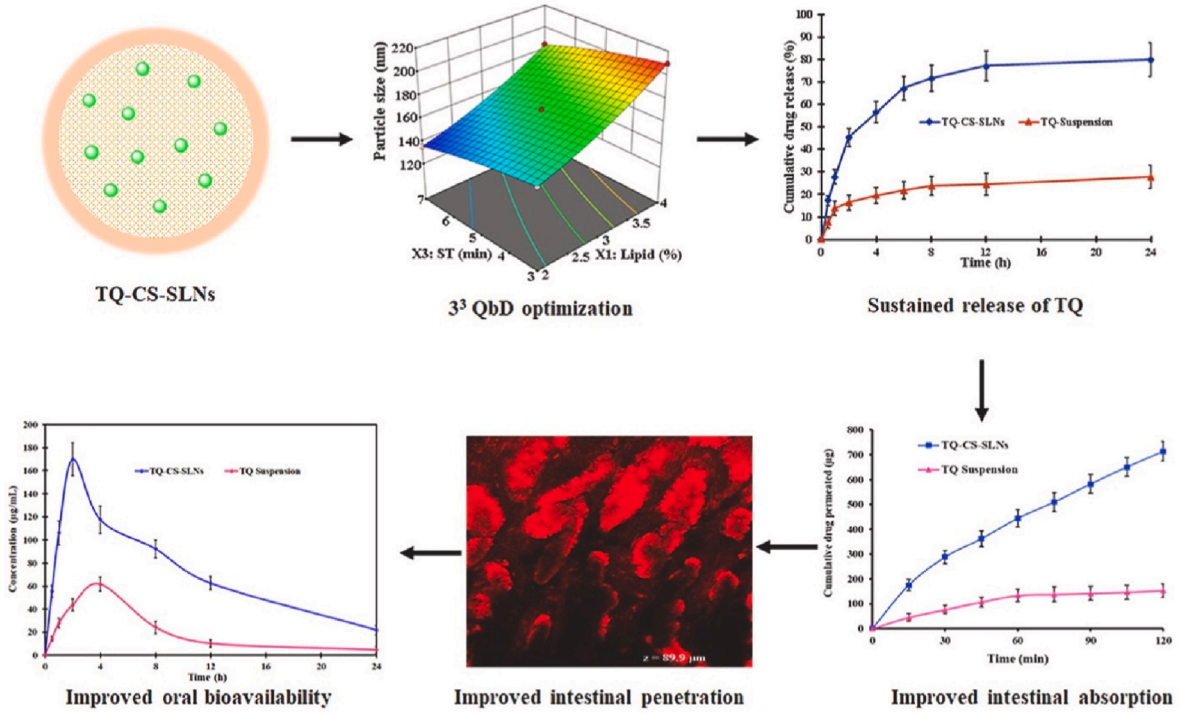

Fig. 6. SLNs with improved bioavailability.

this conventional form of cancer chemotherapy [55]. Because of the numerous advantages SLN can offer, this relatively new drug carrier is considered an emerging drug carrier system in the field of anti-cancer drug delivery.

A tumour is usually associated with a defective, leaky vascular architecture due to the poorly regulated nature of tumour angiogenesis [56]. Recent studies have shown improved SLN uptake and accumulation in tumour tissue, due to physiological tumour tissue characteristics, such as abnormalities and dysfunctional tumour vasculature, which allow SLN in nano range size to easily permeate the tumour [57]. This is often quoted as the "enhanced permeability and retention" EPR effect (Y. Matsumura & H. Maeda, 1986). This EPR effect can be taken advantage of by a properly designed nanoparticle system such as SLN to achieve passive tumour targeting. Moreover, higher SLN concentrations are maintained in the tumour for long periods due to low venous return and lymphatic drainage [57]. By doing this, the poor tissue specificity problem can be partly solved. Furthermore, with the advances in surface-engineering technology, the bio-distribution of SLN can be further manipulated by modifying the surface physicochemical properties of SLN to target them to the tissue of particular interest [13]. As a result, the chances of drugs reaching the tumour sites can be further enhanced, and systemic drug toxicity can be reduced.

