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Breast Cancer Drug Delivery Using Solid Lipid Nanoparticles

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ABSTRACT

The current drug delivery system is anticipated to be revolutionized by nanotechnology. Solid lipid nanoparticles are at the forefront of the fast-growing nanotechnology sector in the breast cancer drug delivery. Solid lipid nanoparticles are a new form of colloidal drug carrier system consisting of a nanometer (50-1000 nm) spherical lipid particles dispersed in aqueous surfactant or co-surfactant solution. This review highlights and presents an overview of the types of solid lipid nanoparticles, drug delivery mechanisms, selection of common ingredients, different ways of producing solid lipid nanoparticles and problems associated with solid lipid nanoparticles production. Prospects of solid lipid nanoparticle stabilization can be enhanced through freezing and spray drying. To characterize solid lipid nanoparticles, suitable analytical methods are required. This article also summarizes the study findings of the various researchers on the different methods of preparing solid lipid nanoparticles, additives and their significant results for the delivery of drugs in the treatment of breast cancer.

1. INTRODUCTION

Cancer is one of the world's leading causes of human death and a significant concern for public health [1]. Cancer is a disease classified by an uncontrolled cell proliferation that can invade and spread through the lymphatic system to distant parts of the body [2]. Mostly, cancer chemotherapy includes parenteral administration of anti-cancer drugs, causing severe undesired harmful effects above the maximum tolerable concentration (MTC) due to elevated concentrations of plasma drugs [3]. By comparison, oral chemotherapy increases therapeutic effectiveness by maintaining adequate concentrations of plasma drugs and avoids serious side effects by maintaining the drug level below MTC [4]. Death rates globally due to cancer are estimated at 9.6 million in 2018, according to the World Health Organization (WHO) [5]. With over 100 cancer varieties, the planet is predicted to check the risk of seventieth of latest world cancer incidences solely inside the future two decades. The American Cancer Society estimates about 17,35350 new cancer instances diagnosed and 6,09640 cancer deaths in the United States by 2018 [6].

Breast cancer is one of the most prevalent female cancers in the globe; it rarely varies in males (less than 1% of all instances of breast cancer). Most breast cancers start either in the milk-produced breast tissue, called lobules or in the ducts that connect the lobules to the nipple [7]. In general, breast tumors are classified into four distinct phases based on their size, place and metastasis proof. Primary breast cancer treatment was initially based on original surgery (including local excision or partial or complete mastectomy) followed by radiation and multiple types of systemic adjuvant therapy such as cytotoxic chemotherapy, hormonal therapy, and most lately immunotherapy. These therapies, however, have often failed and are followed by many side effects, including organ toxicity [8]. Breast cancer is the 2nd most common cancer with 1.7 million diagnosed cases worldwide [9]. According to the World Health Organization (WHO) 2018 study, it is estimated that 62,700 females died from breast cancer, approximately 14.5 % of all female cancers [10]. Overall, breast cancer incidence rates have increased by about 1.5 % annually since 1990. Finding a solution to this issue would have a major impact on the lifestyle of patients, particularly those suffering from metastatic breast cancers.

In the latest years, by creating effective drug delivery systems, nanotechnology has been extended the therapeutic possibilities of prior effective molecules. In reality, the implementation of nanotechnology in drug delivery has brought significant progress in

medicine. There is a broad range of nanocarriers in nanotechnology offering a broad range of alternatives for dealing with each therapeutic issue through a tailor-made strategy [11-13]. Solid lipid nanoparticles (SLNs) is an alternative carrier system for traditional colloidal carriers such as polymeric nanoparticles, dendrimers, liposomes, polymer-drug / protein conjugates, mesoporous silica nanoparticles and carbon nanotubes [14].

Combination benefits from different carriers such as polymeric nanoparticles, dendrimers, and liposomes are the primary reasons for the growth of SLNs. Like dendrimers and liposomes, they are made up of biocompatible additives (surfactants and lipids) accepted physiologically. The solid core of SLN can effectively protect the loaded active pharmaceutical ingredient against chemical degradation under severe biological environments. Further, solid lipid nanoparticles can be produced at a large industrial scale by high-pressure homogenization. All these positive characteristics make the SLN an outstanding drug delivery carrier [15-17].

2. SOLID LIPID NANOPARTICLES (SLNs)

Compared to inorganic or compound nanoparticles, it is recognized that lipid-based nanocarriers have less toxicity and biocompatibility. Solid lipid nanoparticles in specific constitutea useful and promising approach. These are nanometre-sized colloidal particles ranging from 50 to 1000 nm. These lipidic materials may comprise triglycerides, complicated mono, di and triglyceride mixtures, fatty acids which are solid at human body temperature and room temperature and stabilized by appropriate surfactants.

Solid lipid nanoparticles is an another lipid-based drug carrier to traditional colloidal carriers such as polymeric nanoparticles, nanotubes and liposomes for a lot of reasons, including (i) drug targeting at specific sites and possibility of controlled drug release kinetics, (ii) particle size ranges between 50-1000nm, (iii) possibility of incorporating hydrophilic and lipophilic drugs, (iv) high long-term stability and large productivity scale, (v) the lipid core reduces the risk of acute and chronic toxicity, (vi) enhancing the bioavailability of entrapped bioactive, (vii) possibility of lyophilisation [17- 19].

Despite these benefits, SLNs have certain constraints, such as (i) poor drug loading capability, (ii) drug expulsion after polymeric transformation at storage condition, (iii) comparatively high dispersions water content (70-99.9%) [15, 19]. Solid lipid nanoparticles can be produced using different techniques such as solvent emulsification-diffusion, solvent

injection, high shear homogenization and ultra-sonication, high-pressure homogenization and double emulsion [20].

3. TYPES OF SOLID LIPID NANOPARTICLES

These lipid-based nanoparticles are classified mainly into three types based on lipidic materials concentration, surfactant concentration, the chemical character of active pharmaceutical ingredients (API) and lipids, drug solubility in melted lipids, preparation process type (Table 1, Fig. 1).

Table No. 1: Types and description of solid lipid nanoparticles

Types of SLNs	Description	Ref.
Type 1 (homogeneous matrix model)	The active pharmaceutical ingredients (API) in the type 1 model are either molecularly placed in the lipid nucleus or present in amorphous clusters. The homogeneous matrix model is achieved by using optimized API and lipid proportions that pass above the lipid's melting point through the technique of high-pressure homogenization. This model can demonstrate controlled release kinetics as a result of their structure.	[16,21- 27]
Type 2 (drug enriched shell model)	The type 2 model is acquired when the concentration of the API is small in the melted lipid. After applying the technique of hot high-pressure homogenization, first, the lipid phase precipitates during the cooling of homogenized nanoemulsions, resulting in a gradual increase in API concentration in the remaining lipid melt with an enhanced solidified lipid portion. A lipid core without API is created; once the active pharmaceutical ingredient reaches its saturation solubility within the remaining melt, an external shell containing each lipid and API can solidify around this core. It is not suitable for extended drug release but it is useful to get an API burst release.	
Type 3 (drug enriched core model)	This model is acquired when the mechanism of recrystallization is contrary to the type 2 model. In this approach, near its solubility in saturation, the drug is solubilized in lipid melt. Subsequent cooling of the lipid emulsion leads the drug to over-saturate in the lipid melts; leading to the recrystallization of the drug before lipid recrystallization. Further cooling results in lipid recrystallization forming a membrane around the drug-enriched core that has already been crystallized. This SLN model is appropriate for drugs over a period that requires an extended-release.	

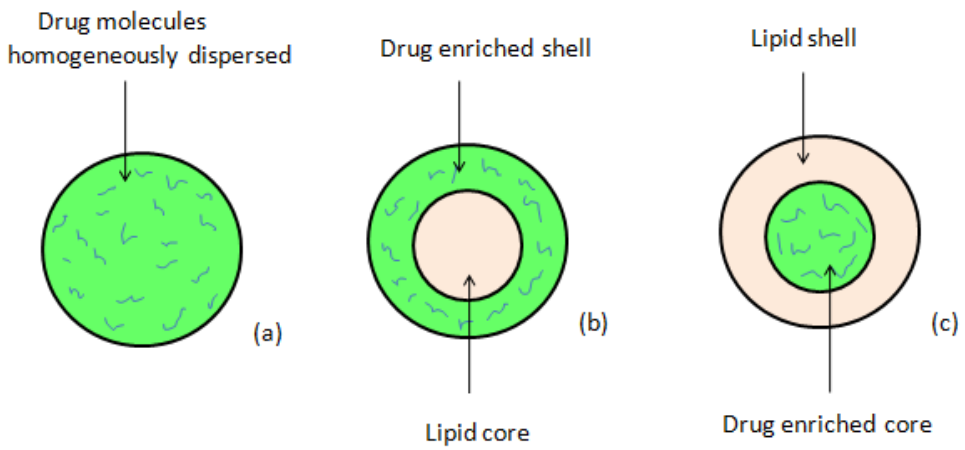

Figure No. 1: Different types of models of solid lipid nanoparticles (SLNs): (a) Homogeneous matrix model, (b) Drug enriched shell model, (c) Drug enriched core model.

4. TARGETING MECHANISM OF SOLID LIPID NANOPARTICLES :

Solid lipid nanoparticles can be enhanced their drug delivery by different mechanisms such as passive drug delivery mechanism, active drug delivery mechanism.

4.1. Passive drug delivery mechanisms:

In situ antitumor injections can achieve specific accumulation of drugs in tumors. However, owing to the difficulty in identifying cancerous masses, it is more complex therapy [28]. To overcome this challenge, some delivery technologies, especially SLNs, enable tumor tissue targeting by taking advantage of tumor microenvironment features owing to the enhanced permeability and retention effect (EPR) (Fig. 2). The enhanced permeability and retention effect relies primarily on the type and size of the tumor. This effect is based on the rapid angiogenesis of solid tumors. The angiogenesis process encourages uneven vessel growth of the blood in tumor areas with discontinuous epithelium. These discontinuities between epithelial cells with a size range of 100-800 nm make it possible for nanoparticles to migrate through the interstitial space to boost their permeability [29].

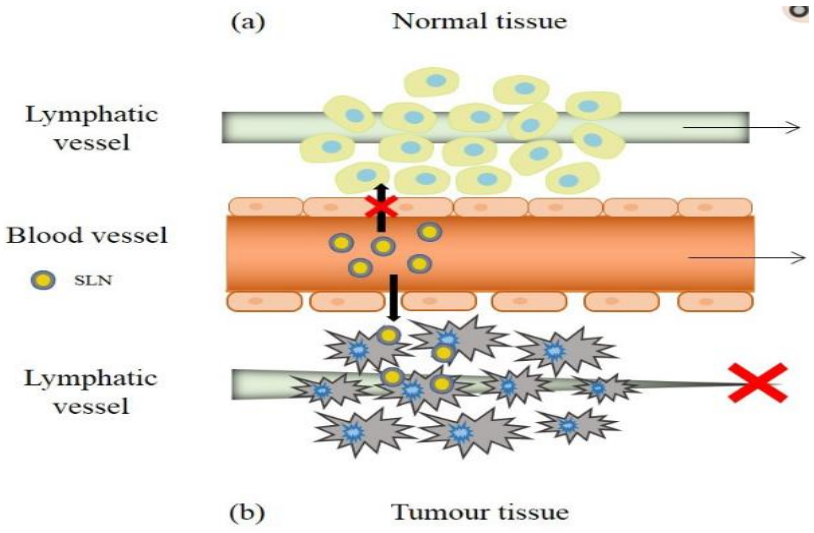

Figure No. 2: Enhanced permeability and retention effect (EPR) in tumor tissues. Under normal conditions (a) nanoparticles are not extravasated but in tumor region (b) the discontinuity of the vascular epithelium and the poor functionality of lymphatic drainage increase the permeability and retention of solid lipid nanoparticles (SLN) in the tumor microenvironment [31].

Furthermore, according to the EPR effect, three interrelated procedures determine the molecule distribution: extravasation of nanoparticles from blood vessels, nanoparticles diffusion through the tumor tissue and interaction with extracellular or intracellular objectives in the tumor's microenvironment [30]. The highest accumulation of nanomedicines is discovered in breast tumors in relation to the impact of EPR [31].

4.2. Active drug delivery mechanisms:

Active drug delivery mechanisms focus on identifying target molecules on the tumor cell's surface such as receptors or transporters.

This treatment, therefore, provides the drug to tumor cells selectively by altering the surface of the nanoparticles to decrease ordinary cell damage and undesired effects [29].

Specifically, the nanoparticle's surface modification enables them to show numerous copies of the ligand of concern so that transporter's binding avidity is high. Also, the nanocarriers need to be close to their target site for the ligand-target interaction [30].

