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Dual Drug Loaded Solid Lipid Nanoparticles For Cancer Treatment: A Recent Advancement And Future Prospectives

Pranshu Tangri[1], Surabhi Pokhriyal[2], Pawan Deoli[1], Ashish Dimri[1], Gagandeep Singh[3], Monika Gariya[*1], Mansi Pal[4], Abhit Kumar[5]

[1]School of Pharmacy, GRD Institute of Management and Technology, Dehradun, Uttarakhand, India

[2]College of Pharmacy, Shivalik Campus, Dehradun, Uttarakhand, India

[3]School of Pharmacy, Maya Devi University, Selaqui, Dehradun, Uttarakhand, India

[4]Assistant Professor, College of Pharmacy, COER University Roorkee-(Uttarakhand) 247667, India

[5]Assistant Professor, School of Pharmacy and Research, Dev Bhoomi Uttarakhand University, Manduwala, Naugaon Dehradun (Uttarakhand) 248007, India

Corresponding author:

Monika Gariya

Guru Ram Das (PG) Institute of Management and Technology, 214- Rajpur Road, Dehradun, Uttarakhand

Email ID : gariyamonika23@gmail.com

ABSTRACT

Cancer therapy often requires combination treatment to achieve optimal efficacy. Solid lipid nanoparticles (SLNs) have emerged as a promising platform for co-delivery of multiple drugs. The current review discusses the methods of formulation for SLNs, such as high-pressure homogenization, microemulsion, solvent evaporation, solvent injection, and ultrasonication, based on their applicability for heat-sensitive and low-solubility drugs. This study developed dual-drug loaded SLNs combining hydrophilic and lipophilic anticancer agents. The SLNs were characterized for particle size, zeta potential, entrapment efficiency, and in vitro release. SLNs act through passive targeting by the Enhanced Permeability and Retention (EPR) effect, active targeting by surface ligands, and effective intracellular release of drugs, providing intense cytotoxicity at tumor sites while reducing systemic toxicity. The results suggested that dual-drug loaded SLNs offer a promising approach for cancer therapy, enabling simultaneous delivery of multiple drugs and potentially overcoming resistance.

Keywords: *Solid Lipid Nanoparticles (SLNs), Cancer Treatment, Passive targeting, active targeting, nanocarriers, gene therapy, Enhanced Permeation and Retention (EPR)*

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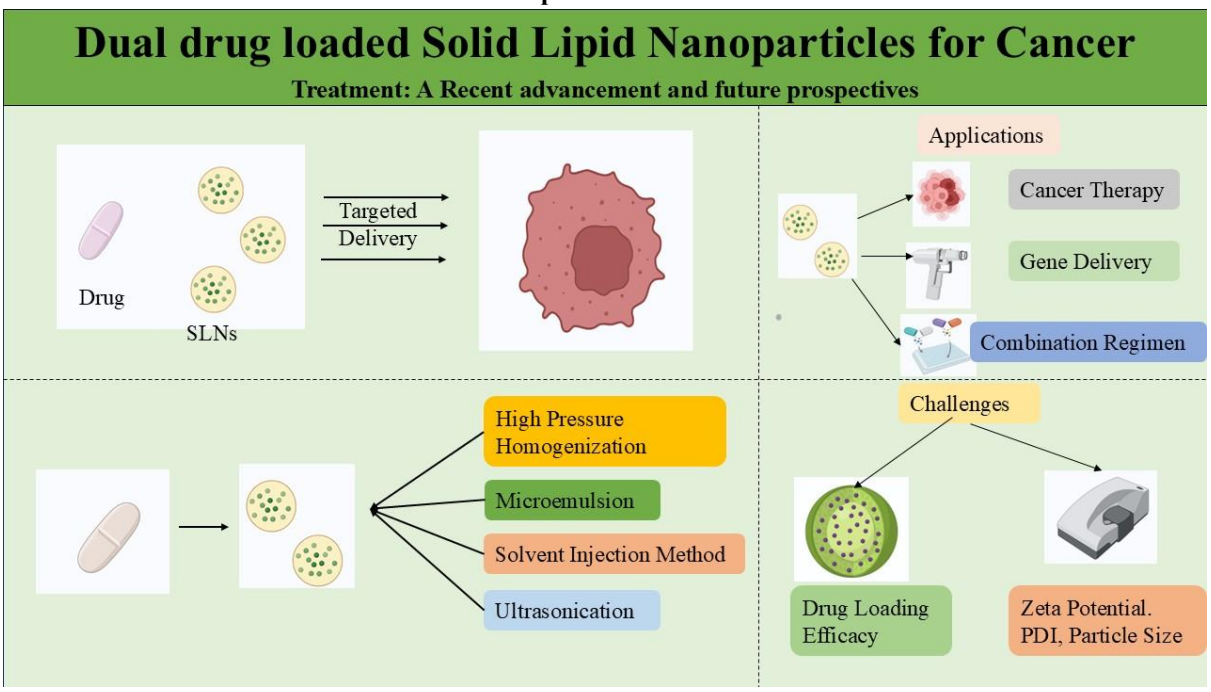
1. INTRODUCTION

Nanotechnology offers a groundbreaking solution in cancer therapy, especially in the development of drug delivery systems. Various nanocarriers are developed which can hold and deliver the drugs more efficiently to their target destination such as dendrimers, micelles, polymeric nanoparticles, liposomes and inorganic and lipid-based nanostructures[1,2]. Those nanocarriers which are having diameter typically around 10-200 nm, are able to utilize the Enhanced Permeability and Retention (EPR) effect, which occurs when nanoparticles have the ability to accumulate particularly in tumor tissue due to their leaky vasculature and impaired lymphatic drainage [3]. To acquire the dual advantage of passive targeting of SLNs by active targeting and EPR effect by receptor-ligand binding, nanocarriers are functionalized with targeting ligands e.g., antibodies, peptides, or aptamers which actively target the tumor markers on the cancer cells. Nanocarriers also protects labile drugs, which makes their release sustained and controlled, and can be designed to respond to microenvironmental stimuli in the tumor, e.g., pH, temperature, and enzyme [4–6].