Cytotoxic drug delivery systems such as polymeric nanoparticles and liposomes possess several problems regarding physical stability, protection of labile drugs from degradation, and controlled release. SLNs tend not to demonstrate such disadvantages [3]. Delivery of drugs to solid tumours is challenging, and it is known that most anti-cancer agents have a large volume of distribution upon i.e., administration and subsequently narrow therapeutic index due to a high level of toxicity in healthy tissues. Through the successful encapsulation of these drugs in a drug delivery system, such as SLN, the volume of distribution can be significantly reduced, and the concentration of drug in the tumour site can be increased [58]. SLN formulations of different anti-cancer agents are less toxic than the free drug. Table 3 shows a list of anti-cancer drugs encapsulated SLN. Although there is still a lack of clinical studies on using SLN for cancer treatment, preclinical studies using cell culture systems or animal models have been very promising

Table 3
A summary of SLN formulations used for the delivery of drugs with anti-cancer properties.

Anticancer Drug	Focus of studies	Reference
Linalool	SLN prep*, char*, in vitro evaluation	[59]
Doxorubicin	SLN prep, in vitro evaluation	[48,60,61]
Docetaxel	SLN prep, char	[62]
Erlotinib	SLN prep, in vitro evaluation	[63]
Oxaliplatin	SLN prep, in vitro evaluation	[64]
Ellagic acid	SLN prep, in vitro evaluation	[65]
Berberine HCl	SLN prep, in vitro evaluation	[66]
Resveratrol	SLN prep, in vitro evaluation	[67]
Oridonin	SLN prep, in vitro evaluation	[66]
Aloe-emodin	SLN prep, char, in vitro evaluation	[68]
Etoposide	SLN prep and char, BD* studies in tumour-bearing mice	[69]
Retinoic acid	SLN prep and char, drug stability studies, in vitro cytotoxicity studies on various human cancer cell lines	[31]
Camptothecin	SLN prep, char, SLN char, PK* studies in mice	[70]
Paclitaxel	SLN prep, char, in vitro evaluation	[6,61]
Temozolomide	SLN prep, in vitro, in vivo evaluation	Clemente et al., 2018
Fluorouracil	SLN prep, in vitro evaluation	Smith et al., 2020
Indirubin	SLN prep, in vitro evaluation	Rahinineiad et al., 2019
Cyclosporine	SLN Prep, in vitro evaluation	Essaghraoui et al., 2019
Tamoxifen citrate	SLN Prep, in vitro evaluation	Bhagwat et al., 2020

The last names of the corresponding authors are used in the "research group" category. *prep — preparation. *char — characterization. *PK — pharmacokinetics, *BD — bio-distribution.

[71].

[72] developed Fomes fomentarius polysaccharides (FPS) and polysaccharides enriched with selenium loaded SLNs by implementing a Design Experiment. The optimal SLN formulation developed at a drug/lipid ratio of 0.062 wt/wt and surfactants at 8.88 wt/wt%. In vitro

evaluation in *E. coli* and *S. aureus* showed an inhibitory effect at 50% and 78.5%, respectively, within 48h. The SLN-EPS-Se demonstrated strong anticancer activity in AGS and MKN45 gastric cancer cells at 70 and 60%, respectively.

Studies in melanoma cells using azelaic acid-loaded SLNs demonstrated potent tyrosinase inhibition and melanin reduction compared to the marketed cream in B16F10 melanoma cells [73]. Gemcitabine-loaded SLNs comprising glyceryl monostearate, polysorbate 80, and poloxamer 188, manufacturing described in Fig. 7, were tested on patient-derived primary pancreatic cancer cell lines (PPCL-46) and MiaPaCa-2 pancreatic cancer cell lines [][][74]. The SLNs appeared to improve Gemcitabine anticancer activity compared to the pure drug substance.