It is confirmed in another research that SLNs loaded with Paclitaxel and functionalized with pluronic and hyaluronic acid (an inhibitor of the efflux transporter P-glycoprotein) showed

the capacity to overcome drug resistance and decrease cell viability in the breast and cervix tumor lines of MCF-7 and HeLa. Furthermore, in comparison to solid lipid nanoparticles without free drug and hyaluronic acid, these SLNs improve the concentration and efficacy of drugs in mice's tumor tissue in a very significant manner [32].

5. COMPOSITION OF SOLID LIPID NANOPARTICLES:

Mono, di and triglycerides, fatty alcohols and free fatty acids are the most frequently used components in the lipid core because these lipids are biocompatible [16]. All classes of surfactants and co-surfactants are used for stabilizing the lipid dispersion. It is observed that the combination of surfactants must be preventing particle agglomeration more efficiently [33]. The commonly used ingredients are given in Table 2.

Table No. 2: Lipids, Surfactants, and Co-surfactants used to make solid lipid nanoparticles

Ingredients	**Property**	**Ref.**
A. Lipids		
(a)Triglycerides		
Trimyristin(Dynasty 114)	Molecular weight 723.2g/mol Melting point 58.5°c Soluble in chloroform, benzene, ethanol but insoluble in water	[34-38]
Trilaurin (Dynasan 112)	Molecular weight 639g/mol Melting point 46.5°c Soluble in water	[34,36,38-41]
Tristearin(Dynasan 118)	Molecular weight 891.5g/mol Melting point 55°c(α),73°c(β) Soluble in carbon disulfide, chloroform	[34,36,38,40,42,43]
Tripalmitin(Dynasan 116)	Molecular weight 807.3g/mol Melting point 44.7-67.4°c Soluble in chloroform, ethanol, benzene but insoluble in water	[34,36-38,44-46]
Tricaprin(Dynasan 110)	Molecular weight 554.8g/mol Melting point 33°c Insoluble in water	[34,36-38,40,44,45,47]
(b)Mono, di and triglycerides mixture		
Glyceryl monostearate (Imwitor® 900)	Molecular weight 358.6g/mol Melting point 74°c Soluble in an organic solvent like ethanol	[48,49]
Glyceryl behenate (Compritol® 888 ATO)	Molecular weight 414.7g/mol The melting point range 69-74°c HLB value 2	[17,50-53]
Glyceryl palmitostearate	Molecular weight 633g/mol	[17,54]

(Precirol® ATO 5)	The melting point range 50-60°c	
Witepsol® W 35	Melting point 34°c Hydroxyl value 40-50	[37,55-57]
Witepsol® H 35	Melting point range 33.5-35.5°c Hydroxyl value 3	[35,37,56]
Witepsol® E 85	Melting point 42-44°c Hydroxyl value 5-15	[35,56]
(c) Free fatty acids		
Stearic acid	Molecular weight 284.5g/mol Melting point 69.3°c Soluble in acetone, chloroform, carbon disulfide	[58-61]
Palmitic acid	Molecular weight 256.43g/mol Melting point 62.49°c Very soluble in chloroform	[62,63]
Decanoic acid	Molecular weight 172.26g/mol Melting point 31.5°c Very soluble in ethanol, acetone	[62,64,65]
Behenic acid	Molecular weight 340.59g/mol Melting point 80°c Soluble in chloroform	[66,67]
(d) Free fatty alcohols		
Stearyl alcohol	Molecular weight 270.5g/mol Melting point 59.5°c Soluble in chloroform	[68-71]
Cetyl alcohol	Molecular weight 242.44g/mol Melting point 49.3°c Soluble in alcohol, ether, chloroform	[70,72-74]
Myristyl alcohol	Molecular weight 214.39g/mol Melting point 37.7°c Very soluble in ethanol, acetone, chloroform	[70,75]
Lauryl alcohol	Molecular weight 186.33g/mol Melting point 24°c Soluble in ethanol	[70,76,77]
(e) Waxes		
Beeswax	Melting point range 62-65°c Soluble in chloroform, ether but insoluble in water	[78-80]
Carnauba wax	Melting point range 82-86°c Freely Soluble in warm benzene	[78,81,82]
B. Surfactants		
(a) Non-ionic surfactants		
(i)Poloxamers		
Poloxamer 188(F-68)	Average Molecular weight 7680-9510g/mol Melting point range 52-57°c Freely soluble in water, ethanol HLB value >24	[17,37, 45,51,52,55, 83,84]
Poloxamer 182	Melting point -4°c HLB value 1-7	[83-85]
Poloxamer 407(F-127)	Average molecular weight 9840-14600g/mol	[17,50,83,84

	Melting point 56°c Very Soluble in water HLB value 18-23	]
Poloxamine 908	Soluble in warm water HLB value >24	[17,50,86]
(ii)Polyoxyethylene sorbitan fatty esters		
Polysorbate 20	Molecular weight 1128g/mol Soluble in water, ethanol, methanol Hydroxyl value 96-108 HLB value 16.7	[87-89]
Polysorbate 60	Molecular weight 1312g/mol Soluble in water, ethanol HLB value 14.9 Hydroxyl value 81-96	[88,89]
Polysorbate 80	Molecular weight 1310g/mol Very soluble in water HLB value 15 Hydroxyl value 65-80	[85,89]
(b)Anionic Surfactants		
Sodium cholate	Molecular weight 430.6g/mol Melting point 198°c Soluble in water HLB value 18	[85,90]
Sodium glycocholate	Molecular weight 487.6g/mol HLB value 14.9	[35,45,55, 91]
Sodium taurocholate	Molecular weight is 537.7g/mol Melting point 230°c Soluble in water	[92-94]
Sodium lauryl sulfate	Molecular weight 288.38g/mol Melting point 204-207°c Freely soluble in water HLB value~40	[95-98]
(c) Cationic surfactant		
Cetrimonium bromide	Molecular weight is 364.4g/mol Melting point 240.0°c Freely soluble in ethanol (95%)	[68,69,72,99 ,100]
DOTAP	Molecular weight 663.1 g/mol Transition temperature < 5°c Soluble in water-miscible organic solvents DMSO and ethanol	[101,102]
(d) Amphoteric surfactant		
Soybean lecithin (Lipoid® S 75, Lipoid® S 100)	Average molecular weight 800-908 g/mol Transition temperature < 0°c Soluble in diethyl ether, chloroform, fatty acids	[35,39,55,10 3-105]
Egg lecithin (Lipoid® E 80)	Molecular weight 815.2g/mol Soluble in petroleum ether, fatty acids, chloroform	[103-105]
Phosphatidylcholine (Epikuron® 170, Epikuron 200)	Average molecular weight 621-898g/mol Soluble in ethanol, chloroform	[45,92,93,10 6]

C. Co- surfactants		
Low molecular weight PEG (e.g. PEG 200, PEG 400)	Average molecular weight 190-600g/mol Melting point range 15-25°c Soluble in water, alcohols Hydroxyl value 178-394	[107,108]
Propylene glycol	Molecular weight 76.09g/mol Melting point -60°c Soluble in ether; miscible with acetone and chloroform	[109-111]
Sorbitan monostearate	Molecular weight 430.6g/mol Melting point range 49-65°c Soluble in isopropanol, ethanol	[95,112]

Abbreviations: HLB: Hydrophilic Lipophilic Balance; DOTAP: 1, 2-dioleoyl-3-trimethyl ammonium-propane; DMSO: Dimethyl sulphoxide; PEG: Polyethylene (glycol).

6. SLNs PREPARATION METHODS:

6.1. High-pressure homogenization technique:

High-pressure homogenization is a powerful technique for the preparation of solid lipid nanoparticles. High-pressure homogenizers force through a small gap (varying from several microns) a high-pressure fluid (100–2000 bar). The fluid accelerates to very high velocity (over one thousand km / h) on a brief range. Very high shear stress and cavitations forces disrupt all manner of particles down to the submicron. For the homogenizer, typical lipid content (from 5–10 %) is no issue. Even greater concentrations of lipids (up to 40 %) are homogenized to lipid nanodispersions [113]. High-pressure homogenization, i.e. hot and cold homogenization, primarily has two particular techniques [19, 27, 39, 114].

6.1.1. Hot homogenization technique:

This technique is performed at greater temperatures than the lipid's melting point. A nanoemulsion due to the liquid state of the lipid is the primary product of hot homogenization. The high-shear mixing unit obtains a pre-emulsion of the drug-loaded lipid melt and the aqueous surfactant phase at the same temperature.

Higher temperatures generally lead to reduced particle sizes owing to reduced internal phase viscosity [115]. High temperatures, however, may increase the drug and carrier's degradation rate. It is possible to repeat the homogenization step several times. It should be remembered

that the homogenization of high pressure increases the sample temperature (about 108 ° C for 500 bar) [116].

Solid particles are created by cooling the sample to room temperature or temperature below. The sample can last several months as a supercooled melt [117]. The above process is shown in Fig. 3.

Pros [118-120]**:**

- It can be used for drugs that are lipophilic and insoluble.
- Many heat-sensitive drugs can be treated securely.

Cons [118-120]**:**

- Not appropriate for incorporating hydrophilic drugs in SLN owing to low entrapment efficiency.
- Temperature-induced drug degradation.

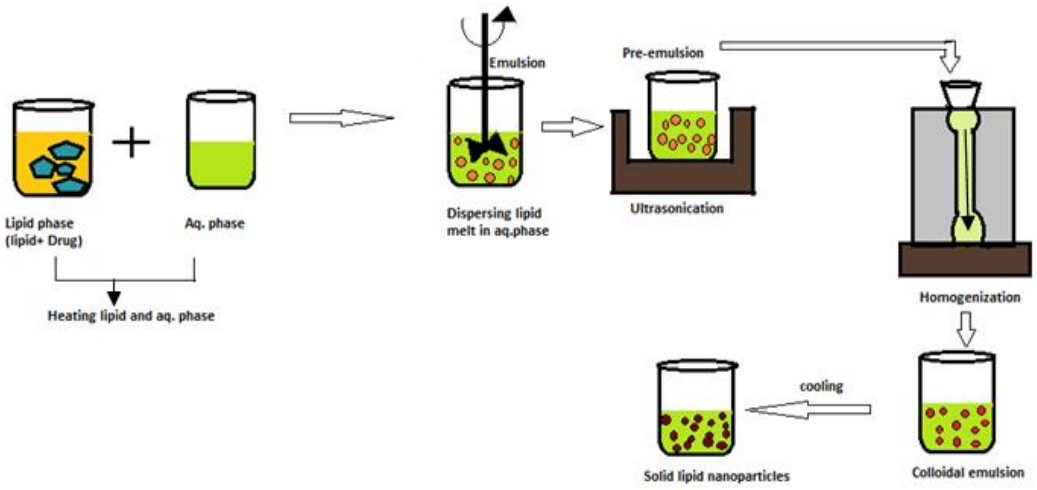

Figure No. 3: Hot homogenization technique.

6.1.2. Cold homogenization technique:

Cold homogenization technique is created to beat the subsequent three hot homogenization problems such as temperature-induced drug degradation, drug allocation into the aqueous stage and complexity of the nanoemulsions crystallization step leading to multiple medications and/or supercooled melts.

The first propaedeutic stage is the dispersal or solubilization of the drug in the lipid melt. However, the remaining steps are distinct. The drug-loaded lipid melt is rapidly cooled (e.g.using liquid nitrogen or dry ice). The drug is homogenously spread within the lipid matrix due to the elevated cooling rate. By ball or mortar milling, the solid, drug-loaded lipid is milled to microparticles in the size range between 50 to 100 µm. In a cooled emulsifiers solution, the solid lipidic microparticles are distributed. The pre-suspension is homogenized at or below room temperature by elevated pressure [121]. The cold homogenization minimizes sample thermal exposure due to the melting of the lipid/drug-mixture in the preliminary phase.

Pros [19]**:**

- Low capital cost.
- Demonstrated at lab scale.

Cons [19]**:**

- Energy-intensive process.
- Polydispersity distributions.

6.2. High-pressure homogenization and ultrasonication technique:

For the formation of solid lipid nanodispersions, both high-pressure homogenization and ultrasonication techniques are used [27, 122, 123].

Lipidic material is heated above its melting point to about 5–10 ° C. The lipid melt is spread in an aqueous surfactant solution to form an emulsion under large velocity stirring at the same temperature. Thereafter, sonication decreases the emulsion droplet size. Continuous cooling of the hot emulsion below the temperature of lipid crystallization results in the dispersion of lipid nanoparticles. Dispersions of lipid nanoparticles can be acquired through the method of ultracentrifugation [124]. The method above is shown in Fig. 4.

Pros [19, 125]**:**

- Reduced shear stress.

Cons [19, 125]**:**

- Potential metal contamination.
- During the storage conditions, physical instability likes particle growth.