Graphical Abstract



Solid lipid nanoparticles are the submicron colloidal carriers which are typically made up of lipids that are biodegradable and biocompatible, are solid at room temperature as well as at body temperature. Triglycerides, partial glycerides, fatty acids, and waxes are some of the lipids that the regulatory agencies classifies under the generally recognized as safe (GRAS) category. SLNs can entrap both lipophilic and hydrophilic drugs which possess greater stability as compared to other lipid carriers that are less toxic and biocompatible as they use physiological lipids, and exhibit controlled and extended drug release, all requirements for reducing dosing frequency and improving patient compliance [7–9]. A variety of drugs, ranging from novel macromolecules such as siRNA genes and immunomodulatory drugs to classic chemotherapeutics such as doxorubicin and paclitaxel, may be administered by SLN in cancer therapy [10]. SLNs have the ability to enhance intracellular delivery and bypass drug efflux pumps, providing potential remedies for drug resistance. Table 1.1 illustrates a comparison between conventional chemotherapy and solid lipid nanoparticles.

Table 1.1 Comparison of Solid Lipid Nanoparticles over Conventional Chemotherapy

Parameter	Conventional Chemotherapy	Solid Lipid Nanoparticles (SLNs)	References
Drug Specificity	Non-Specific, affects both cancerous and normal cells	Tumor-targeted	[3]
Systemic Toxicity	High	Significantly Lower	[19]
Drug Solubility Issues	Common, especially for hydrophobic drugs	Solubilizes both hydrophilic and hydrophobic drugs	[19]
Stability	Poor	High	[20]
Drug Resistance	Frequent due to efflux mechanisms	Capable of bypassing efflux transporters	[21]
Release Profile	Immediate, Uncontrolled	Controlled and Sustained Release	[2]
Dosage Frequency	High	Low	[22]

Cancer is a multicausal disease with uncontrolled cell growth, invasion, and metastasis. It is still one of the leading causes of global disease burden, responsible for around 10 million deaths each year, as per the World Health Organization [11]. The treatment of cancer continues to be a major problem in spite of advances in tumour biology and the development of new drugs. This is in great part due to the shortcomings of the treatment modalities presently available, especially chemotherapy, which, though widely used, is often linked with uncontrolled toxicity, lack of specificity, and inadequate patient outcome [12,13]. Both malignant and normal cells grow rapidly all over the body. Since they are generally cytotoxic to growing cells, traditional chemotherapeutic agents are unable to differentiate between neoplastic and normal cells. Therefore, they generate dangerous side effects like systemic toxicity, gastrointestinal toxicity, alopecia, and immunosuppression [14,15]. Tumours form biological obstacles that limit drug entry and accumulation, e.g., abnormal vasculature, increased interstitial fluid pressure, and compact extracellular matrix.

Multidrug Resistance (MDR), a second major issue, arises when tumour cells acquire defences against drugs, e.g., by overexpressing efflux pumps (like P-glycoprotein), which lowers the intracellular concentration and efficacy of the drugs [16]. The necessity for targeted drug delivery systems (TDDS) that are able to deliver therapeutic agents to cancer cells with minimum damage to normal tissues which increases therapeutic efficacy and reduce toxicities is evoked by these issues. [17,18].

2. SOLID LIPID NANOPARTICLES (SLNS)

SLN are the sub-micron size particles ranging from 50-1000nm and are developed by using biodegradable lipids[19,20]. These particles are generally composed of a solid hydrophobic core, which is surrounded by a phospholipid or by a phospholipid derivative as shown in Fig. 1.1. The active pharmaceutical agent is often dissolved or distributed in the interior of the fat matrix, where the hydrophobic portion of the phospholipid chain is imbedded in it [19,21].low toxicity[22], high biocompatibility, prevention of degradation of chemically labile drugs, enhancement of bioavailability[23], and targeted delivery [24] are all enabled by SLNs.

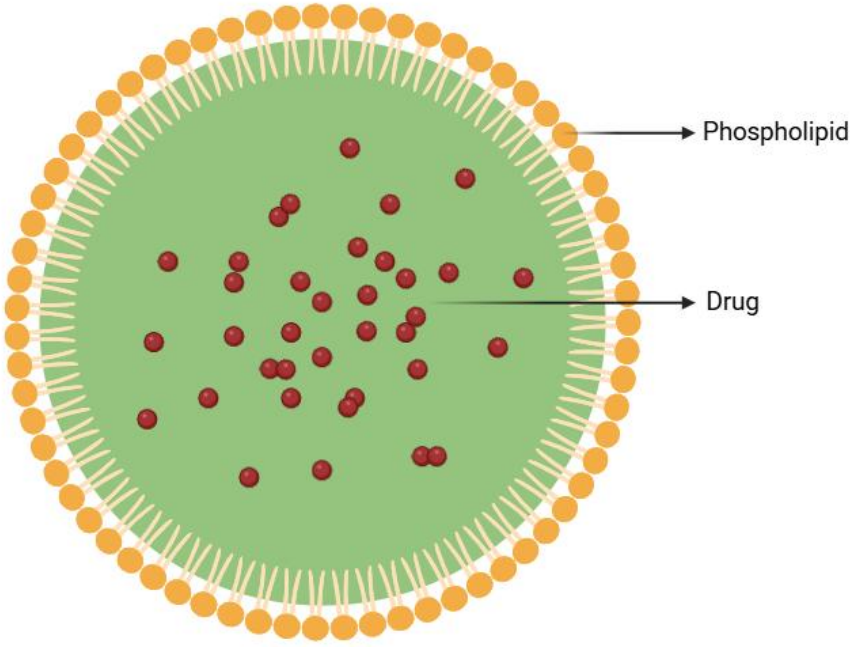


Fig. 1.1 Structure of Solid Lipid Nanoparticles

Since 1990, SLNs and NLCs have been acknowledge as good alternatives to liposomes, emulsions and polymeric nanoparticles as a carrier system. Lipid parts that are solid at room temperature and body temperature, like waxes, complex mixtures of glycerides, or simple triglycerides, constitute SLNs. Surfactants are used in order to stabilize it. The proper choice of surfactants and lipids has the ability to influence two SLN physiochemical characteristics: particle size and drug loading. SLNs are thought to be safer compared to liposomes and provide better medication stability and increased release for longer periods since they are produced without using organic solvents.

The high biocompatibility, absence of biotoxicity, high reliability, and capacity to enhance the stability of the active component are among features making solid lipid nanoparticles (SLNs) stand out due to their potential for large-scale production and controlled release of the active component without the utilization of organic solvents during the production process. That the majority of lipids utilized in SLNs are recognized to have UV-blocking effects also contributes to their utilization [25].