5.1.1. Breast cancer

Breast cancer is one of the most frequently occurring cancers in women and the second leading cause of cancer deaths in women. Among the significant challenges in effective breast cancer chemotherapies are inadequate drug concentrations reaching the tumour, their rapid elimination, systemic toxicity, and adverse effects. SLN has the potential to overcome current chemotherapeutic barriers in breast cancer treatment and to solve the problems associated with traditional chemotherapy and multidrug resistance [75,76]. Chemo-resistance or multidrug resistance can generally result from either of the two means firstly, by physically impairing delivery to the tumour (e.g., poor absorption, increased metabolism/excretion, or poor diffusion of drugs into the tumour mass); secondly, through intracellular mechanisms that raise the threshold for cell death. It is widely known that nanoparticles are beneficial tumour targeting vehicles due to their passive targeting properties by the

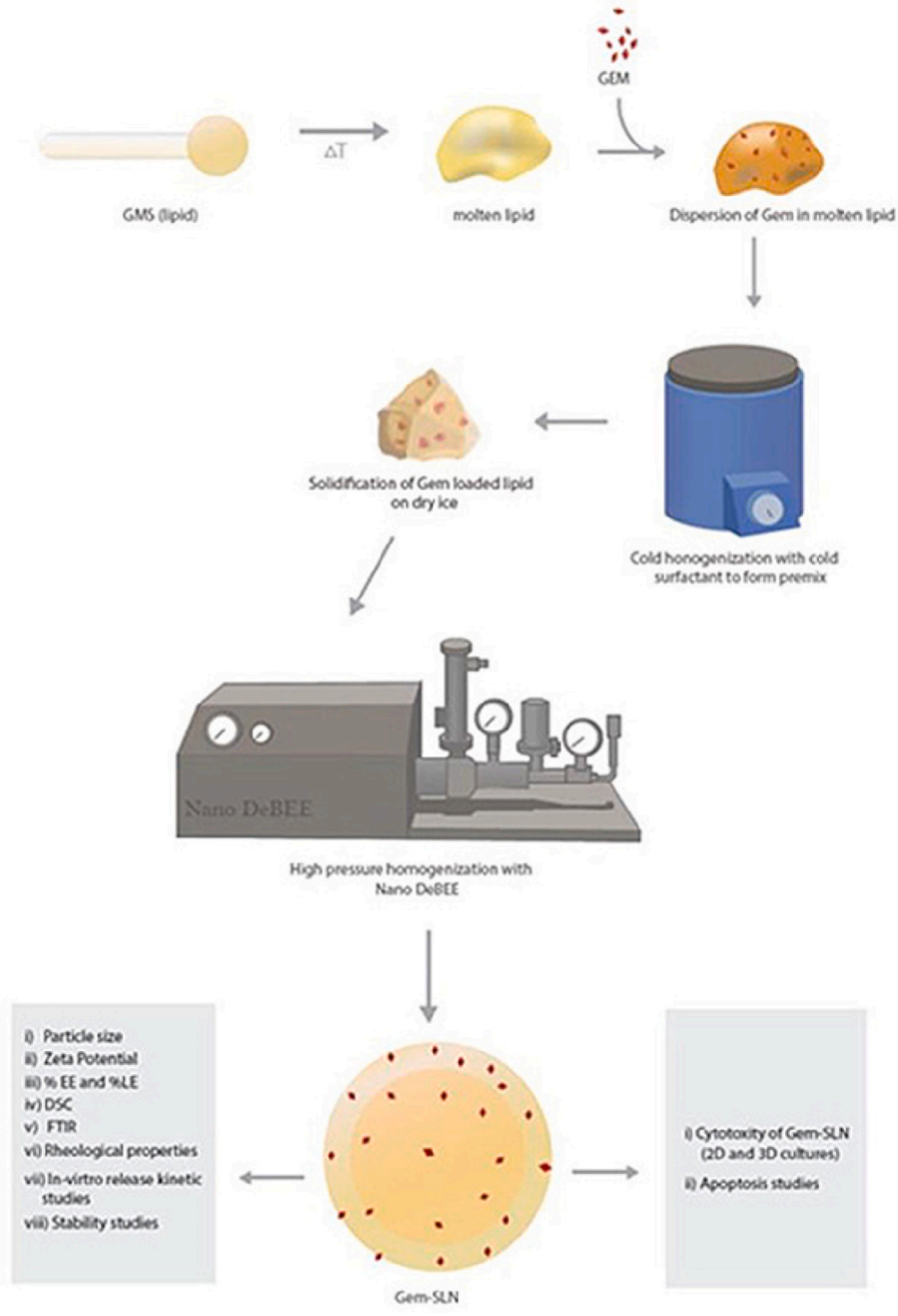

Fig. 7. Manufacturing of gemcitabine-loaded solid lipid nanoparticles in pancreatic cancer cells.