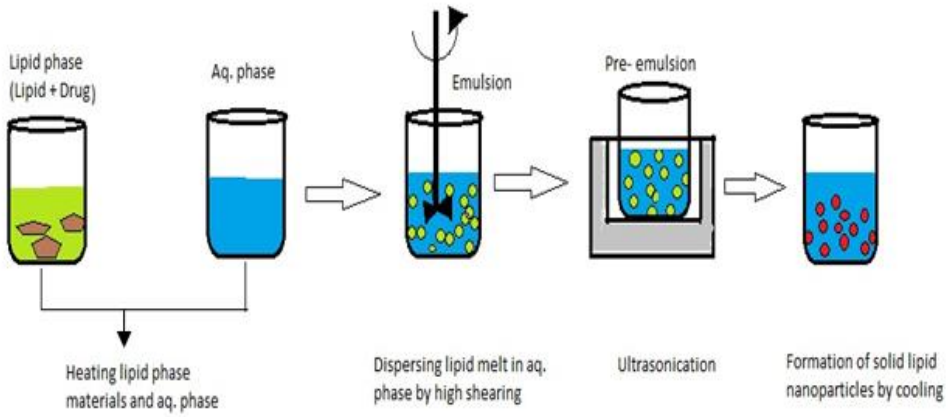

Figure No. 4: High-pressure homogenization and ultrasonication technique.

6.3.Solvent emulsification or evaporation method:

The hydrophobic drug and lipophilic material are dissolved in a water-immiscible organic solvent (e.g. cyclohexane, toluene, chloroform) using this method. It is then emulsified using a high-speed homogenizer in an aqueous solution. The coarse emulsion moved through the microfluidizer instantly. Then, mechanical stirring evaporates the organic solvent at room temperature and decreased pressure to precipitate SLNs [45, 126].

The mean particle size here relies on the organic phase lipidic concentration. With low lipid load (about 5 percent) related to organic solvent, it is possible to acquire a very tiny particle size [16].

Pros [16, 19, 45, 126, 127]**:**

- Small particle size around 24 nm.
- Formed a low viscous system.
- Low input of energy.
- Continuous process and scalable.

- Commercially demonstrated.

Cons [16, 19, 45, 126, 127]**:**

- Polydispersity distributions.
- Instability of emulsion.
- Lipid insolubility in an organic solvent.
- Damage to the biomolecular system.

6.4.Solvent emulsification-diffusion method:

The solvent (e.g. ethyl acetate, isopropyl acetate, benzyl alcohol, methyl acetate) must be partly miscible with water in the solvent emulsification-diffusion method. Primarily, both water and solvent are saturated equally to guarantee both liquid's original thermodynamic balance. The saturation step is conducted at that temperature when heating is needed to solubilize the lipid. Both drug and lipidic material are dissolved in the water-saturated solvent. This organic phase is emulsified using a mechanical stirrer with a solvent-saturated aqueous solution that contains a stabilizer. Following this development of oil in water emulsion, water in proportion varies from 1:5 to 1:10 added to the scheme allowing solvent diffusion into the continuous phase for forming lipid aggregation in the nanoparticles. Ultimately, vacuum distillation or lyophilization eliminates the diffused solvent and produces SLNs [18]. The above process is shown in Fig. 5.

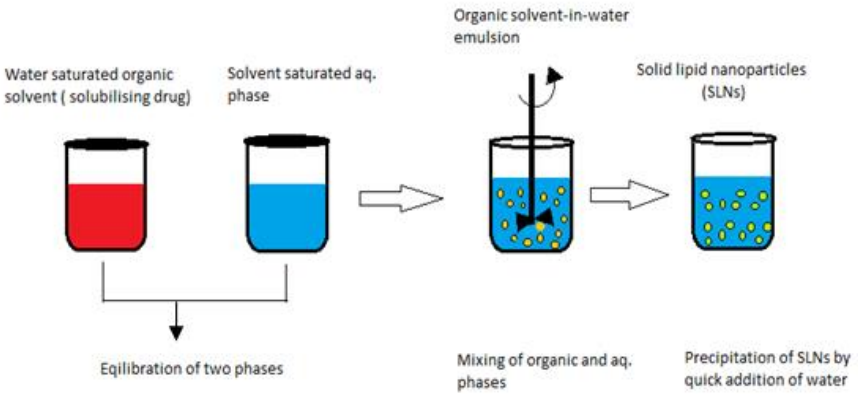

Figure No. 5: Solvent emulsification-diffusion method.

6.5.Micro emulsion-based method:

The micro emulsion-based method relies on microemulsion dilution. Microemulsions are biphasic systems consisting of internal and external phases (e.g. w/o microemulsions). They are made by stirring an optically transparent blend at a temperature 65 to 70 ° C, which generally consists of free fatty acids (e.g. stearic acid) at the low melting range, surfactants (e.g. poloxamer 188), co-surfactants (e.g. polyethylene glycol) and water. The hot microemulsion is dispersed under mechanical stirring in cold water at a temperature of 2-3 ° C to form lipid particle suspension. Ultrafiltration scheme washes the lipid-containing particles with dispersive medium and obtains SLNs. High-temperature gradients promote quick lipoid crystallization and prevent aggregation [128]. The method above is shown in Fig. 6.

Pros [19, 128]**:**

- Low mechanical energy input.
- Theoretical stability.

Cons [19, 128]**:**

- Highly susceptible to change.
- Low levels of nanoparticles.

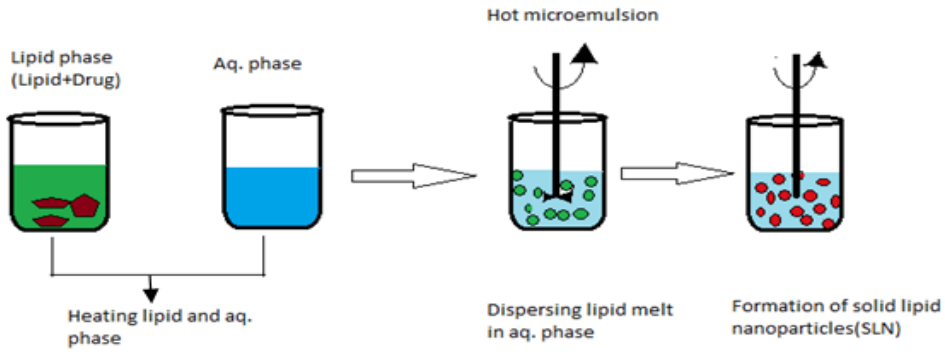

Figure No. 6: Micro emulsion-based method.

6.6.Supercritical fluid (SCF) technology:

Supercritical fluid technology is a novel SLN manufacturing technique. When its pressure and temperature exceed their respective critical value, a fluid is called supercritical. A gas cannot be liquefied above the critical temperature by raising the pressure. As the pressure rises, the gas density improves without important viscosity rises. Many gasses such as ethane, ammonia, carbon dioxide (CO_2) and CH_2FCF_3 have been tested, but carbon dioxide is the good choice for this method as it is secure, readily available critical point (31.5 °C, 75.8 bar), does not cause drug product oxidation, it is cheap, non-inflammable, environmentally acceptable. Organic solvents (e.g. Dimethyl sulphoxide) are generally totally miscible in carbon dioxidein the SCF technique. This technology includes a number of procedure for producing nanoparticles such as aerosol solvent extraction solvent (ASES), rapid expansion of supercritical solution (RESS), particles from gas saturated solution(PGSS), supercritical fluid extraction of emulsions (SFEE), solution enhanced dispersion by supercritical fluid (SEDS), gas/supercritical antisolvent (GAS/SAS). PGSS and SAS are mostly used to prepare SLNs [26]. The method above is shown in Fig. 7.

Pros [129]**:**

- Particles are produced in the form of dry powder.
- Moderate temperature and pressure conditions are required.

Cons [129]**:**

- Very expensive method.

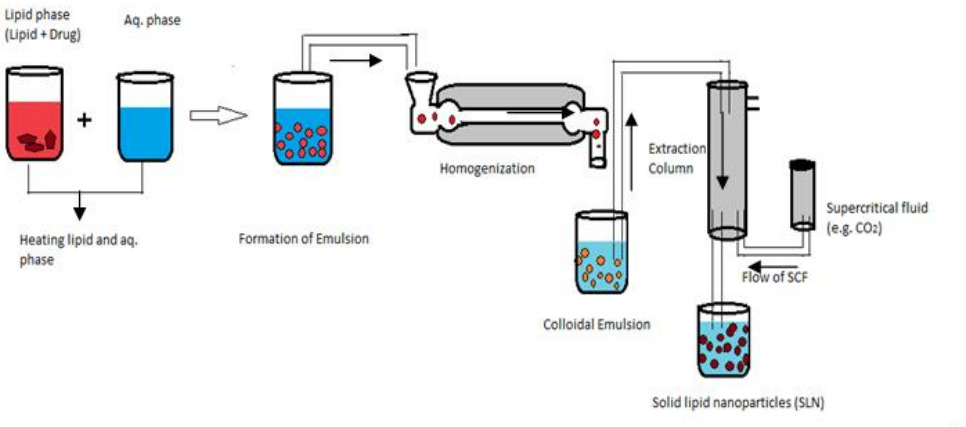

Figure No. 7: Supercritical fluid (SCF) technology.

6.6.1. Gas/supercritical antisolvent (GAS/SAS) method:

The supercritical fluid acts as antisolvent in this process to generate solids that are insoluble in SCF. Initially, SCF is dissolved in an organic solvent. The solid material is then crystallized, causing the intimate mixture of liquid and fluid to result in liquid growth and precipitation of particles. The absence of control over the formation of particles is the major drawback of this method. For the preparation of spherical lysozyme nanoparticles, a modified SAS method is used [26].

6.6.2. Particles from gas saturated solution (PGSS) method:

In the PGSS method, the SCF is dissolved in a solvent substratum solution, or a liquid substratum, or a solvent substratum suspension followed by a quick depressurization of the mixture by a nozzle to form SLNs. This method has the benefit of producing particles of a wide range of substances that have no solubility in supercritical fluid CO_2. This method produces insulin nanoparticles in which the dimethyl sulphoxide solvent used is atomized to supply insulin SLN (< 500 nm) with the lipid blend (Tristearin, Phosphatidylcholine, Dioctylsulfosuccinate) [26].

6.7.Solvent injection method :

In solvent injection method, the lipidic material is dissolved in water-miscible solvent (e.g. isopropanol, acetone, and ethanol). Then, by constant stirring, this lipidic material and solvent combination is injected in aqueous solution with or without surfactants through an injection needle. The resulting dispersion is filtered to remove any surplus lipidic materials with a filter paper. The existence of a surfactant in the aqueous phase enables the injection site to generate lipid droplets and stabilizes solid lipid nanoparticles [19, 130]. This process is shown in Fig. 8.

Pros [19]**:**

- Use of organic solvent that is pharmacologically appropriate.
- Easy to use.
- Fast manufacturing without any advanced machinery.

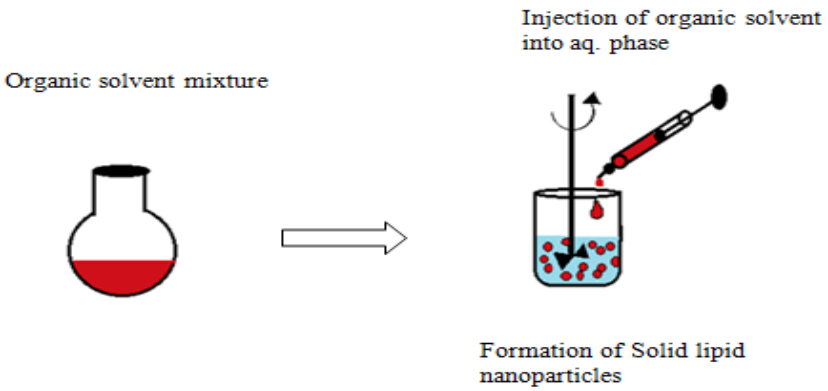

Figure No. 8: Solvent injection method.

6.8.Membrane contactor technique:

Recently, the method of membrane contactors is a novel technique for preparing SLNs. In this technique, the liquid phase is pushed through the membrane pore at a temperature above the lipid's melting point, swallowing the formation of tiny droplets as shown in Fig. 9. The aqueous solution is continuously stirred and circulates in the membrane module tangentially, sweeping away the droplets formed at outlets. By cooling the above solution at room temperature, solid lipid nanoparticles are created [26].

Pros [26, 129]**:**

- Control of the SLN size.
- Scaling up ability.
- The facility of use.

Cons [26, 129]**:**

- Clogging of the membrane.