1.2.1 Drug Incorporation Models

The medication can be integrated into the lipid in a number of ways. The drug can be incorporated in three different ways: directly dispersing the drug molecule within the lipid; creating a drug-encapsulated shell that covers the lipid and creates a core of lipid material; and, finally, forming a lipid shell over the drug-enriched core by encapsulating the drug with a lipid that further creates a lipid shell around the drug[26,27] as shown in the Fig. 1.2.

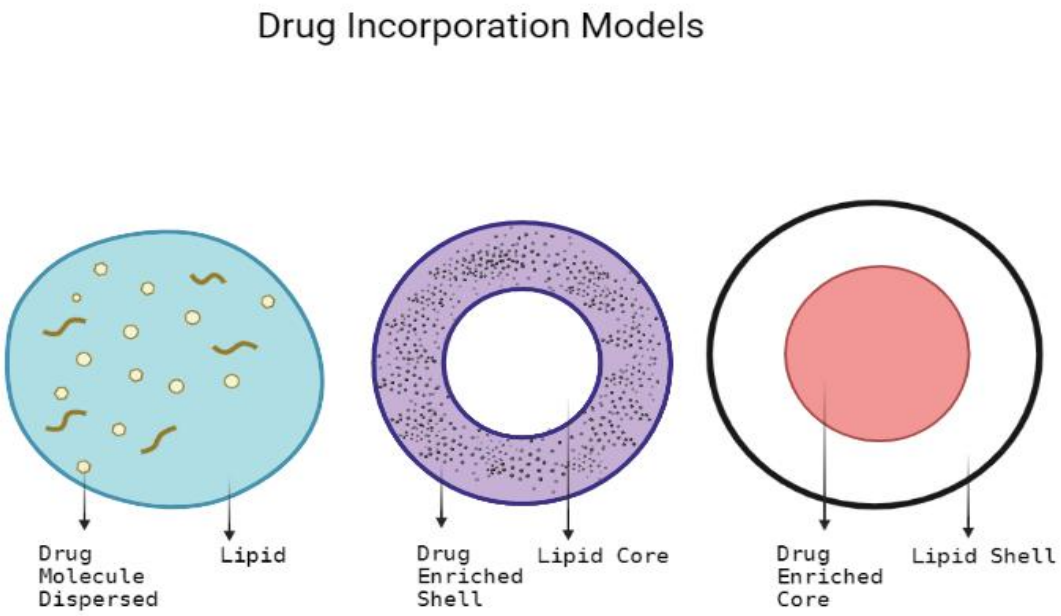


Fig. 1.2 Drug Incorporation Models in SLNs

SLNs offer a number of benefits, including as a wide range of administration routes and a high degree of physical stability that shields medications from adverse conditions. A promising carrier technology for a range of therapeutic applications, SLNs also provide tailored drug delivery and are biocompatible and biodegradable. Notwithstanding their many benefits, SLNs have certain drawbacks, such as the possibility of a low drug loading capacity because of the crystalline form of the lipids they use. The propensity of the dispersed phase to gel during storage is another frequent problem with SLNs that can impair their stability and efficacy as a drug delivery device[27–29].

3. METHOD OF PREPARATION

The synthesis technique affects the physicochemical characteristics such as stability, drug loading and release profile of Solid lipid nanoparticle. Several preparations methods are developed, each tailored to the physicochemical characteristics of the drug and lipid, along with the necessary particle size, and temperature sensitivity. The most commonly used methods for preparation are solvent emulsification-evaporation, solvent injection method, microemulsion-based processes, high-pressure homogenization and ultrasonication.

1.3.1 High Pressure Homogenization (HPH)

Hot Homogenization

Thermal HPH initiates by melting the lipid (drug-containing) above its melting point, generally 5-10ºC above, before emulsifying it into a surfactant solution at the same temperature. The resulting pre-emulsion is then subjected to high-pressure homogenization (100-2000 bar), typically for 3-10 cycles, and subsequent rapid cooling to room temperature, which allows for crystallization of the lipid into SLNs[30]. Major processing parameters are number of cycles, lipid and surfactant content homogenization pressure, and cooling rate. Multicycles and higher pressures tend to decrease particle

size, but can result in heat degradation at too high temperatures[31,32]. The process yields unilamellar particles with a narrow distribution (50-300 nm) and does not require solvents or scale-up in industry, thus being particularly suitable for thermostable lipophilic drugs [Fig. 1.3]. However, it is inappropriate for thermosensitive drugs, and polymorphic lipid changes on cooling can lead to a decrease in drug loading efficiency.