enhanced permeability and retention (EPR) effect. Another added advantage of SLN drug delivery system is the development of proteins (transferrin) and commercial antibody-conjugated SLN formulations for the active targeting of breast cancer [77]. [78] evaluated the cytotoxicity of SLN formulations carrying Docetaxel on human breast cancer cell line MCF-07. SLN of docetaxel showed significantly higher cytotoxicities than the equivalent amount of free drug. Another study conducted using curcumin, a widely used anti-cancer cytotoxic drug, on an MCF-7 breast cancer cell line showed a significant cytotoxic effect compared to the drug alone [79]. Bhagwat et al. developed transferrin conjugated Tamoxifen citrate-based SLN in the treatment of breast cancer. The increased targeting affinity of Tamoxifen citrate against breast cancer cells MCF-7 confirmed the potential of SLN for breast cancer therapy (Bhagwat et al., 2020).

5.1.2. Colorectal cancer

Colorectal cancer is considered to be the second leading cause of cancer-related deaths in the United States. It is also known to be the most common cancer in several other western countries. SLN has been proposed as a new approach to a drug carrier for colorectal cancer [80]. SLN-carrying cholesteryl butyrate, doxorubicin, and paclitaxel had previously been developed [80]. More recently, oxaliplatin-loaded SLN showed prolific anti-cancer activity in human colorectal cancer cell line HT-29 [64]. The higher sensitivity of HT-29 cells was reported compared to oxaliplatin solution and oxaliplatin incorporated SLNs.

Another study involved, the successful incorporation of papain into SLN. Papain-loaded SLN delivery system enhanced cytotoxic efficacy against HT-29 colorectal cells [81]. Investigation of Fluorouracil-loaded SLN has shown efficacy in targeting colorectal cancer cell line HCT-116. SLN-encapsulated Fluorouracil was highly cytotoxic against HCT-116 cells and significantly inhibited mouse subcutaneous tumour growth (Smith et al., 2020).

5.1.3. Lung cancer

One of the leading causes of cancer-related deaths worldwide is lung cancer. Adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma, which comprise the majority of lung cancers, are referred to as "non-small cell lung cancers" (NSCLCs). Patients with early-stage NSCLC are typically treated with surgery, with a 5-year survival rate ranging from 25% to 80%. This survival rate also depends vastly on the stage of the disease [82]. The causes of lung cancers are generally characterized by mutations in the p53 gene [83]. These mutations can lead to an exponential loss of tumour-suppressor function, an increase drug resistance, loss of mutational repair, an increase of angiogenesis, inhibition of cells, and proliferation of apoptosis [84]. SLNs have gained increasing attention as promising colloidal carrier systems. As a substitution for viral delivery systems, the use of p53 gene/cationic lipid complexes was reported to treat early endobronchial cancer [85]. A broad spectrum of anti-cancer cytotoxic drugs is used in line with SLN for lung cancer treatment. Investigation of Sclareol loaded SLN on human lung epithelial cancer cells (A-549), revealed a higher impact of Sclareol SLNs when compared with a plain drug. Cytotoxicity assay results showed that the plain sclareol inhibited A549 growth with an IC50 value of 19 μg/mL after 24 h, yet sclareol-SLNs inhibition was perceived after 48 h [86]. Naringenin (NRG), a flavonoid compound, had been reported to exhibit extensive pharmacological effects and improved bioavailability when incorporated into SLNs. NRG SLNs showed enhanced cytotoxicity on A549 cancer cells, compared to the equivalent amount of free drug in solution [87]. SLN of the ceramidase inhibitor, B13 (D-NMAPPD), with modified targeting property showed enhanced efficiency against lung cancer cells (Comelkci et a., 2020).