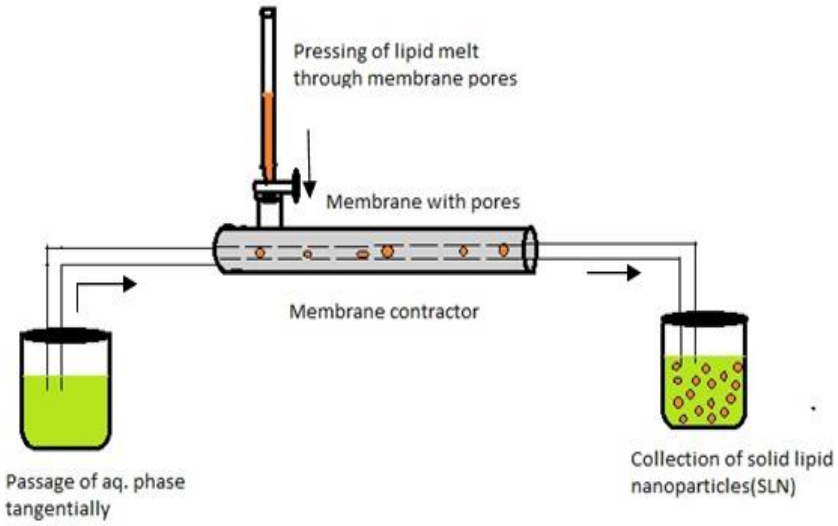

Figure No. 9: Membrane contactor technique.

6.9.Double emulsion method :

The double emulsion method is appropriate for SLNs comprising peptides and hydrophilic active pharmaceutical ingredients. In melted lipid mixture, an aqueous drug solution is emulsified to form primary W / O emulsion and stabilized with appropriate excipients. The primary W / O emulsion is dispersed to form a double W / O / W emulsion in the aqueous solution of the hydrophilic emulsifier. Then, through filtration, the double W / O / W emulsion is continually stirred and isolated. Comparatively, this method obtains big particles [131]. The method above is shown in Fig. 10.

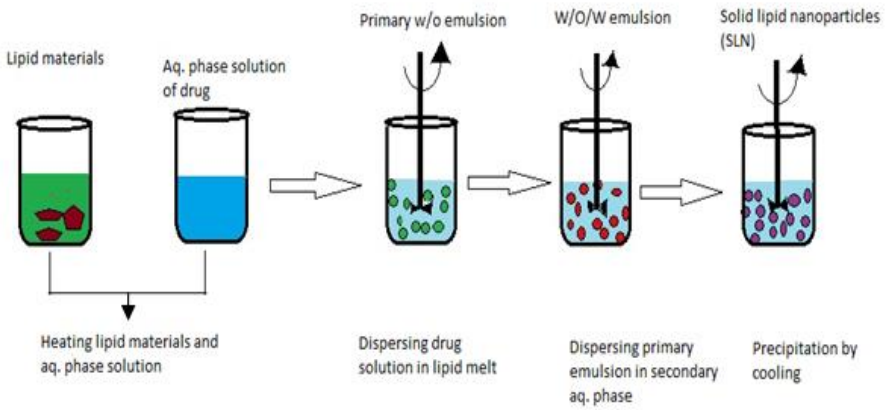

Figure No. 10: Double emulsion method.

7. STABILIZATION OF SOLID LIPID NANOPARTICLES:

The stability of solid lipid nanoparticles depends primarily on the physicochemical stability of lipid in its form of nanoparticles, as it is more likely to degrade and coalesce [119, 132]. Some external parameters like light and temperature seem to be of main significance during storage and shipping for long-term stability. Components of SLNs should have a small size distribution in the event of chemical stability to prevent crystal growth through Ostwald ripening [121].

For the improvement of SLN's physical and chemical strength, the lyophilization technique is successful. Also, conversion into a solid shape will stop Ostwald ripening and prevent the hydrolysis. The solid-state of lyophilizes is anticipated to have greater physical and chemical stability than aqueous dispersions of lipids. There is a need for two extra transitions between the formulations that could be the cause of extra stability issues. The first transition includes the freezing of the sample from water dispersion by evaporating the water under a vacuum. Sample freezing may trigger issues of stabilization owing to the freezing effect resulting in modifications in osmolarity and pH. The next transition is resolubilization involving at least in its preliminary phases, favoring particle aggregation (high particle and low water content, elevated osmotic pressure) [16, 21].

To get rid of this problem, it is necessary to add specific excipients before freezing and protects the suspension of the nanoparticulate. Adding cryoprotective agents (e.g. sorbitol, glucose, mannose, and trehalose) will be crucial to decrease SLN aggregation and improve dry product redispersion [16, 133]. The cryoprotective agent is added to the sample when the highest outcomes are achieved before homogenization [134]. The spray drying may be another operation for lyophilization to turn aqueous solid lipid nanoparticles dispersion into a dry form. This technique is rarely used to form SLNs [27].

8. CHARACTERIZATION TECHNIQUES OF SOLID LIPID NANOPARTICLES :

The techniques of characterization should be susceptible to the main SLN performance parameters. However, the characterization of solid lipid nanoparticles is a severe task owing to the complexity of the system and colloidal particle size [16]. Table 3 shows the different techniques used to characterize SLNs.

Table No. 3: various techniques used to characterize SLNs

Evaluation parameters	Analytical techniques or instrumentations	Ref.
Morphology study of shape and surface	Scanning electron microscopy Transmission electron microscopy Atomic force microscopy Phase-contrast optical microscopy	[135-139]
Vesicles size and size distribution study	Scanning electron microscopy Photon correlation spectroscopy Optical microscopy	
Surface charge, surface pH and electrophoretic mobility study	Measurement of zeta potential pH-sensitive probes Laser light scattering technique	
Density measurement	Gas pycnometer	
Molecular weight	Size exclusion chromatography	
Viscosity measurement	Brookfield Viscosimeter	
In vitro drug release study	Dialysis membrane apparatus	
Surface hydrophobicity study	X-ray photoelectron spectroscopy Synchrotron radiation X-ray Contact angle measurement	

8.1.Particle size and zeta potential measurement:

The strongest methods for particle size measurements are photon correlation spectroscopy and laser diffraction. Due to problems in evaluating tiny nanoparticles, the Coulter Counter technique is rarely used to measure SLN particle size.

Photon correlation spectroscopy (commonly known as dynamic light scattering) measures the fluctuation of the scattered light intensity induced by the motion of particles. A size variety from a few nanometers to about three microns is covered by this technique. Photon correlation spectroscopy is, therefore, a useful instrument for characterizing nanoparticles. Laser diffraction measurements can visualize them. This technique is primarily based on the diffraction angle on the particle radius. Smaller particles cause additional intense scattering at large angles compared to bigger particles [140].

A sophisticated microscopic technique, Atomic Force Microscopy is used to picture the particle's initial unchanged shape and surface characteristics. Atomic Force Microscopy

measures the force acting between the sample surface and the tip of the probe, when the probe is held close to the sample, resulting in a spatial resolution of up to 0.01 nm for imaging [19]. It is sufficient to prepare specimens for biological compounds by putting a drop of sample dispersion or solution on a washed mica substratum or microscope slide. The benefits of this technique are the simplicity of sample preparing, as there is no need for vacuum during the procedure and the sample must not be conducive [141, 142].

In a study, Dingler used Electron microscopy and Atomic force microscopy to investigate cetyl palmitate solid lipid nanoparticles (stabilized by polyglycerol methyl glucose distearate, TegoCare ® 450) [143, 144]. Both techniques indicate an almost spherical particle shape. Westesen recorded different SLN shapes such as platelet or cubic patterns for SLN, composed of high purity lipidic materials like free fatty acids, triglycerides [55, 145].

Measurement of the zeta potential is crucial for estimating the colloidal dispersion storage stability. The physical stability of the optimized distributed SLN generally exceeds 12 months. Overall, particle aggregation is a smaller amount that can happen to owe to electrical repulsion for the particles which have high zeta potential. However, it cannot be applied to systems that contain steric stabilizers, as the adsorption of steric stabilizers will reduce the zeta potential owing to the shift in the particle's shear plane [19, 146].

8.2.Crystallinity measurement, lipidic material modification, and evaluation of another colloidal structure including time scale of distribution procedures:

Analysis of particle size is crucial for characterizing the quality of SLN. Special consideratio n must be given to characterizing the degree of lipid crystallinity and lipidic material modification, as these parameters are heavily correlated with release rate and drug incorporation [135].

X-ray scattering and Differential scanning calorimetry are used to study lipid status. Differential scanning calorimetry utilizes the fact that different lipid modification possess different melting enthalpies and melting points. Using X-ray scattering, the length of the lipid lattice’s long and short spacing can be assessed. Synchrotron irradiation can solve sensitivity issues and measure the standard X-ray sources for a long time [55].

Rheometry study helps characterize SLN dispersion viscoelastic characteristics. Brookfield Viscometer tool can perform it using an appropriate spindle number. Mainly, the viscosity

relies on the lipidic material dispersed. Newtonian flow becomes non-Newtonian with increasing lipid content [19, 147]. Lippacher's research showed that the solid lipid nanoparticles dispersion has greater elastic property than similar lipid content emulsions [113].

Raman and Infrared qualitative analysis are useful instruments for researching lipids' structural characteristics. They have yet to explore their ability to characterize SLN dispersions [148].

8.3.Incorporated drug determination :

The amount of drug incorporated in the formulation of SLN affects the properties of drug release. The amount of drug contained per unit weight of nanoparticles is determined after the lipidic materials and free drugs are separated from the liquid medium. This separation can be accomplished by centrifugation filtration, ultracentrifugation. Standard analytical techniques such as spectroflurophotometry, spectrophotometer, liquid scintillation counting or high-performance liquid chromatography can be used to test the drug [128, 149, 150].

8.4.*In-vitro* drug release :

8.4.1. Dialysis tubing:

The release of drugs *in-vitro* is performed by a dialysis tube. The SLN dispersion is put in a pre-washed, hermetically sealable dialysis tube. The dialysis tube is dialyzed at room temperature against an appropriate dissolution medium. At appropriate time intervals, the samples are removed from the medium, centrifuged and analyzed for the drug content using an appropriate analytical technique [128, 149, 150].

8.4.2. Reverse dialysis method:

Several tiny dialysis bags comprising 1 ml of dissolution medium are put in the solid lipid nanoparticle dispersion in the reverse dialysis method. Then the nanoparticles are moved into the medium. At appropriate periods, the samples are removed from the medium, filtered and evaluated for drug content using an analytical technique [128, 149].

8.4.3. Franz diffusion cell:

The solid lipid nanoparticle dispersion is put in a Franz diffusion cell's donor chamber equipped with a cellophane membrane. Then, at room temperature, the dispersion of SLN is dialyzed against a suitable medium. The samples are withdrawn from the medium at a time intervals and assessed using an analytical method for drug content. Maintaining the sink condition is necessary [149].

9. PROBLEMS ASSOCIATED IN SLN PREPARATION AND PERFORMANCE:

There are some constraints to these carrier systems. These constraints include drug degradation caused by high pressure, the small ability for drug loading, the coexistence of various lipid modification and various colloidal species, the distribution kinetics.

9.1.Drug degradation caused by high pressure:

Free radical is formed due to high pressure and resulting in a reduction in polymers ' molecular weight. For the process of polymer degradation, cavitations are less essential. Without significant improvements in homogenization efficiency, cavitations can be suppressed by applying reverse pressure [115, 151].

The most significant parameters to predict drug degradation are the overall molecular structure and molecular weight. Compounds of long-chain molecules and high molecular weight are more susceptible than drugs of spherical molecules of low molecular weight [152].

9.2.Considerations of lipid crystallization and inclusion of drugs:

Lipid crystallization is a key parameter for SLN carriers ' efficiency. For the debate of drug incorporation into the solid lipid nanoparticles, the following four main elements should be regarded.

- Lipid nanodispersions shape
- Gelation phenomena
- The existence of super-cooled melts
- Presence of several lipid modifications

9.2.1. Lipid nanodispersions shape:

Lipid nanoparticles shape may vary substantially from a sphere. Compared to the sphere form, lipids favor crystallizing in the platelet. Platelet shapes compared to spheres have much bigger surface regions. For stability, greater quantities of surfactants are required. A much larger quantity of the drugs will be located directly on the particle surface [153].

9.2.2. Gelation phenomena:

Gelation phenomena portray the conversion into a viscous gel of low-viscosity SLN dispersion. Siekmann researcher proposed that the formation of gel is associated with procedures of crystallization. Odd surfaces cause the lipid crystals to crystallize or alter. This process is associated with a rise in the surface of the particles owing to preferred platelet formation (in b-modification). The new surfaces cannot be sufficiently covered by surfactant molecules longer. Particle aggregation is, therefore, noted [154]. Gelation can be avoided or retarded by adding co-emulsifying surfactants (e.g. glycocholate) with high mobility at optimum temperature range [155].