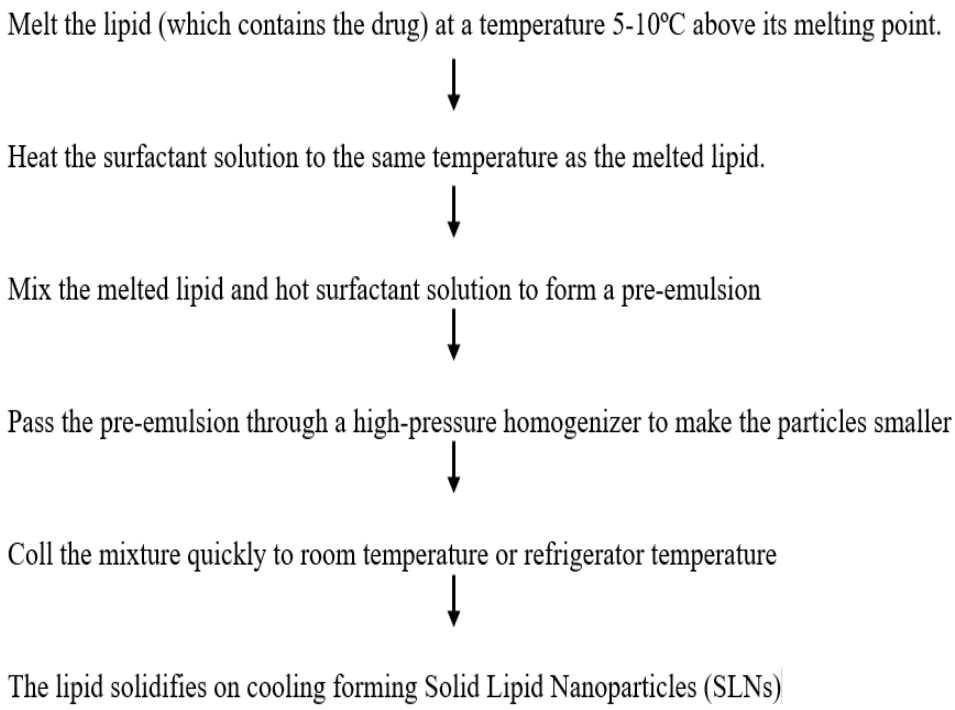


Fig. 1.3 Hot Homogenization for SLN production

Cold Homogenization

Cold HPH was created to shield thermally sensitive drugs. Following the melting of the lipid and dissolution of the drugs, the blend is immediately solidified in liquid nitrogen or dry ice and then milled into microparticles (50-100 μm). The microparticles are resuspended in an icy (close to room temperature) surfactant solution and homogenized with a high-power homogenizer, yielding SLNs [Fig. 1.4]. This method largely minimizes the exposure to heat, enhancing drug penetration and stability, especially for hydrophilic drugs. It is more complicated, needs good micronization, and usually produces particles with a larger size distribution[33,34] Table 1.2 shows the comparison between Hot high pressure homogenization and cold high pressure homogenization.

Table 1.2 Comparison of Hot HPH and cold HPH

Parameter	Hot HPH	Cold HPH
Temperature	High	Low
Suitable for Heat-Sensitive Drugs	No	Yes
Particle Size	Narrow Distribution	Slightly broader
Drug Loss	Higher	Reduced
Complexity	Simple	More Complex
Solvent Use	None	None

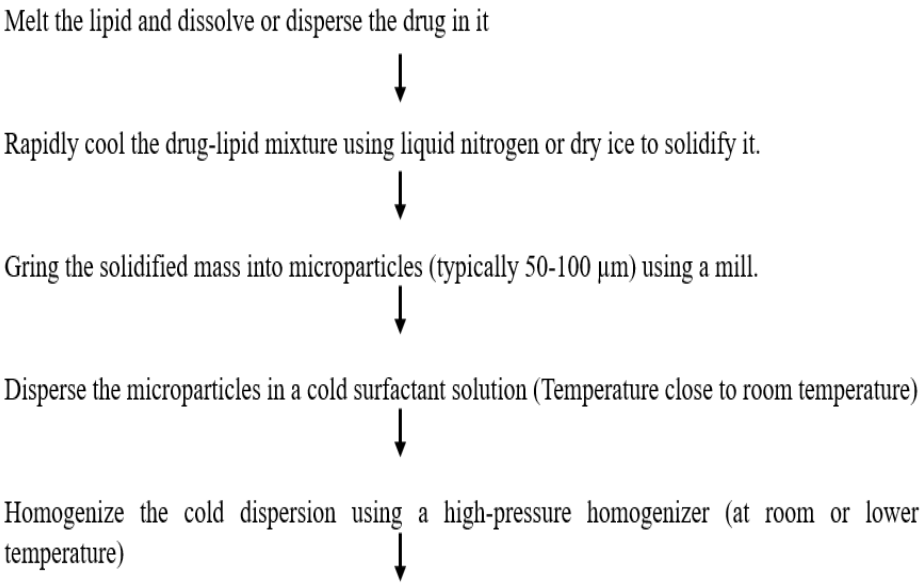


Fig. 1.4 Cold Homogenization for SLN Production

1.3.2 Microemulsion Technique

The microemulsion technique produces a thermodynamically stable microemulsion by heating the lipid (solid at ambient temperature), and a surfactant, a co-surfactant(such as short-chain alcohol), and water to the lipid's melting point, ranging from 65-70ºC. The combination provides a clear, isotropic phase because of low interfacial tension and the best surfactant composition. When such warm microemulsion is injected into cold water (2-10ºC) under mild stirring, usually in the ratio of 1:25 to 1:50, lipid droplets precipitate out and convert to SLNs as the lipid crystallizes on cooling [Fig. 1.5]. The obtained SLNs will have a uniform size distribution (100-200 nm) and good drug entrapment efficiency, particularly for lipophilic drugs[35,36]. This technique has several significant benefits compared to other SLN techniques, as it avoids high-pressure procedures and organic solvents, employs low temperatures, and is conveniently scalable. the microemulsion can be manufactured in bulk and pumped into chilled water tanks. Studies have revealed effective scale-up, good encapsulation efficiency, and reproducible SLN properties. It is necessary to use high surfactant loads, and the huge amount of dilution water may require post-processing to yield a concentrated product[37].

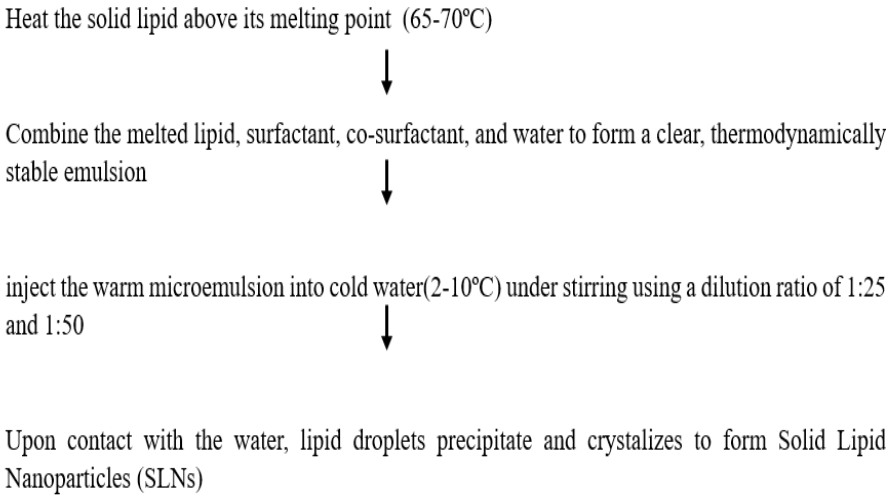


Fig. 1.5 Microemulsion procedure for SLN production

1.3.3 Solvent Emulsification and Solvent Injection Method

This method is effective for drugs that are water loving, sensitive to heat, or have low lipid solubility. First, an organic solvent that doesn't mix with water, such as dicloromethane or chloroform, is utilized to dissolve the drug and the lipid. High-speed or high-pressure homogenization is utilized to mix the organic phase into an aqueous phase, resulting in a coarse or nano-emulsion. After that, the solvent is removed, often by gentle agitation or rotational evaporation, producing precipitated lipid and solid lipid nanoparticles (SLNs)[Fig. 1.6] [42, 43]. When the lipid and surfactant optimized, this procedure produces dense nanoparticles having particles size in the range of 30-100 nm with high encapsulation efficiency. However, in order to gurantee toxicity and regulatory compliacen, remaining solvent must be completely removed.