5.1.4. Prostate cancer

Prostate cancer is known to be one of the most important cancers (Jo et al., 2008) in men, especially in the industrialized countries of the western world. According to several reports, the incidence of prostate cancer has been increasing over the last decade [88]. The reason behind this rapid increase of incidence is thought to be because of the heterogeneous and peculiar nature of individual cancers, and the inability to target therapies to neoplastic cells [88]. The usage of SLN as a drug delivery system is considered to be advantageous for the inhibition of prostate cancer cells, such as LNCaP. One of the many advantages of using SLN is because of the usage of well-tolerated compound's while making these nanoparticles, and the avoidance of organic solvents, alongside good physical stability (Jesus et al., 2010). SLN has a great potential as a drug delivery system for prostate cancer cells since it is capable of enhanced accumulation in the target tissue through a passive targeting mechanism (i.e., enhanced permeability and retention effect, EPR), an increased accumulation and cell uptake through receptor-mediated endocytosis can be obtained if specific binding agents are attached on the surface of SLNs [65]. reported an evaluation of ellagic acid loaded SLN in preventing prostate cancer cell growth. Ellagic acid (EA) is a polyphenol, whose anti-cancer properties have been demonstrated in several cancer studies, but the poor water solubility and low bioavailability have limited its therapeutic potential. Cytotoxicity evaluations demonstrated that ellagic acid loaded SLNs prevented prostate cancer cell (PC3) growth in a low IC50 value compared to the free drug in a solution [65]. [89] developed retinoic acid-loaded SLN for improving the anti-cancer capability of retinoic acid on LNCaP human prostate cancer cell line [89]. Chen et al., developed a multi drug delivery system using the SLN technology, where Curcumin & Cabazitaxel loaded SLN were successfully developed. These SLNs showed great potential in prostate cancer therapy [68].

5.1.5. Brain tumour

The incidences of primary brain tumours in the United States have been estimated at approximately 43,800 per year [90]. SLNs are considered to be one of the best nanoscale lipid-based systems for brain tumour drug delivery [91]. Although the exact mechanism by which these SLNs cross BBB (Blood Brain Barrier) is still unknown, internalization is hypothesized to be mediated by endocytosis of SLN's by endothelial cells. The endocytosis procedure is initiated by the strong absorption of circulating plasma proteins to the SLN surface [92]. Drug loading and any possible drug degradation can be altered by the lipid matrix. Drug unloading within the tumour tissues can also be controlled. This control can be achieved by the respective surface coating of the SLN with its constituent lipids [3]. Different studies suggested that nanoparticles with tween (surfactants) resulted in the transport of drugs across the blood-brain barrier [93]. SLN has the potential to revolutionize both preoperative and intraoperative brain tumour detection. Andrographolide, which possesses several biological activities, including protection against oxidative stress-mediated neurotoxicity and cerebral ischemia was incorporated into SLNs by Graverini et al. SLNs were successful in enhancing Andrographolide permeation in vitro BBB models and human temporal lobe cell line hCMEC/D3. Furthermore, the ability of SLNs to cross the BBB and reach brain tissues was confirmed by in vivo tests in healthy rats [94]. Cano et al., developed Methotrexate loaded SLN to investigate its efficacy in improving brain biodistribution. In vitro and in vivo findings suggested Methotrexate SLNs can overcome BBB and has potential in treating grade IV glioma such as, Glioblastoma multiforme (Cano et al., 2020). Compared to other vehicles, SLN seems to offer more advantages (such as higher physical stability, greater protection from degradation and better release profile of incorporated drugs, good tolerability, and the possibility of site-specific targeting) and could be regarded as an effective carrier for chemotherapeutic drugs, gene therapeutical agents, and diagnostic tools in neuro-oncology [91].