9.2.3. The existence of supercooled melts:

The primary cause of supercooled melts being formed is the size reliance of crystallization processes. Crystallization needs to begin with a critical number of nuclei of crystallization. Small droplets are less probable to form this critical number of molecules. Therefore, with reducing droplet size, the tendency to form supercooled melts rises. The particle size should be tracked during the entire process [148, 156].

9.2.4. Presence of several lipid modifications:

Lipid modification determines the performance of the SLN system. This parameter causes the inclusion of drugs and the release of drugs. Lipid modification involves quality improvement, reduced density and eventually, increased the ability to integrate guest molecules (e.g. drugs) [153, 157].

9.3.The coexistence of different colloidal species:

Different colloidal species may cause the formulation to degrade. To clarify the structure of colloidal lipid dispersions, only detecting the existence of many colloidal species is not

adequate. Therefore, the kinetics of degradation is determined in the aqueous medium by the drug's chemical reactivity and drug concentration. Viscosity reduces the diffusion coefficient of the drug within the carrier by raising the matrix and thus stabilizing the formulation [27, 158].

10. DIFFERENT STUDY FINDINGS ON SLN FORMULATIONS FOR BREAST CANCER REPORTED BY VARIOUS RESEARCHERS:

Solid lipid nanoparticles have been recognized to be helpful in breast cancer treatment. In this chapter, we concentrated on numerous research results on SLN formulations for breast cancer reported by multiple researchers to demonstrate the potential and application of solid lipid nanoparticles as an antitumor drug carrier. Table 4 shows the examples described in this chapter.

Table No. 4: Different study findings of SLN formulations for breast cancer reported by various researchers

Sl.No	Drug	Additives	Methods	Size	Outcomes	Ref.
1.	Docetaxel	Soybean lecithin, Trimyristin	High-pressure homogenization method	37.17±0.35 nm	• High docetaxel encapsulation of in the solid lipid nanoparticles. • Reduced the myelosuppression toxicity to bone marrow cells.	[159]
2.	Pamityl prodrug analog of Capecitabine	Poloxamer 407	High-pressure homogenization method	~700 nm	• A higher dosage tolerated. • Improve effectiveness. • To create the sustained release capacity.	[160]
3.	Docetaxel and curcumin(combination therapy)	Compritol 888 ATO ®,GMS, Poloxamer 188, PEG–SA	Hot melt emulsification method	247.5±3.40nm	• Improved the efficacy and pharmacokinetic profile of docetaxel. • Reduced the toxicity in the heart and kidney.	[161-163]
4.	Tamoxifen citrate	GMS, Poloxamer 188, Stearic acid, Tween 80, Sodium lauryl sulfate	Solvent injection method	130.40±9.45, 243.80±12.33nm	• Enhanced oral bioavailability.	[130]

5.	Curcumin	Stearic acid, Lecithin, Tween® 80,	Emulsification and low-temperature solidification method	40nm	• Improved breast cancer therapeutic effectiveness. • Stronger cytotoxicity against SKBR3 cells.	[164]
6.	Doxorubicin and α-Tocopherol succinate(combination therapy)	TEA, Glyceryl behenate, Monooleate of sorbitan ethoxylated(super-refined polysorbate 80™; Tween 80™)	The hot melting homogenization method	298±1 to 79±1 nm	• Improved encapsulation of doxorubicin in SLN. • Suppressed tumor growth.	[165]
7.	Docetaxel	DOPE-PEG-2000, Egg PC, Tween 80, Poloxamer 188 Trimyristin, Trilaurin, Tristearin, Tripalmitin	Modified emulsion/solvent evaporation method	150.7±14.5 to 178.4±2.3nm	• Higher cytotoxicity against cancer cells. • More effectiveness.	[166]
8.	Raloxifene	Precirol ATO 5, Compritol 888 ATO, Gelucire 43/01, Poloxamer 407, Poloxamer 188, Tween 80, Sodium taurocholate, DMBA	Modified micro-emulsion method	288.0±28.5nm	• Improved effectiveness and chemopreventive activity. • Enhanced oral bioavailability.	[167]
9.	Camptothecin	Palmitic acid, GMS, Poloxamer 188	High-shear homogenization and ultrasonication techniques	112.2 ±8.6 nm	• Enhanced oral bioavailability and reduced intestinal side effects. • Great cytotoxicity of various cancer cell lines.	[168]
10.	Tamoxifen	stearic acid, Tween 80	Hot homogenization technique	277.4 to 298.6nm	• Good physical stability with small particle size. • Higher electiveness.	[169]

11.	Doxorubicin and Sclareol(combination therapy)	oleic acid, TEA, Glyceryl behenate and monooleate of sorbitan ethoxylated (Super Refined Polysorbate 80™; Tween 80™)	The hot melting homogenization method	128.0±10 to 219.0±45 nm	• Showed controlled doxorubicin release at pH 7.4 with enhanced drug release at lower pH. • More efficient potential.	[170]
12.	Doxorubicin	Glyceryl caprate(Capmul®MCM C10),Polyethylene glycol660hydroxystearate(Solutol®HS15),Curdlan	Solvent emulsification-diffusion method	206 to 306 nm	• Increased release of drug at pH 5 and pH 7.4. • More efficacies.	[138]
13.	Paclitaxel	Pluronic 85, GMS, Hyaluronic acid	Modified hot homogenization technique	92.5 ±2.7 to 160.3 ±5.4 nm	• Greater sustained drug release profiles. • Exhibited higher tumor drug concentration.	[32]
14.	Methotrexate	Pluronic F68, Phospholipon 90NG, Stearyl amine, L-fucose, Tween-80	Hot micro-emulsion method	174.51 ± 5.1nm	• Maximum bioavailability and tumor targeting efficiency.	[171]
15.	Paclitaxel	Trimyristin, Egg L-α-PC DSPE–PEG-2000	Sonication method	210.5±86.3 nm	• Enhanced anticancer activity in MCF7/ADR cell lines.	[172,173]
16.	Paclitaxel and Verapamil(combination therapy)	Stearic acid, Poloxamer 188, Soy lecithin	Modified hot Sonication method	287.2±10.2 to 325.9±8.5nm	• Higher cytotoxic activity and cellular uptake in MCF-7 cells. • Great potential in breast cancer therapy.	[174]

Abbreviations: GMS: Glycerol monostearate; PEG-SA: Polyoxyethylene (40) stearate; TEA: Triethanolamine; DOPE-PEG-2000: 1, 2-dioleoyl-Sn-glycero-3-phosphoethanolamine-N-[amino (polyethylene glycol)-2000]; PC: Phosphatidylcholine; DMBA: Dimethyl benzanthracene; DSPE: 1, 2-distearoyl-sn-glycero-3-phosphoethanolamine.

11. DISCUSSION AND FUTURE PERSPECTIVES:

In this job, we assessed the features, benefits, and disadvantages of the SLN as well as the recent work linked to the implementation of SLNs to enhance the real effectiveness of drugs for breast cancer.

As careful throughout this job, solid lipid nanoparticles are an innovative drug carrier that enables many of the difficulties associated with traditional drug carriers to be overcome. However, it is also worth noting that these nanoparticles themselves have certain drawbacks or issues which demonstrate the need to optimize some of their features.

Overall, many drugs have been integrated with beneficial outcomes in SLNs, [175, 176]as well as tumors that have been verified for their action [172, 177]. These are the primary supports for advancement in tumor treatment studies on the use of SLNs.

Therefore, as a future view, a study line centered on the growth of surface-modified SLN could be of excellent importance in the specific and effective delivery of different types of tumors, involving separate resistance mechanisms. To find individualized and extremely efficient therapies, this could be very helpful.

12. CONCLUSION:

It is apparent from this review that the different study groups are increasingly drawn to solid lipid nanoparticles (SLN) owing to their distinctive characteristics and many benefits over traditional dosage forms. However, as we stated in this paper, a stronger knowledge of the formation, nanostructure, and characterization of solid lipid nanoparticles would result in the rational design of customized SLNs for the therapy of breast cancer.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Wicki A, Witzigmann D, Balasubramanian V, Huwyler J. Nanomedicine in cancer therapy: challenges, opportunities, and clinical applications. J Control Release. 2015; 200:138–157. Doi: 10.1016/j.jconrel.2014.12.030.

[2] Madani SY, Naderi N, Dissanayake O, Tan A, Seifalian AM. A new era of cancer treatment: carbon nanotubes as drug delivery tools. Int J Nanomedicine. 2011; 6:2963–2979. Doi: 10.2147/IJN.S16923.

[3] Mei L, Zhang Z, Zhao L, Huang L, Yang XL, Tang J, et al. Pharmaceutical Nanotechnology for Oral Delivery of Anticancer Drugs. Adv Drug Deliv. 2012; 1-50.Doi: 10.1016/j.addr.2012.11.005.

[4] Feng SS, Zhao I, Iang J. Nanomedicine for oral chemotherapy. Nanomedicine. 2011; 6(3):407-410.Doi: 10.2217/nnm.11.7.

[5] World Health Organization. Cancer statistics report worldwide. 24/8/2019.Available from: https://www.who.int/news-room/fact-sheets/detail/cancer

[6] American cancer society. Cancer Facts Figures. 24/8/2019. Available from: https://www .cancer.org/content/dam/cancer-org/research/cancer-facts-and statistics/annual-cancer-facts-and-figures/2018/cancer-facts and-figures-2018.pdf

[7] Girish C, Vijayalakshmi P, Ramesh M, Chandu BR, Sreekanth N. A review on breast cancer. Int J Pharm Bio Sci. 2014; 4(2):47–54. https://www.ijpbs.com/ijpbsadmin/upload/ijpbs_5376cc6913114.pdf.

[8] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomized trials. Lancet. 2005; 365(9472):1687-1717. Doi: 10.1016/S0140-6736(05)66544-0.

[9] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics,2014. CA Cancer J Clin. 2014; 64(1):9–29. Doi: 10.3322/caac.21208.

[10] World Health Organization. Breast cancer statistics report worldwide. 24/8/2019. Available from:https://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en/

[11] Linares MJ, Moretton MA, Bernabeu E, Chiappetta DA, Cuestas ML. Thinking small, doing big: Current success and future trends in drug delivery systems for improving cancer therapy with special focus on liver cancer. Mater Sci Eng C Mater Biol Appl. 2019; 95:328–341. Doi: 10.1016/j.msec.2018.11.001.

[12] Fakhar D, Waqar A, Izhar U, Omer SQ, Omer M, Shumaila S. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. Int J Nanomedicine. 2017; 12:7291–7309. Doi: 10.2147/IJN.S146315.

[13] Pramod VP, Tulsidas GS. Nanotechnological contribution to drug delivery system: A reappraisal. J Biomater Nanobiotechnol. 2014; 5:194–199.http://dx.doi.org/10.4236/jbnb.2014.53023.

[14] Kumar S, Dilbaghi N, Saharan R, Bhanjana G. Nanotechnology as emerging tool for enhancing solubility of poorly water-soluble drugs. Bio-Nano Sci. 2012; 2:227-250. Doi: 10.1007/s12668-012-0060-7.

[15] Muller RH, Shegokar R, Keck CM. 20 years of lipid nanoparticles (SLN & NLC): Present state of development & industrial applications. Curr Drug Discov Technol. 2011; 8(3):207–227.

[16] Mehnert W, Mäder K. Solid lipid nanoparticles: Production, characterization, and applications. Adv Drug Deliv Rev. 2001; 47(2-3): 165–196. https://doi.org/10.1016/S0169-409X(01)00105-3.

[17] Müller RH, Maassen S, Weyhers H, Mehnert W. Phagozytic uptake and cytotoxicity of solid lipid nanoparticles (SLN) sterically stabilized with poloxamine 908 and poloxamer 407. J Drug Target. 1996; 4(3): 161–170. Doi: 10.3109/10611869609015973.

[18] Kumar N, Kumar R. Nanotechnology and Nanomaterials in the Treatment of Life-threatening Diseases. 1st ed. Waltham, MA, USA: William Andrew; 2013.

[19] Ramteke KH, Joshi SA, Dhole SN. Solid Lipid Nanoparticle: A Review. IOSR J Pharm. 2012; 2(6):34-44. http://www.iosrphr.org/papers/v2i6/Part_1/F0263444.pdf.

[20] Geszke MM, Moritz M. Solid lipid nanoparticles as attractive drug vehicles: Composition, properties and therapeutic strategies. Mater Sci Eng C Mater Biol Appl. 2016; 68: 982–994. Doi: 10.1016/j.msec.2016.05.119.

[21] Souto EB. SLN and NLC for topical delivery of antifungals. Ph.D. Thesis. Berlin: Free University of Berlin; 2005.

[22] Souto EB, Müller R. Application of lipid nanoparticles (SLN and NLC) in the food industry. J Food Technol. 2006; 4(1): 90–95. http://medwelljournals.com/abstract/?doi=jftech.2006.90.95.