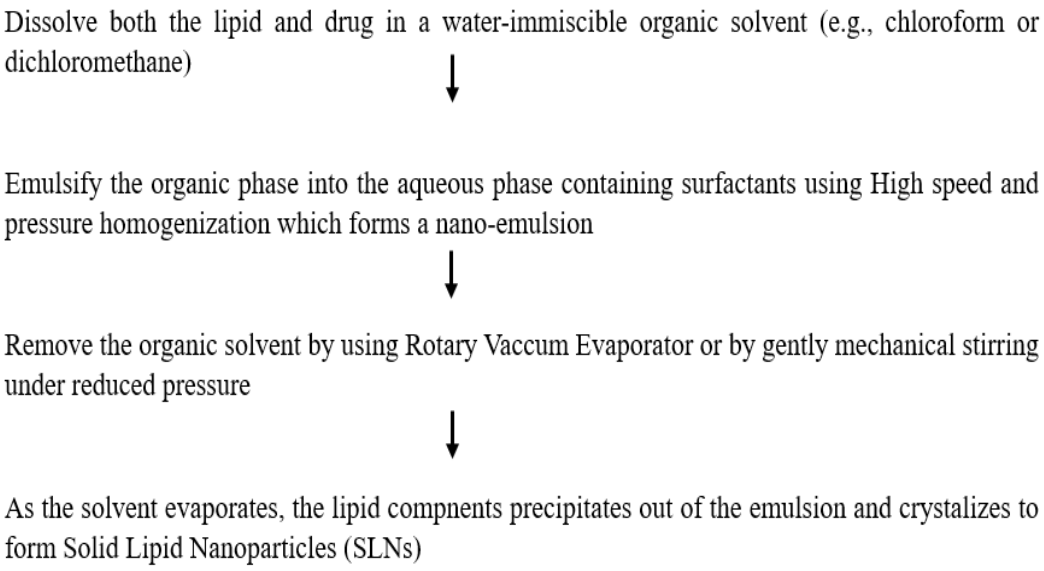


Fig. 1.6 Solvent Emulsification-Evaporation Method for the production of SLN

In the solvent injection method, the drug-lipid solution in a water-soluble organic solvent (such as ethanol or ethyl acetate) is injected into an aqueous medium under sonication or stirring[Fig. 1.7]. The solvent diffuses quickly in the water, leading to instantaneous nucleation and lipid nanoparticle formation[38,39]. Because there is no heat or harsh shear stress involved, this method is ideal for thermolabile drugs. Injection rate, solvent polarity, and type of emulsifier are all varied in this process.

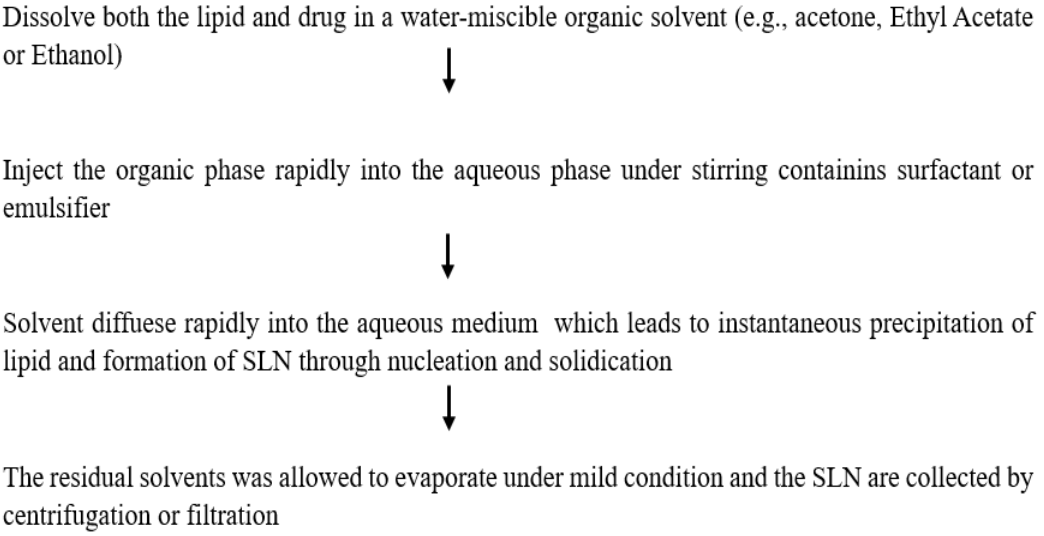


Fig 1.7 Solvent injection method process

1.3.4 Sonication

Ultrasonication employs high-frequency sound waves to create cavitation bubbles that collapse and produce extensive mechanical shear stresses. These forces then break up molten lipid droplets into nanoparticles, upon cooling, which solidify to form solid lipid nanoparticles (SLNs). First, the drug is mixed with melted lipid and pre-heated surfactants to produce a pre-emulsion. For decreasing the size of the droplets and polydispersity, this prior pre-emulsion is sonicated with a probe ultrasonicator [40,41].

4. MECHANISM OF ACTION

1.4.1 Drug Loading and Release Mechanisms

Solid Lipid Nanoparticles (SLNs) entrap anticancer agents in a solid lipid matrix through several approaches, including molecular dispersion, embedding in the amorphous state, or adsorption on the surface. The medication is stabilized by the lipophilic core, which consists of biocompatible lipids such as tripalmitin or glyceryl monostearate and is resistant to chemical and enzymatic degradation. The drugs are released by desorption from the surface of the particle, erosion of the lipid matrix by lipase, or diffusion. The physicochemical properties of the lipid used significantly influence the release pattern. For example, enhanced drug trapping and extended release are facilitated by lipids that possess a less ordered crystalline structure, which is desirable for long-term maintenance of therapeutic drug concentration. In Chemotherapy, where stable medication levels can optimize efficacy and minimise toxicity, this is especially desirable. Doxorubicin and paclitaxel drugs have been successfully incorporated into SLNs to provide targeted and sustained delivery[42–44].