6. Marketed products and current studies on SLNs

Since the early nineties, researchers turned their attention to lipid nanoparticles because of their non-toxicity and cost/effectiveness

relationship [17]. Despite the advantages, formulating with lipid nanoparticles has been suffering some drawbacks. Because of the gastrointestinal tract (GIT) conditions, most of the promising drugs do not reach clinical trials. The stability of particles must be comprehensively tested due to pH changes and ionic strength as well as the drug release upon enzymatic degradation [80]. Lipid nanoparticles absorption through GIT occurs via transcellular (through M cells or enterocytes) or paracellular (diffusion between cells). If the major drug uptake occurs through M cells, the portal vein to the liver is bypassed, resulting in higher drug concentrations to the lymph rather than to plasma [95]. Despite the low number of lipid nanoparticles formulations on the market for drug delivery, Mucosolvan retard capsules (Boehringer Ingelheim) is a success story [96] for the first generation of solid lipid nanoparticles. It was produced by highspeed stirring of a melted lipid phase in a hot surfactant solution obtaining an emulsion. This emulsion was then cooled down to room temperature obtaining lipid nano-pellets for oral administration [40]. Speiser developed lipid microparticles and nanopellets using spray congealing process [97]; Eldem et al., 1991 [98], SLN formulations are extensively developed and characterized for their in vitro and in vivo applications by various routes like parenteral, oral, pulmonary, ocular, and dermal. SLNs are being widely investigated as carriers for the delivery of macromolecules like proteins, oligonucleotides, and DNA [99]. Successful in vivo studies with SLN include rifampicin, isoniazid, and pyrazinamide that are used in tuberculosis treatment. These drugs achieved higher bioavailability when incorporated into SLN compared to the free solutions [100]. Newer methods for the production of SLNs and their applications are being reported and patented. The first patent for SLN was granted in 1993 [101] while various other patents in SLNs are summarized below in Table 4.

7. Some commonly used anti-cancer agents with SLNs

7.1. Curcumin - an anti-cancer agent

The potency of curcumin has been evaluated in multiple human carcinomas, which include; melanoma, head, neck, breast, colon, prostate and ovarian cancers [][][107]. In addition, urcumin has anti-inflammatory, antioxidant, anti-parasitic and anticancer properties [108]. The mechanisms of action followed by curcumin in exerting its anti-cancer effects are comprehensive and diverse. Curcumin can efficiently target many levels of regulation in the processes of cellular growth and apoptosis [109–111]. Apart from the vertical effects of curcumin on various transcription factors, oncogenes, and signaling proteins, curcumin has also the capabilities of acting at various temporal stages of carcinogenesis. These stages start from the initial stages leading to DNA mutations through the process of tumour genesis, growth, and metastasis (Fig. 8)

Curcumin suppresses the activation of NF-κB via inhibition of IκKB activity, leading to suppression of many NF-κB regulated genes involved in tumourigenesis including TNF, COX-2, cyclin D1, c-myc, MMP-9, and interleukins. Curcumin is involved in cell cycle control and stimulation of apoptosis via up-regulation of p16 and p53. It directly binds to a variety of surface and intracellular proteins causing direct cellular pathway inhibition or activation of secondary cellular responses [112, 113]. Also, curcumin is a modulator of autophagy and has inhibitory effects on tumour angiogenesis and metastasis via suppression of a variety of growth factors including VEGF, COX-2, MMPs, and ICAMs [110]. Due to curcumin's potent antioxidant and free radical quenching properties, it plays a vital role in exerting the inhibitory effects on the initial stages of carcinogenesis. Studies reveal that curcumin can suppress UV irradiation-induced DNA mutagenesis and cause induction of the cellular functions [114]. In addition to the inhibitory effects on the production of nitric oxide (NO) and the ability to scavenge DNA damaging superoxide radicals, curcumin also affects both the Phase I and Phase II enzymes of the hepatic cytochrome p450 enzyme system involved in the oxidation and detoxification of toxic substances. As curcumin has significant effects on cell growth with its multiple targeting capabilities, it possesses much promise as a potential chemotherapeutic agent for many human cancers [110].