[23] Souto EB, Wissing SA, Barbosa CM, Müller RH. Evaluation of the physical stability of SLN and NLC before and after incorporation into hydrogel formulations. Eur J Pharm Biopharm. 2004; 58: 83–90. Doi: 10.1016/j.ejpb.2004.02.015.

[24] Souto EB, Müller RH. Lipid nanoparticles (solid lipid nanoparticles and nanostructured lipid carriers) for cosmetic, dermal, and transdermal applications. In: Thasu D, Deleers M, Pathak Y, editors. Nanoparticulate drug delivery systems, Boca Raton, US: CRC Press Inc; 2007, p. 213-233. Doi: 10.1201/9781420008449.ch14.

[25] Souto EB, Müller RH. Lipid nanoparticles: effect on bioavailability and pharmacokinetic changes. In: Schäfer KM, editor. Drug Delivery, New York: Springer-Verlag Berlin Heidelberg Inc; 2010, p. 115–141. Doi: 10.1007/978-3-642-00477-3_4.

[26] Rabinarayan P, Padilama. Production of Solid Lipid Nanoparticles-Drug Loading and Release Mechanism. J Chem Pharm Res. 2010; 2(1): 211-227.Doi: 80813a6f879d451a9fe5ccf6367f7a7ca531b262.

[27] Poovi G, Damodharan N. Lipid nanoparticles: Different preparation techniques, characterization, hurdles, and strategies for the production of solid lipid nanoparticles and nanostructured lipid carriers for oral drug delivery. Sustain Chem Pharm. 2017; 6:37–56. http://dx.doi.org/10.1016/j.scp.2017.07.002.

[28] Moon JH, Moxley JW, Zhang P, Cui H. Nanoparticle approaches to combating drug resistance. Future Med Chem. 2015; 7(12): 1503–1510. Doi: 10.4155/fmc.15.82.

[29] Sun T, Zhang YS, Pang B, Hyun DC, Yang M, Xia Y. Engineered nanoparticles for drug delivery in cancer therapy. Angew. Chem. Int. Ed. Engl. 2014; 53:12320–12364.https://doi.org/10.1002/anie.201403036.

[30] Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC. Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology. Adv Drug Deliv Rev. 2014; 66: 2–25. Doi: 10.1016/j.addr.2013.11.009.

[31] Bayón-Cordero L, Alkorta I, Arana L. Application of Solid Lipid Nanoparticles to Improve the Efficiency of Anticancer Drugs. Nanomaterials. 2019; 9: 1-20. Doi: 10.3390/nano9030474.

[32] Wang F, Li L, Liu B, Chen Z, Li C. Hyaluronic acid decorated pluronic P85 solid lipid nanoparticles as a potential carrier to overcome multidrug resistance in cervical and breast cancer. Biomed Pharmacother. 2017; 86: 595–604.Doi: 10.1016/j.biopha.2016.12.041.

[33] Maryam BZ, Akram P. Effect of surfactant concentration on the particle size, stability and potential zeta of beta carotene nano lipid carrier. Int J Curr Microbiol App Sci. 2015; 4(9):924-932. Doi: 80b15fb4db9e21a42a73ee270ea414f37f2502b3.

[34] Westesen K, Bunjes H. Do nanoparticles prepared from lipids solid at room temperature always possess a solid lipid matrix?. Int J Pharm. 1995; 115(1): 129–131.https://doi.org/10.1016/0378-5173 (94)00347-8.

[35] Westesen K, Bunjes H, Koch MHJ. Physicochemical characterization of lipid nanoparticles and evaluation of their drug loading capacity and sustained release potential. J Control Release. 1997; 48(2-3):223–236.https://doi.org/10.1016/S0168-3659(97)00046-1.

[36] Bunjes H, Westesen K, Koch MHJ. Crystallization tendency and polymorphic transitions in triglyceride nanoparticles. Int J Pharm. 1996; 129(1-2):159–173.https://doi.org/10.1016/0378-5173 (95)04286-5.

[37] Ahlin P, Kristl J, Smid KJ. Optimization of procedure parameters and physical stability of solid lipid nanoparticles in dispersions. Acta Pharm. 1998; 48(4): 257–267.https://eurekamag.com/research/011/094/011094882.php.

[38] Johnson W, Cosmetic Ingredient Review Experts Panel. Final report on the safety assessment of trilaurin, triarachidin, tribehenin, tricaprin, tricaprylin, trierucin, triheptanoin, triheptylundecanoin, triisononanoin, triisopalmitin, triisostearin, trilinolein, trimyristin, trioctanoin, triolein, tripalmitin, tripalmitolein, triricinolein, tristearin, triundecanoin, glyceryl triacetyl hydroxy stearate, glyceryl triacetyl ricinoleate, and glyceryl stearate diacetate.Int j Toxicol. 2001; 20:61-94.https://www.ncbi.nlm.nih.gov/pubmed/11800053.

[39] Mühlen 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): 149–155. https://doi.org/10.1016/S0939-6411(97)00150-1.

[40] Domb AJ. Long-acting injectable oxytetracycline-liposphere formulation. Int J Pharm. 1995; 124(2):271–278. https://doi.org/10.1016/0378-5173(95)00098-4.

[41] PubChem. Property of Trilaurin. 25/8/19. Available from:https://pubchem.ncbi.nlm.nih.gov/compound/Trilaurin

[42] Weast RC. CRC Handbook of Chemistry and Physics. 60th ed. Boca Raton, FL: CRC Press; 1980.

[43] Lewis RJ, Sr. Hawley's Condensed Chemical Dictionary. 13th ed. New York: John Wiley & Sons; 1997, p. 1047.
[44] Siekmann B, Westesen K. Melt-homogenized solid lipid nanoparticles stabilized by the nonionic surfactant tyloxapol.I.preparation and particle size determination. Pharm Pharmacol Lett. 1994; 3(5):194-197.
[45] Siekmann B, Westesen K. Investigations on solid lipid nanoparticles prepared by precipitation in o/w emulsions. Eur J Pharm Biopharm. 1996; 43:104-109.
[46] Charbonnet GH, Singleton WS.Thermal properties of fats and oils VI. Heat capacity, heats of fusion and transition, and entropy of trilaurin, trimyristin, tripalmitin, and tristearin. J Am Oil Chem Soc. 1947; 24(5):140-142. https://doi.org/10.1007/BF02643296.
[47] Chemicalland21. Property of Tricaprin. 25/8/2019. Available from:http://www.chemicalland21.com/lifescience/foco/TRICAPRIN.htm
[48] Cavalli R, Peira E, Caputo O, Gasco MR. Solid lipid nanoparticles as carriers of hydrocortisone and progesterone complexes with b-cyclodextrin. Int J Pharm. 1999; 182(1):59–69. Doi: 10.1016/s0378-5173(99)00066-6.
[49] PubChem. Property of Glyceryl monostearate. 25/8/2019. Available from:https://pubchem.ncbi.nlm.nih.gov/compound/Glycerylmonostearate
[50] Muller RH, Olbrich C. Solid lipid nanoparticles: phagocytic uptake, in vitro cytotoxicity and in vitro biodegradation, 1st communication. Pharm Ind. 1999; 61: 462–467.
[51] Freitas C, Müller RH. Correlation between long-term stability of solid lipid nanoparticles (SLN™) and crystallinity of the lipid phase. Eur J Pharm Biopharm. 1999; 47(2): 125–132. Doi: 10.1016/S0939-6411(98)00074-5.
[52] Müller RH, Maaβen S, Weyhers H, Specht F, Lucks JS. Cytotoxicity of magnetite-loaded polylactide, polylactide/glycolide particles, and solid lipid nanoparticles. Int J Pharm. 1996; 138(1): 85–94. https://doi.org/10.1016/0378-5173(96)04539-5.
[53] Aburahma MH, Badr-Eldin SM. Compritol 888 ATO: a multifunctional lipid excipient in drug delivery systems and nanopharmaceuticals. Expert Opin Drug Deliv. 2014; 11(12):1865-1883. Doi: 10.1517/17425247.2014.935335.
[54] PubChem. Property of Precirol. 25/8/2019. Available from:https://pubchem.ncbi.nlm.nih.gov/compound/Precirol
[55] Westesen K, Siekmann B, Koch MHJ. Investigations on the physical state of lipid nanoparticles by synchrotron radiation X-ray diffraction. Int J Pharm. 1993; 93(1-3):189–199. https://doi.org/10.1016/0378-5173(93)90177-H.
[56] Pharma Compass. Details on Witepsol Grades. 25/8/2019. Available from:https://www.pharmacompass.com/pAssets/pdf/edqm/application/witepsol.pdf
[57] Abdelbary G, Fahmy RH. Diazepam-loaded solid lipid nanoparticles: design and characterization. AAPS Pharm Sci Tech. 2009; 10(1):211-219.Doi: 10.1208/s12249-009-9197-2.
[58] Cavalli R, Gasco MR, Morel S. Behaviour of timolol incorporated in lipospheres in the presence of a series of phosphate esters. STP Pharm Sci. 1992; 6:514–518.
[59] Morel S, Ugazio E, Cavalli R, Gasco MR. Thymopentin in solid lipid nanoparticles. Int J Pharm. 1996; 132(1-2): 259–261. https://doi.org/10.1016/0378-5173(95)04388-8.
[60] Yang S, Zhu J, Lu Y, Liang B, Yang C. Body distribution of camptothecin solid lipid nanoparticles after oral administration. Pharm Res. 1999; 16(5): 751–757.Doi: 10.1023/a: 1018888927852.
[61] Haynes WM. CRC Handbook of Chemistry and Physics. 95th ed. Boca Raton, FL: CRC Press LLC; 2014-2015, p. 3-488.
[62] Gasco MR, Cavalli R, Carlotti ME. Timolol in lipospheres. Pharmazie. 1992; 47(2):119.
[63] Haynes WM. CRC Handbook of Chemistry and Physics. 95th ed. Boca Raton, FL: CRC Press LLC; 2014-2015, p. 3-294.
[64] Lewis RJ, Sr. Hawley's Condensed Chemical Dictionary. 14th ed. New York: John Wiley & Sons; 2001, p. 203.
[65] Lide DR. CRC Handbook of Chemistry and Physics. 86th ed.Boca Raton, FL: CRC Press; 2005-2006, p. 3-134.

[66] Cavalli R, Caputo O, Carlotti ME, Trotta M, Scarnecchia C, Gasco MR. Sterilization and freeze-drying of drug-free and drug-loaded solid lipid nanoparticles. Int J Pharm. 1997; 148(1):47–54. https://doi.org/10.1016/S0378-5173(96)04822-3.
[67] O'Neil MJ.The Merck Index: An Encyclopaedia of Chemicals, Drugs, and Biological 14 thed.Whitehouse Station, NJ: Merck and Co; 2006, p. 169.
[68] Siddiqui A, Alayoubi A, El-Malah Y, Nazzal S. Modeling the effect of sonication parameters on size and dispersion temperature of solid lipid nanoparticles (SLNs) by response surface methodology (RSM). Pharm Dev Technol. 2013; 19(3):342-346. Doi: 10.3109/10837450.2013.784336.
[69] Siddiqui A, Gupta V, Liu YY, Nazzal S. Doxorubicin, and MBO-as GCS oligonucleotide loaded lipid nanoparticles overcome multidrug resistance in adriamycin resistant ovarian cancer cells (NCI/ADR-RES). Int J Pharm. 2012; 431(1-2):222-229. doi: 10.1016/j.ijpharm.2012.04.050.
[70] Sanna V, Caria G, Mariani A. Effect of lipid nanoparticles containing fatty alcohols having different chain lengths on the ex vivo skin permeability of Econazole nitrate. Powder Technol. 2010; 201(1):32-36. Doi: 10.1016/j.powtec.2010.02.035.
[71] Lide DR, Milne GWA. Handbook of Data on Organic Compounds. Volume I. 3rd ed. Boca Raton, FL: CRC Press; 1994, p.V4:3687.
[72] Siddiqui A, Alayoubi A, Nazzal S. The effect of emulsifying wax on the physical properties of CTAB-based solid lipid nanoparticles (SLN). Pharm Dev Technol. 2013; 19(1):125-128. Doi: 10.3109/10837450.2012.751401.
[73] Lide DR, Milne GWA. Handbook of Data on Organic Compounds. Volume I. 3rd ed. Boca Raton, FL: CRC Press; 1994, p. V3:3026.
[74] O'Neil MJ. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals.13th ed. Whitehou se Station, NJ: Merck and Co; 2001, p. 347.
[75] Haynes WM. CRC Handbook of Chemistry and Physics. 95th ed. Boca Raton, FL:CRC Press LLC; 2014 -2015, p. 3-498.
[76] O'Neil MJ. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals.15th ed.Cambridge , UK: Royal Society of Chemistry; 2013, p. 621.
[77] Haynes WM. CRC Handbook of Chemistry and Physics. 95th ed. Boca Raton, FL:
CRC Press LLC; 2014-2015, p. 3-238.
[78] Kheradmandnia S, Vasheghani-Farahani E, Nosrati M, Atyabi F. Preparation and characterization of ketoprofen-loaded solid lipid nanoparticles made from beeswax and carnauba wax. Nanomedicine. 2010; 6(6): 753-759. Doi: 10.1016/j.nano.2010.06.003.
[79] Brown RH. Beeswax. 2nd ed. Burrow Bridge, Somerset, UK: Bee Books New and Old; 1981.
[80] Raymond CR, Paul JS, Walter GC, Mariam EF. Handbook of pharmaceutical excipients. 7th ed. London, PHL: Pharmaceutical press, American pharmacists association; 2012, p.893-894.
[81] Steinle JV. Carnauba wax: An expedition to its source. Ind Eng Chem. 1936; 28 (9): 1004–1008.https://doi.org/10.1021/ie50321a003.
[82] Raymond CR, Paul JS, Walter GC, Mariam EF. Handbook of pharmaceutical excipients.7th ed. London, PHL: Pharmaceutical press, American pharmacists association; 2012, p.886-887.
[83] Hitesh RP, Rakesh PP, Patel MM. Poloxamers: A pharmaceutical excipients with therapeutic behaviors. Int J Pharm Tech Res. 2009; 1(2):299-303.http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.619.7361&rep=rep1&type=pdf.
[84] Raymond CR, Paul JS, Walter GC, Mariam EF. Handbook of pharmaceutical excipients. 7th ed. London, PHL: Pharmaceutical press, American pharmacists association; 2012, p.573-577.
[85] Almeida AJ, Runge S, Müller RH. Peptide-loaded solid lipid nanoparticles (SLN): influence of production parameters. Int J Pharm. 1997; 149(2): 255–265.https://doi.org/10.1016/S0378-5173(97)04885-0.
[86] Alvarez-Lorenzo C, Rey-Rico A, Sosnik A, Taboada P, Concheiro A. Poloxamine-based nanomaterials for drug delivery. Front Biosci (Elite Ed). 2010; 2: 424-440.Doi: 10.2741/e102 .
[87] Cavalli R, Caputo OM, Marengo E, Pattarino F, Gasco MR. The effect of the components of microemulsions on both size and crystalline structure of solid lipid nanoparticles (SLN) containing a series of model molecules. Pharmazie. 1998; 53: 392–396.