1.4.2 Passive targeting through Enhanced Permeability and Retention (EPR) Effect

Due to the Enhanced Permeability and Retention (EPR) effect, SLNs tend to accumulate in tumour tissue. Nanoparticles having diameters less than 200 nm can passively extravasate and accumulate in the tumour interstitum because tumours possess irregular vasculature with fenestration between the range of 100 and 800 nm and an impaired lymphatic drainage system, This process does not depend on ligand-receptor interaction alone as it takes advantage of the pathophysiology of the tumor to enhance drug concentration at the target site. Passive targeting not only improves the therapeutic index of chemotherapeutic drugs but also reduces their systemic toxicity. For instance, docetaxel-loaded SLNs have shown preferential uptake in tumors via this route, and thus enhanced anticancer efficacy at minimal cardiotoxicity and myelosuppression[45,46].

1.4.3 Active Targeting by Surface Modification

To enhance selectivity over passive targeting, SLNs can be designed with ligands that actively bind to and identify more than normal receptors expressed on cancer cells. Ligands like folic acid, antibodies (e.g., trastuzumab), and peptides are attached to the surface of the nanoparticle to enable receptor-mediated endocytosis. This approach provides enhanced cellular uptake within the receptor-rich tumor microenvironment, even within tumors that have unfavorable EPR properties[Fig. 1.8]. For example, folate-conjugated SLNs that deliver paclitaxel or curcumin have been found to exhibit greatly increased delivery in folate-receptor positive cancer cells like ovarian and breast cancers. By minimizing off-site drug delivery, active targeting enhances cytotoxic impact on the tumour mass while reducing side effects[47].

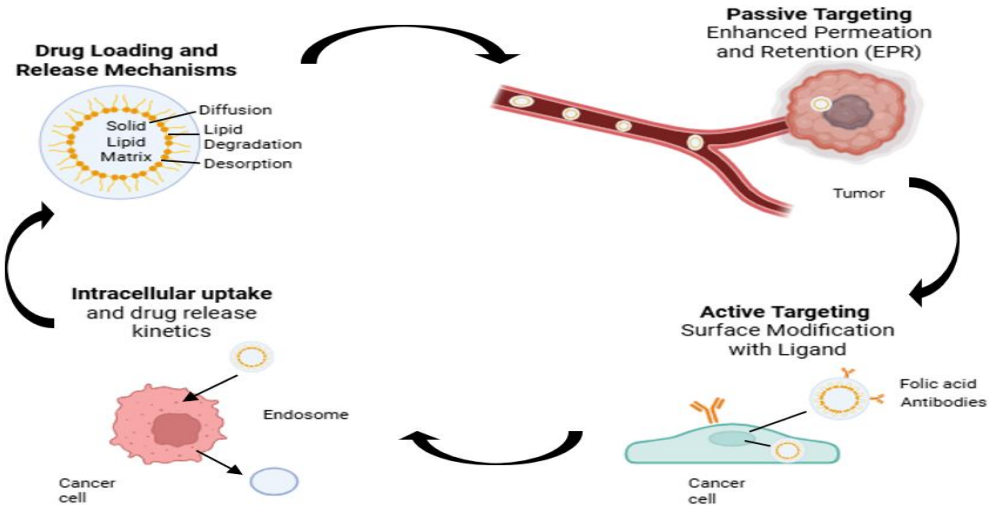


Fig. 1.8 Mechanism of Action of SLNs

1.4.4 Intracellular Uptake and Drug Release Kinetics

The energy-requiring endocytic processes such as clathrin or caeolin-mediated endocytosis internalize SLNs at the point, they are located within the tumour microenvironment. Upon internalization, they are directed to endosomes or lysosomes, where the lipid matrix is dissolved and the therapeutic medicament is released owing to low pH and enzymatic degradation, which maximizes the therapeutic effectiveness of the drug by releasing the drug within the cellular environment, in the vicinity of subcellular targets such as the nucleus or mitochondria. The adjustment of formulation properties such as PEGylation status, surfactant balance and lipid structure can enhance release kinetics. For example, doxorubicin-encapsulating PEGylated SLNs exhibited sustained intracellular release and circulation half-life, which translated to increased cytotoxicity against tumour cells and decreased systemic exposure [48].

5. SLNS FOR THE DELIVERY OF ANTICANCER AGENTS

1.5.1 Chemotherapeutic Drug Delivery

Solid Lipid Nanoparticles (SLNs) are briefly studied for the delivery of hydrophobic chemotherapeutic drugs like paclitaxel, doxorubicin, and docetaxel. These drugs are surrounded with problems like limited water solubility and high systemic clearance rates, usually requiring toxic excipients like Cremophor in traditional formulations. SLNs provide a more biocompatible matrix that increases solubility, prolongs drug release, and facilitates passive tumor targeting through the EPR effect. For example, paclitaxel-loaded SLNs (168 nm) displayed sustained release in serum and similar cytotoxicity against MCF-7 and MDR MCF-7/ADR cell lines, displaying improved efficacy in MDR cells through the ability to bypass efflux pumps [49]. Likewise, sterically stabilized paclitaxel SLNs enhanced pharmacokinetics and tumor uptake in vivo[50]. Doxorubicin-loaded SLNs also reversed MDR in breast cancer cells and caused apoptosis without hemolytic toxicity[44].