7.2. Retinoic acid as an anti-cancer agent

Retinoids are natural and synthetic compounds of similar structure, and the term retinoids refer to entire compounds including both naturally occur and synthetic retinol (vitamin A) metabolites and analogues [115]. So far, three generations of retinoids have been developed. Retinoic acid (RA) is a physiologically active form of a metabolic product of vitamin A. It belongs to the first-generation retinoids. It is a yellow or light orange crystalline powder with a molecular weight of 300.44. It is a poorly water-insoluble substance while several experimental studies have shown the antiproliferative activity of RA in both in vitro and in vivo [116]. Many researchers have examined the ability of retinoids to treat various diseases such as acute promyelocytic leukaemia (APL), Kaposi's sarcoma, head and neck squamous cell carcinoma, ovarian carcinoma, bladder cancer, prostate cancer and neuroblastoma [117]. The mechanism of action of RA in chemoprevention and therapy of cancers involves the modulation of cell proliferation and differentiation [118]. Retinoids exert their effects by modulation of gene expression by two distinct classes of nuclear receptors: retinoic acid receptors (RAR α, β, γ) and rexinoid receptors (RXR α, β, γ). The receptors belong to the steroids or thyroid hormone super-family [119]. These nuclear RA

Table 4
List of patents of solid lipid nanoparticles.

Serial No	Name	Patent number	Filling date	Publication date	Inventor	Reference
1	Topical dermal delivery composition using selfassembling nanoparticle with cetylated componants.	US 2014/0234,428 A1	February 15, 2013	August 21, 2014	Barathur RR.	[102]
2	Formulation of UV absorbers by incorporation in solid lipid nanoparticles	US 7147841 B2	June 13, 2003	December 12, 2006	Herzog B.	[103]
3	A process for preparing solid lipid sustained release nanoparticles for delivery of vitamins	WO2013105026 A1	January 09, 2013	July 18, 2013	Kaur IP.	[104]
4	Method for producing solid lipid microspheres having a narrow size distribution	US 5250236	02-08-1991	05-10-1993	Gasco MR.	[105]
5	Solid lipid particles, particles of bioactive agents and methods for the manufacture and use	US 5785976	12-04-1994	28-07-1998	Westesen K. Siekmann B.	[106]
6	Curcumin solid lipid particles and methods for their preparation and use	US10166187B2	N/A	N/A	Christopher Diorio	Capsugel et al., 2019
7	Salvianolate lipid nanoparticle and preparation method thereof	CN105902530A	N/A	N/A	Yong	Yongzhong et al., 2019
8	Nanostructured lipid carriers and stable emulsions and uses thereof	WO2018232257A9	N/A	N/A	Fox Khandhar	Fox et al., 2019