[88] Cavalli R, Marengo E, Rodriguez L, Gasco MR. Effect of some experimental factors on the production process of solid lipid nanoparticles. Eur J Pharm Biopharm. 1996; 43:110-115.
[89] Raymond CR, Paul JS, Walter GC, Mariam EF. Handbook of pharmaceutical excipients. 7th ed. London, PHL: Pharmaceutical press, American pharmacists association; 2012, p.620-624.
[90] PubChem. Property of sodium cholate. 28/8/2019. Available from:https://pubchem.ncbi.nlm.nih.gov/compound/sodium-cholate
[91] PubChem. Property of sodium glycocholate. 28/8/2019. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/sodium-glycocholate
[92] Bocca C, Caputo O, Cavalli R, Gabriel L, Miglietta A, Gasco MR. Phagocytic uptake of fluorescent stealth and non-stealth solid lipid nanoparticles. Int J Pharm. 1998; 175(2): 185–193. https://doi.org/10.1016/S0378-5173(98)00282-8.
[93] Cavalli R, Bocca C, Miglietta A, Caputo O, Gasco MR. Albumin adsorption on stealth and non-stealth solid lipid nanoparticles. STP Pharma Sci. 1999:183–189.
[94] PubChem. Property of sodium taurocholate. 28/8/2019. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/sodium-taurocholate
[95] Paolicelli P, Cerreto F, Cesa S, Feeney M, Corrente F, Marianecci C, et al. Influence of the formulation components on the properties of the system SLN-dextran hydrogel for the modified release of drugs. J Microencapsul. 2009; 26(4): 355-364. Doi: 10.1080/02652040802372899.
[96] Gramdorf S, Kumpugdee-Vollrath M, Bilek H, Perlich J. Influence of emulsifiers on the crystallization of Solid Lipid Nanoparticles (SLN). Annual Report HASYLAB, DESY 2010. 25/8/2019. http://photon-science.desy.de/annual_report/files/2009/2009622.pdf
[97] Cosmetic Ingredient Review Expert Panel. Final report on the safety assessment of sodium laureth sulfate and ammonium laureth sulfate. J Am Coll Toxicol.1983; 2 (5): 127-181. https://doi.org/10.3109%2F10915818309142005.
[98] Raymond CR, Paul JS, Walter GC, Mariam EF. Handbook of pharmaceutical excipients. 7th ed. London, PHL: Pharmaceutical press, American pharmacists association; 2012 p.744-747.
[99] PubChem. Property of Cetrimonium Bromide. 25/8/2019. Available from: https://pubchem.ncbi.nlm.nih.gov//#query=Cetrimoniumbromide
[100] Raymond CR, Paul JS, Walter GC, Mariam EF. Handbook of pharmaceutical excipients.7th ed. London, PHL: Pharmaceutical press, American pharmacists association; 2012, p.163-165.
[101] Xue HY, Wong HL. Tailoring nanostructured solid-lipid carriers for time-controlled intracellular siRNA kinetics to sustain RNAi-mediated chemosensitization. Biomaterials. 2011; 32(10):2662-2672. Doi: 10.1016/j.biomaterials.2010.12.029.
[102] Simberg D, Weisman S, Talmon Y, Barenholz Y. DOTAP (and other cationic lipids): chemistry, biophysics, and transfection.Crit Rev Ther Drug Carrier Syst. 2004;21(4):257-317. Doi: 10.1615/CritRevTherDrugCarrierSyst.v21.i4.10.
[103] Westesen K, Siekmann B. Investigation of the gel formation of phospholipid-stabilized solid lipid nanoparticles. Int J Pharm. 1997; 151(1):35–45.https://doi.org/10.1016/S0378-5173(97)04890-4.
[104] Schneider M. Achieving purer lecithin. Drug cosmet Ind. 1992; 150(2):54-66.
[105] Raymond CR, Paul JS, Walter GC, Mariam EF. Handbook of pharmaceutical excipients. 7th ed. London, PHL: Pharmaceutical press, American Pharmacists Association; 2012, p. 437-439.
[106] Raymond CR, Paul JS, Walter GC, Mariam EF. Handbook of pharmaceutical excipients. 7th ed. London, PHL: Pharmaceutical press, American pharmacists association; 2012, p.565-569.
[107] Patel BD, Modi RV, Thakkar NA, Patel AA, Thakkar PH. Development and characterization of solid lipid nanoparticles for enhancement of oral bioavailability of Raloxifene. J Pharm Bioall Sci. 2012; 4:14-6. Doi: 10.4103/0975-7406.94121.
[108] Raymond CR, Paul JS, Walter GC, Mariam EF. Handbook of pharmaceutical excipients. 7th ed. London, PHL: Pharmaceutical press, American pharmacists association; 2012, p.585-590.
[109] Bhalekar MR, Pokharkar V, Madgulkar A, Patil N, Patil N. Preparation and evaluation of miconazole nitrate-loaded solid lipid nanoparticles for topical delivery. AAPS Pharm Sci Tech. 2009; 10(1):289-296. Doi: 10.1208/s12249-009-9199-0.

[110] Lide DR. CRC Handbook of Chemistry and Physics. 88th ed. Boca Raton, FL: CRC Press; 2007-2008, p. 3-444.
[111] O'Neil MJ. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals.14th ed.Whitehouse Station, NJ: Merck and Co; 2006, p. 1350.
[112] Budavari S. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals.12th ed.Whitehouse Station, NJ: Merck and Co; 1996, p. 1490.
[113] Lippacher A, Müller RH, Mäder K. Investigation on the viscoelastic properties of lipid-based colloidal drug carriers. Int J Pharm. 2000; 196(2): 227–230.Doi: 10.1016/S0378-5173(99)00428-7.
[114] Mühlen A, Mehnert W. Drug release and release mechanism of prednisolone loaded solid lipid nanoparticles. Pharmazie. 1998; 53: 552–555.
[115] Lander R, Manger W, Scouloudis M, Ku A, Davis C, Lee A. Gaulin homogenization: a mechanistic study. Biotechnol Prog. 2000; 16(1): 80–85.Doi: 10.1021/bp990135c.
[116] Jahnke S, Müller RH, Benita S.The theory of high-pressure homogenization, In B. Böhm, editor. Emulsions and nanosuspensions for the formulation of poorly soluble drugs. Stuttgart, DE: Medpharm Scientific Publishers Inc; 1998, p. 177–200.
[117] Bunjes H, Siekmann B, Westesen K. Emulsions of supercooled melts- a novel drug delivery system, in Benita S, editor. Submicron Emulsions in Drug Targeting and Delivery. Amsterdam, NL: Harwood Academic Publishers Inc; 1998, p. 175–204.
[118] Gohla SH, Dingler A. Scaling up the feasibility of the production of solid lipid nanoparticles (SLN). Pharmazie. 2001; 56: 61-63.
[119] Schwarz C, Mehnert W, Lucks JS, Müller RH. Solid lipid nanoparticles (SLN) for controlled drug delivery: I. Production, characterization, and sterilization. J Control Rel. 1994; 30: 83-96. https://doi.org/10.1016/0168-3659(94)90047-7.
[120] Swathi MP, Bala P. A review on solid lipid nanoparticles. Int J Pharm Sci Rev Res. 2013; 20 (2): 196–206.
[121] Muhlen A. Feste Lipid-Nanopartikel mit prolongierter ¨ Wirkstoffliberation: Herstellung, Langzeitstabilitat, Charak. Terisierung, Freisetzungsverhalten und mechanismen. Ph.D. Thesis. Berlin: Free University of Berlin; 1996.
[122] Speiser P. Lipidnanopellets als Tragersystem fur Arzneimittel zur peroralen Anwendung. EP 0167825, 1990.
[123] Domb AJ. Lipospheres for controlled delivery of substances. USP 188837, 1993.
[124] Rohan S, Daniel E, Enzo P, Ian H. Lipid Nanoparticles: Production, Characterization and Stability.USA: Springer international publishing; 2015.
[125] Eldem T, Speiser P, Hincal A. Optimization of spray-dried and congealed lipid microparticles and characterization of their surface morphology by scanning electron microscopy. Pharm Res. 1991; 8(1): 47-54. Doi: 10.1023/a:1015874121860.
[126] Pooja D, Tunki L, Kulhari H, Reddy BB, Sistla R. Optimization of solid lipid nanoparticles prepared by a single emulsification-solvent evaporation method. Data Brief. 2015; 6: 15-19.Doi: 10.1016/j.dib.2015.11.038.
[127] Kang KW, Chun MK, Kim O, Subedi RK, Ahn SG, Yoon JH, et al. Doxorubicin-loaded solid lipid nanoparticles to overcome multidrug resistance in cancer therapy. Nanomed- Nanotechnol. 2010; 6(2): 210–213. Doi: 10.1016/j.nano.2009.12.006.
[128] Jain NK. Controlled and Novel Drug Delivery. 1st ed. New Delhi: CBS Publishers and Distributors; 1997, p. 3-28.
[129] Iqbal MA, Md S, Sahni JK, Baboota S, Dang S, Ali J. Nanostructured lipid carriers system: recent advances in drug delivery. J Drug Target. 2012; 20(10):813–830.Doi: 10.3109/1061186X.2012.716845.
[130] Fahima MH, Mohamed N, Ahmed K. In vitro cytotoxicity and bioavailability of solid lipid nanoparticles containing tamoxifen citrate. Pharm Dev Technol. 2014; 19(7): 824–832. Doi: 10.3109/10837450.2013.836218.
[131] Svilenov H, Tzachev C. Solid lipid nanoparticles–a promising drug delivery system. In: Selfalian A, Mel A, Kalaskar DM, editors. Nanomedicine. Manchester, UK: One Central Press Inc; 2014, p.187–237.
[132] Libo W, Jian Z, Wiwik W. Physical and chemical stability of drug nanoparticles. Adv. Drug Deliv. Rev. 2011; 63(6): 456–469. https://doi.org/10.1016/j.addr.2011.02.001.