1.5.2 SLNs in Gene Delivery

Solid Lipid Nanoparticles (SLNs) is a non-viral vector that has been proposed as a delivery vehicle for genetic payloads like small interfering RNA, microRNA (miRNA), messenger RNA (mRNA), and plasmid DNA. Such genetic materials tend to be unstable in biological fluids and are degraded very quickly by nucleases. SLNs, especially those composed of cationic lipids (e.g., stearyl amine or cetyltrimethylammonium bromide), provide a cationic protective environment that protects the nucleic acids from enzymatic degradation while promoting electrostatic complexation and intracellular delivery. Upon administration, the cationic SLNs can successfully bind nucleic acids to create stable nanocomplexes, which are internalized through clathrin caveolae-mediated endocytosis. Upon entering the cell, endosomal escape is essential, which can be facilitated by SLNs through osmotic swelling or lipid exchange to deliver the genetic cargo into the cytoplasm or nucleus. SLNs that have been loaded with genes have been most helpful in oncogene silencing. Targeting siRNA against anti-apoptotic genes such as BCL-2 or surviving has been encapsulated within SLNs in order to make cancer cells chemotherapy-sensitive. These blends caused apoptosis and substantially reduced oncogene expression in drug-resistant cell lines such as A549 cells and MCF-7/ADR cells. SLNs can further be surface-functionalized by the incorporation of targeting ligands (such as folic acid or RGD peptides) to allow selective targeting to tumour cells overexpressing particular receptors, enhancing transfection efficacy and therapeutic ratio with minimal off-target effects[51–53].

1.5.3 Combination Therapy Using SLNs

Combination therapy, where two or more therapeutic drugs are tightly co-loaded into a single nanocarrier system in close physical association with each other, represents one of the most innovative and clinically promising applications of SLNs. This technique leverages the best of both strategies: the cytotoxicity induced by chemotherapy and the immunomodulatory or gene-silencing effects of nucleic acids. Since SLNs electrostatically attach nucleic acids onto the surface or in the hydrophilic shell of the particle and encapsulate hydrophobic drugs inside the lipid phase, they are especially suited for this purpose. For example, BCL-2 siRNA and the hydrophobic anthracycline drug doxorubicin have been co-loaded in one SLN formulation. In the lymphoma models, siRNA inhibited anti-apoptotic pathways and doxorubicin destroyed DNA, leading to synergistic apoptosis and abrogation of multidrug resistance (MDR). The co-encapsulation of curcumin with paclitaxel or docetaxel with miRNA is another method for extreme oxidative stress or gene deregulation in tumours with a high risk of tumours. Both therapies both target the tumour microenvironment simultaneously due to coordinated delivery, enhancing their synergistic efficacy. Co-delivery systems make patient compliance easier and lessens adverse effects by lowering the number of doses administered and the dosage level. Such systems are also being investigated for application in immunotherapy when immune checkpoint inhibitors or antigen-coding mRNA is co-loaded with anticancer drugs to enhance the tumour-targeting immune response. For enhanced circulatory half-lives and targeting to tumour, such dual-loaded SLNs may be surface PEGylated and ligand-targeted [54–56] as shown in Table 1.3.

Table 1.3 SLN for delivery of anticancer agents

Application	Agents	SLN Mechanisms	Benefits	References

Delivery of chemotherapeutics	Paclitaxel, Doxorubicin, Docetaxel	Encapsulation in lipid matrix, passive/active tumor targeting	Enhanced solubility, reduced toxicity, improved tumor accumulation	[54]
Gene Therapy	siRNA (e.g., anti-BCL2), mRNA, Plasmid DNA	Surface-modified SLNs for nucleic acid protection and intracellular delivery	Protection from degradation, targeted gene silencing, and improved transfection efficiency	[57]
Combination Therapy	Paclitaxel + siRNA, Doxorubicin + curcumin, Docetaxel + Quercetin	Co-delivery of drugs and biomolecules for synergistic effects	Synchronized release, enhanced efficacy, reduced drug resistance, simplified treatment regimen	[58]

6. FORMULATION, CHALLENGES, AND OPTIMIZATION OF SLNS

1.6.1 Stability and Scalability Issues

Lipid polymorphism transitions during storage present a serious threat to the long-term physical and chemical stability of solid lipid nanoparticles (SLNs). The less ordered α or β form of SLNs crystallises initially, then changes into the more ordered β form. This restriction minimizes defects in the lipid matrix, thus contributing to its drug expulsion, crystal growth, and shelf-life compromise[57,58]. Ostwald ripening and poor electrostatic stabilization can also lead to particle aggregation and growth. Production at large scales further exacerbates these issues, high-pressure homogenization (HPH) or microemulsion processes, lab-scale parameters like shear force, temperature, mixing, and cooling rates, well controlled in a laboratory processes can all differ markedly in industrial settings, influencing particles size homogeneity, encapsulation yield, and batch-to-batch reliability[57,59]. For example, Paclitaxel-loaded SLNs left for three months at 25ºC showed increased size and decreased drug content, coinciding with the change to a β crystal form, demonstrating the destabilizing consequences of lipid crystallization[3]. To overcome these problems, mixed-lipid systems such as nanostructured lipid carriers (NLC), which combine solid and liquid lipids, assist in shattering crystal packing and preserving matrix imperfections. Stabilizers like PEGylated surfactants and poloxamers offer steric hindrance to aggregation, whereas lyophilization in the presence of cryoprotectants (e.g., trehalose) prevents aggregation and improves shelf stability[60].

1.6.2 Drug Loading Efficiency and Entrapment Capacity

Specifically for hydrophilic drugs, Solid Lipid Nanoparticles (SLNs) possess a finite inner lipid matrix that becomes denser and crystal lattice with advancing solidification of the lipid, which restricts the encapsulating volume. Drug molecules can be incorporated in three models: a homogenous matrix, where the drug is molecularly dispersed[61], a drug-enriched shell or core, which results from differential cooling profiles[62], and surface adsorbed drug on the particles' exterior[63]. Hydrophilic drugs such as doxorubicin or 5-FU entrap much less unless methods such as co-surfactant incorporation, ion pairing, or the employment or Nanostructured Lipid Carriers NLC) are applied. Hydrophobic drugs such as paclitaxel and docetaxel can be successfully incorporated into lipids such as glyceryl behenate. The most efficient method for incorporation is the formation of an ion pair between an anionic surfactant such as deoxycholic acid and a water-soluble drug such as doxorubicin which enhances the lipophilicity of the drug and allows its entry in SLNs with glyceryl monostearate. Selecting amorphous or less-crystalline lipids, conjugating drugs with lipid moieties and adding liquid lipids to enhance drug accommodation and disrupt crystallinity are additional optimization methods. Combined, these techniques enhance entrapment efficiency, reduce drug leakage, and increase more flexible delivery options for hydrophilic and hydrophobic drugs [64].