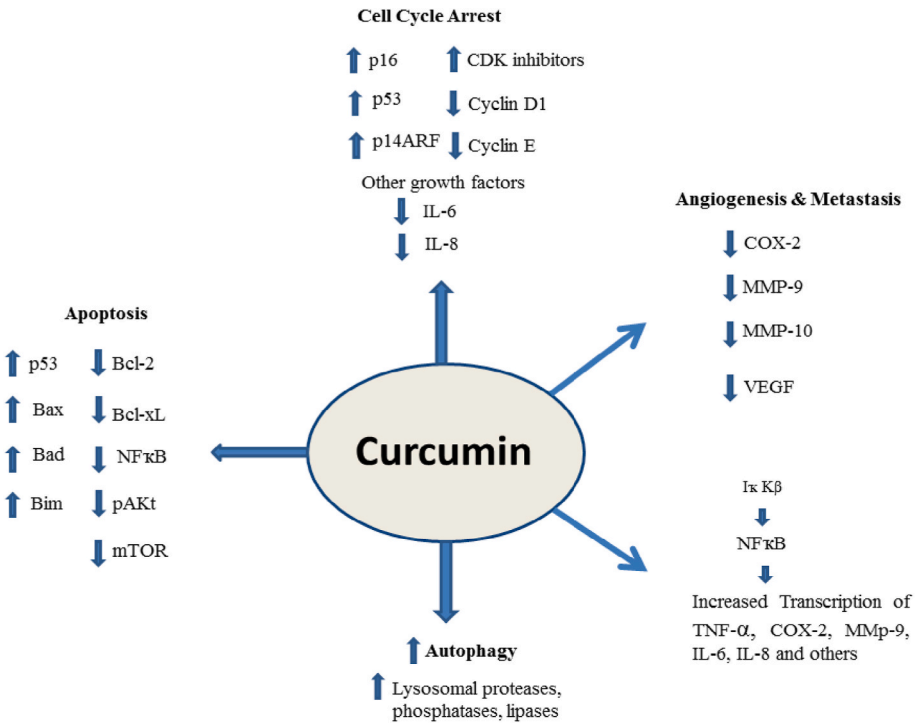

Fig. 8. Overview of the anti-cancer effects of curcumin [110].

receptors are the final mediators of RA action on gene expression that may lead to cell differentiation, inhibited growth and ultimately cell death [116].

7.3. *Mechanism of action of retinoic acid*

Retinoic acid is the most potent form of a trophic factor vitamin A (retinol), and it has been proved effective to inhibit cancer cell survival or to induce apoptosis in a variety of cancers [120,121]. In the human body, vitamin A converts into RA (retinoic acid) through two oxidation steps. First, the retinol is taken up from the blood and bound to CRBP (cellular retinol-binding protein) in the cytoplasm. Afterward the retinol dehydrogenase (RoDH) enzymes metabolize retinol to retinal, and then retinal is metabolized to RA by retinaldehyde dehydrogenases (RALDHs). RA is bound in the cytoplasm by CRABP (cellular RA-binding protein).

RA enters the nucleus and binds to the RA receptors (RARs) and the retinoid X receptors (RXRs), which themselves heterodimerize and bind to a sequence of DNA known as the RARE (RA-response element) (Fig. 9). This activates the transcription of the target gene [122,123]. RAR-RXR heterodimers activated by RA regulates the transcription of the target gene and control various physiological functions such as vision, immune function, cell proliferation, and differentiation (Chen et al., 2012).

8. Conclusions

The SLNs are considered amalgamate the properties of liposomes and polymer-based carriers, where encapsulation of both lipid-soluble and water-soluble drugs could be possible. SLN formulations are useful for sustained/prolonged-release or targeted drug delivery. The excipients approved by the regulatory authorities are used to prepare the lipid nanoparticles. Therefore, excipients used are of GRAS (Generally Recognized As Safe) status or are already used in pharmaceutical or food products. SLNs exhibit extended shelf life, enhanced drug stability upon incorporation while a wide spectrum of lipids is available for tuning the

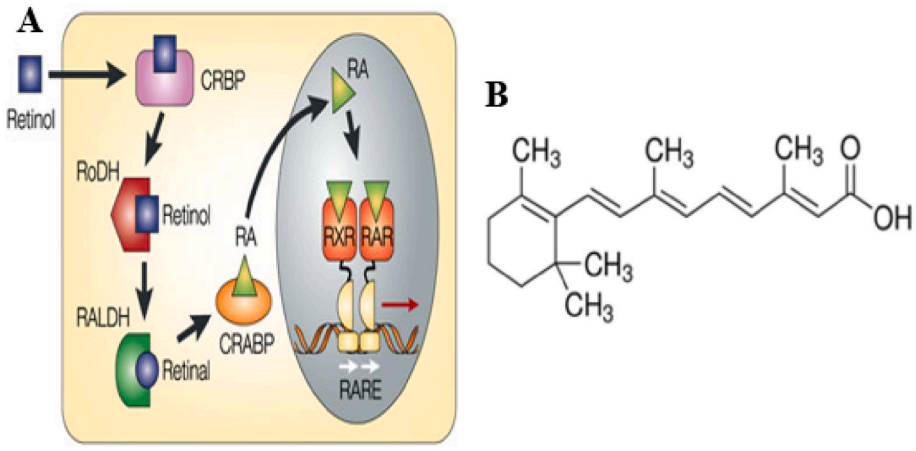

Fig. 9. The cellular mechanism of retinoic acid (RA) action, B) chemical structure of RA [122].

release kinetics. SLNs have emerged as an efficient drug delivery system for cancer treatment due to their unique properties in comparison to other drug carriers.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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