[133] Thomas DM, Marcel BB, Michael JH, Cullis PR, Schieren HP, Janoff AS. Protection of large unilamellar vesicles by trehalose during dehydration: retention of vesicle contents. Biochimica et Biophysica Acta. 1985; 817: 67-74.
[134] Swathi G, Prasanthi NL, Manikiran SS, Ramarao N. Solid lipid nanoparticles: colloidal carrier systems for drug delivery. Int J Pharm Sci Res. 2010; 1 (12): 01-16.
[135] Seetapan N, Bejrapha P, Srinuanchai W, Ruktanonchai UR. Rheological and morphological characterizations on the physical stability of gamma-oryzanol-loaded solid lipid nanoparticles (SLNs). Micron. 2010; 41: 51–58. Doi: 10.1016/j.micron.2009.08.003.
[136] Müller RH, Runge SA, Ravelli V, Thünemann AF, Mehnert W, Souto EB. Cyclosporine-loaded solid lipid nanoparticles (SLN): Drug–lipid physicochemical interactions and characterization of drug incorporation. Eur J Pharm Biopharm. 2008; 68(3): 535–544. Doi: 10.1016/j.ejpb.2007.07.006.
[137] Silvaa AC, González-Mirac E, Garcíac ML, Egeac MA, Fonsecaa J, Silva R, et al. Preparation, characterization and biocompatibility studies on risperidone-loaded solid lipid nanoparticles (SLN): High pressure homogenization versus ultrasound. Colloids Surf B Biointerfaces. 2011; 86(1): 158–165. Doi: 10.1016/j.colsurfb.2011.03.035.
[138] Subedi RK, Kanga KW, Choi HK. Preparation and characterization of solid lipid nanoparticles loaded with doxorubicin. Eur J Pharm Sci. 2009; 37(3-4): 508–513. Doi: 10.1016/j.ejps.2009.04.008.
[139] Mishra DK, Dhote V, Bhatnagar P, Mishra PK. Engineering solid lipid nanoparticles for improved drug delivery: promises and challenges of translational research. Drug Deliv Transl Res. 2012; 2:238–253. Doi: 10.1007/s13346-012-0088-9.
[140] Sato K. Crystallization of fats and fatty acids. In: Garti N, Sato K, editors. Crystallization and Polymorphism of Fats and Fatty Acids. Basel, NYC: Marcel Dekker Inc; 1988, p. 227–266.
[141] Drake B, Prater CB, Weisenhorn AL, Gould SA, Albrecht TR, Quate CF, et al. Imaging crystals polymers and processes in water with the AFM. Science. 1989; 243(4898): 1586–1589. Doi: 10.1126/science.2928794.
[142] Kirby AR, Gunning AP, Morris VJ. Imaging xanthum gum by atomic force microscopy. Carbohydr. Res. 1995; 267(1): 161–166. https://doi.org/10.1016/0008-6215 (94)00294-P.
[143] Dingler A, Blum RP, Niehus H, Muller RH, Gohla S. Solid lipid nanoparticles (SLN™ / Lipopearls™) — a pharmaceutical and cosmetic carrier for the application of vitamin E in dermal products. J Microencapsul. 1999; 16: 751–767. Doi: 10.1080/026520499288690.
[144] Dingler A. Feste Lipid-Nanopartikel als kolloidale Wirkstofftragersysteme zur dermalen Applikation. Ph.D. Thesis. Berlin: Free University of Berlin; 1998.
[145] Siekmann B, Westesen K. Submicron-sized parenteral carrier systems based on solid lipids. Pharm Pharmacol Lett. 1992; 1: 123–126.
[146] Hunter RJ. Zeta potential in colloid science: principles and applications.1st ed. Cambridge, US: Academic press; 1989.
[147] Chawla V, Saraf SA. Rheological studies on solid lipid nanoparticles based carbopol gels of aceclofenac. Colloids Surf B Biointerfaces. 2012; 92:293-298. Doi: 10.1016/j.colsurfb.2011.12.006.
[148] Kobayashi M. Vibrational spectroscopic aspects of polymorphism and phase transition of fats and fatty acids. In: Garti N, Sato K, editors. Crystallization and Polymorphism of Fats and Fatty Acids. Basel, NYC: Marcel Dekker Inc; 1988, p. 139–188.
[149] Pragati S, Kuldeep S, Ashok S. Solid Lipid Nanoparticles: A Promising Drug Delivery Technology. Int J Pharm Sci Nanotech. 2009; 2(2): 509-516.
https://www.researchgate.net/publication/266229322_Solid_Lipid_Nanoparticles_A_Promising_Drug_Delivery_Technology.
[150] Mistry SN, Patel PK, Bharadia PD, Pandya VM, Modi D. Novel Drug Delivery System for Lipophilic Agents: Solid Lipid Nanoparticles. IJPI's J Pharm Cosmet. 2011; 1(4): 76-89.
[151] Kammari R, Das NG, Das SK. Nanoparticulate Systems for Therapeutic and Diagnostic Applications, In Mitra AK, Cholkar K, Mandal A, editors. Emerging nanotechnologies for diagnostics, drug delivery, and medical devices. Amsterdam, NL: Elsevier Inc; 2017, p.105-138. http://dx.doi.org/10.1016/B978-0-323-42978-8.00006-1.

[152] Weyers H. Feste Lipid Nanopartikel (SLN) fur die gewebsspezifische Arzneistoffapplikation — Herstellung ünd Charak terisierung oberflachenmodifizierter For mulierungen. Ph.D. Thesis. Berlin: Free University of Berlin; 1995.
[153] Unruh T, Bunjes H, Westesen K, Koch MHJ. Observation of size-dependent melting in lipid nanoparticles. J Phys Chem B. 1999; 103: 10373–10377. https://doi.org/10.1021/jp9912612.
[154] Siekmann B, Westesen K. Thermo analysis of the recrystallization of melt-homogenized glyceride nanoparticles. Colloids surf B Biointerfaces. 1994; 3(3): 159–175. https://doi.org/10.1016/0927-7765 (94)80063-4.
[155] Westesen K, Siekmann B. Investigation of the gel formation of phospholipid-stabilized solid lipid nanoparticles. Int J Pharm. 1997; 151(1): 35–45.https://doi.org/10.1016/S0378-5173 (97)04890-4.
[156] Parashar AK, Kakde D, Chadhar V, Devaliya R, Shrivastav V, Jain UK. A review of solid lipid nanoparticles (SLN) for controlled and target delivery of medicinal agents. Curr Res Pharm Sci. 2011; 02: 37-47.http://crpsonline.com/index.php/crps/article/view/34/20.
[157] Jenning V, Schafer-Korting M, Gohla S. Vitamin A-loaded solid lipid nanoparticles for topical use: drug release properties. J Control Release. 2000; 66:115–126. Doi: 10.1016/s0168-3659(99)00223-0.
[158] Ahlin P, Kristl J, Sentjurc M, Strancar J, Pecar S. Influence of spin probe structure on its distribution in SLN dispersions. Int J Pharm. 2000; 196(2): 241–244. Doi: 10.1016/s0378-5173(99)00431-7.
[159] Yuan Q, Han J, Cong W, Ge Y, Ma D, Dai Z, et al. Docetaxel-loaded solid lipid nanoparticles suppress breast cancer cells growth with reduced myelosuppression toxicity. Int J Nanomedicine. 2014; 9: 4829–4846. Doi: 10.2147/IJN.S70919.
[160] Gong X, Moghaddam MJ, Sagnella SM, Conn CE, Danon SJ, Waddington LJ, et al. Lamellar crystalline self-assembly behavior and solid lipid nanoparticles of a palmityl prodrug analog of capecitabine- a chemotherapy agent.Colloids surf B Biointerfaces. 2011;85(2):349-359. Doi: 10.1016/j.colsurfb.2011.03.007.
[161] Pawar H, Surapaneni SK, Tikoo K, Singh C, Burman R, Gill MS, et al. Folic acid-functionalized long-circulating co-encapsulated docetaxel and curcumin solid lipid nanoparticles: In vitro evaluation, pharmacokinetics and biodistribution in rats. Drug Deliv. 2016; 23(4):1453-1468. Doi: 10.3109/10717544.2016.1138339.
[162] Mullick RS, Jukka M, Juvonen RO, Mahadik KR, Paradkar AR. Transferrin mediated solid lipid nanoparticles containing curcumin: Enhanced in vitro anticancer activity by induction of apoptosis. Int J Pharm. 2010; 398(1-2):190-203. Doi: 10.1016/j.ijpharm.2010.07.021.
[163] Gupta Y, Jain A, Jain SK. Transferrin-conjugated solid lipid nanoparticles for enhanced delivery of quinine dihydrochloride to the brain. J Pharm Pharmacol. 2007; 59(7):935-940. Doi: 10.1211/jpp.59.7.0004.
[164] Wang W, Chen T, Xu H, Ren B, Cheng X, Qi R, et al. Curcumin-Loaded Solid Lipid Nanoparticles Enhanced Anticancer Efficiency in Breast Cancer. Molecules. 2018; 23(7): 1-13. Doi: 10.3390/molecules23071578.
[165] Oliveira MS, Mussi SV, Gomes DA, Yoshida MI, Frezard F, Carregal VM, et al. α-Tocopherol succinate improves encapsulation and anticancer activity of doxorubicin-loaded in solid lipid nanoparticles. Colloids Surf B Biointerfaces. 2015; 140:246-253.Doi: 10.1016/j.colsurfb.2015.12.019.
[166] Naguib YW, Rodriguez BL, Li X, Hursting SD, Williams RO, Cui Z. Solid Lipid Nanoparticle Formulations of Docetaxel Prepared with High Melting Point Triglycerides: In Vitro and in Vivo Evaluation. Mol Pharm. 2014; 11(4): 1239−1249.Doi: 10.1021/mp4006968.
[167] Battani S, Pawar H, Suresh S. Evaluation of Oral Bioavailability and Anticancer Potential of Raloxifene Solid Lipid Nanoparticles. J Nanosci Nanotechnol. 2014; 14(8): 5638–5645. Doi: 10.1166/jnn.2014.8872.
[168] Du Y, Ling L, Ismail M, He W, Xia Q, Zhou W, et al. Redox Sensitive Lipid-camptothecin Conjugate Encapsulated Solid Lipid Nanoparticles for Oral Delivery. Int J Pharm. 2018; 549(1-2): 352-362. Doi: 10.1016/j.ijpharm.2018.08.010.
[169] Eskiler GG, Cecener G, Dikmen G, Egeli U, Tunca B. Solid lipid nanoparticles: Reversal of tamoxifen resistance in breast cancer. Eur J Pharm Sci. 2018; 120: 73–88.Doi: 10.1016/j.ejps.2018.04.040.
[170] Oliveira MS, Lima BHS, Goulart GAC, Mussi SV, Borges GSM, Oréfice RL, et al. Improved Cytotoxic Effect of Doxorubicin by Its Combination with Sclareol in Solid Lipid Nanoparticle Suspension. J Nanosci Nanotechnol. 2018; 18(8): 5609–5616.Doi: 10.1166/jnn.2018.15418.

[171] Garg NK, Singh B, Jain A, Nirbhavane P, Sharma R, Tyagi RK, et al. Fucose decorated solid-lipid nanocarriers mediate efficient delivery of methotrexate in breast cancer therapeutics. Colloids Surf B Biointerfaces. 2016; 146: 114–126.Doi: 10.1016/j.colsurfb.2016.05.051.
[172] Xu W, Bae EJ, Lee MK. Enhanced anticancer activity and intracellular uptake of paclitaxel-containing solid lipid nanoparticles in multidrug-resistant breast cancer cells. Int J Nanomedicine. 2018; 13: 7549–7563. https://doi.org/10.2147/IJN.S182621.
[173] Lee MK, Lim SJ, Kim CK. Preparation, characterization and in vitro cytotoxicity of paclitaxel-loaded sterically stabilized solid lipid nanoparticles. Biomaterials. 2007; 28(12):2137–2146. Doi: 10.1016/j.biomaterials.2007.01.014.
[174] Baek JS, Cho CW. Controlled release and reversal of multidrug resistance by co-encapsulation of paclitaxel and verapamil in solid lipid nanoparticles. Int J Pharm. 2015; 478(2):617-624. Doi: 10.1016/j.ijpharm.2014.12.018.
[175] Chen Z, Zheng Y, Shi Y, Cui Z. Overcoming tumor cell chemoresistance using nanoparticles: Lysosomes are beneficial for (stearoyl) gemcitabine-incorporated solid lipid nanoparticles. Int J Nanomedicine. 2018; 13: 319–336. Doi: 10.2147/IJN.S149196.
[176] Oliveira MS, Aryasomayajula B, Pattni B, Mussi SV, Ferreira LAM. Torchilin VP. Solid lipid nanoparticles co-loaded with doxorubicin and α-tocopherol succinate are effective against drug-resistant cancer cells in monolayer and 3-D spheroid cancer cell models. Int J Pharm. 2016; 512(1): 292–300. Doi: 10.1016/j.ijpharm.2016.08.049.
[177] Liu B, Han L, Liu J, Han S, Chen Z, Jiang L. Co-delivery of Paclitaxel and TOS-cisplatin via TAT-targeted solid lipid nanoparticles with synergistic antitumor activity against cervical cancer. Int J Nanomedicine. 2017; 12: 955–968. Doi: 10.2147/IJN.S115136.