1.6.3 Polydispersity Index (PDI) and Zeta Potential

The Polydispersity Index (PDI) measures the nanoparticle size distribution uniformity, an aspect crucial to the predictability of pharmacokinetics and biological response. A PDI value less than 0.3 indicates a narrow size distribution; it is an indication of broad polydispersity and possible phase separation or aggregation, implying destabilization of the system and compromising the therapeutic reproducibility[65]. Zeta potential quantifies particle surface charge and colloidal stability; greater than +30 mV or less than -30 mV provides enough electrostatic repulsion to inhibit aggregation. Low zeta potential SLNs tend to flocculate, sediment, or fuse, undermining shelf-life and in vivo efficacy[66]. An example of formulations that were prepared from stearic acid and soy lecithin attained a PDI of 0.18 and zeta potential of -42 mV and were stable

for six months[67]. The composition, concentration, and lipid composition of the surfactant significantly influence these parameters. Although ionic species such as phosphatidylcholine increase surface charge, non-ionic surfactants such as Tween 80 or poloxamer 188 decrease particle collision. For ensuring low PDI and suitable zeta potential, which ensure physical stability under storage and application, optimization requires the precise balancing of surfactant ratios and regulation of homogenization conditions [68].

1.6.4 Regulatory and Quality Control Challenges

Even though they employ generally recognized as safe (GRAS) ingredients, solid lipid nanoparticles (SLNs) have to still meet strict regulatory standards when employed in pharmaceutical development. All the excipients, including the lipids that are safe for consumption but are presently formulated for drug delivery, need to be tested for toxicity. For patient safety, residual solvents should be removed and quantified by following ICH Q3C guidelines. As an example, batch-to-batch variation and poor solvent elimination made curcumin-loaded SLNs prepared with ethanol fail the first clinical translation, highlighting the need for established protocols [60]. A combination of analytical techniques must be used to ensure consistent drug content, particle size, sterility, and morphology: zeta-potential analysis for colloidal stability; TEM, SEM, and DLS for particle size and morphology; DSC and XRD to identify lipid polymorphism; and HLPC/UPLC for analysis of drug and solvent [21]. Residual solvent risks can be minimized by solvent-free methods such as microemulsion technology and high-pressure homogenization(HPH). Nevertheless, mass production has to base itself on good manufacturing practices (GMP) and quality by design (QbD) strategies to track relevant parameters, control process risk, and guarantee reproducibility[69]. The inclusion of solid QC, validated production procedures, and early regulatory strategy is critical to successfully bring SLN-based therapies from laboratory formulation to clinical application.

7. CONCLUSION

Solid Lipid Nanoparticles (SLNs) is a revolutionary delivery system in cancer chemotherapy with a promising biocompatible and versatile platform for encapsulating hydrophilic and lipophilic drugs. The potential for increasing drug stability, enabling drug release, and targeting tumours by both passively and actively specifically by the Enhanced Permeation and Retention (EPR) effect or Ligand-mediated targeting, makes them particularly useful for oncological purposes. SLNs have demonstrated great promise in the delivery of traditional chemotherapeutics such as paclitaxel and doxorubicin and more advanced modalities such as gene therapy and combination therapy. Although potential SLNs present major formulation challenges, which include stability, drug entrapment efficiency, scale-up flexibility, and strict regulatory compliance. Advancements in lipid selection, process development, and surface modification are ongoing and continue to overcome these limitations. With strict quality control tests and implementation of Good Manufacturing Practices (GMP), SLNs are well-positioned to fill the gap between nanotechnology and clinical oncology which could lead to more effective, safer, and patient-specific cancer treatments.

REFERENCES

[1] Wang AZ, Langer R, Farokhzad OC. Nanoparticle Delivery Of Cancer Drugs. Annu Rev Med 2012;63:185–98.

[2] Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC. Nanoparticles In Medicine: Therapeutic Applications And Developments. Clin Pharmacol Ther 2008;83:761–9.

[3] Mehnert W, Mäder K. Solid Lipid Nanoparticles: Production, Characterization And Applications. Adv Drug Deliv Rev 2001;47:165–96.

[4] Kim JO, Ramasamy T, Tran TH, Choi JY, Cho HJ, Kim JH, Et Al. Layer-By-Layer Coated Lipid-Polymer Hybrid Nanoparticles Designed For Use In Anticancer Drug Delivery. Carbohydr Polym 2014;102:653–61.

[5] Wissing SA, Kayser O, Müller RH. Solid Lipid Nanoparticles For Parenteral Drug Delivery. Adv Drug Deliv Rev 2004;56:1257–72.

[6] Mendoza-Muñoz N, Urbán-Morlán Z, Leyva-Gómez G, De La Luz Zambrano-Zaragoza M, Piñón-Segundo E, Quintanar-Guerrero D. Solid Lipid Nanoparticles: An Approach To Improve Oral Drug Delivery. Journal Of Pharmacy And Pharmaceutical Sciences 2021;24:509–32.

[7] Yang S, Zhu J, Lu Y, Liang B, Yang C. Body Distribution Of Camptothecin Solid Lipid Nanoparticles After Oral Administration. Pharm Res 1999;16:751–7.

[8] Suk JS, Xu Q, Kim N, Hanes J, Ensign LM. Pegylation As A Strategy For Improving Nanoparticle-Based Drug And Gene Delivery. Adv Drug Deliv Rev 2015;99:28.

[9] Almeida AJ, Souto E. Solid Lipid Nanoparticles As A Drug Delivery System For Peptides And Proteins. Adv Drug Deliv Rev 2007;59:478–90.

[10] Lu P. Monitoring Cardiac Function In Patients Receiving Doxorubicin. Semin Nucl Med 2005;35:197–201.

[11] Kumar, R., & Saha, P. (2022). A review on artificial intelligence and machine learning to improve cancer

management and drug discovery. International Journal for Research in Applied Sciences and Biotechnology, 9(3), 149-156,

[12] Barenholz Y. Doxil® - The First FDA-Approved Nano-Drug: Lessons Learned. Journal Of Controlled Release 2012;160:117–34.

[13] Dong Y, Siegwart DJ, Anderson DG. Strategies, Design, And Chemistry In Sirna Delivery Systems. Adv Drug Deliv Rev 2019;144:133–47.

[14] Gottesman MM, Fojo T, Bates SE. Multidrug Resistance In Cancer: Role Of ATP-Dependent Transporters. Nat Rev Cancer 2002;2:48–58.

[15] Dean M, Hamon Y, Chimini G. The Human ATP-Binding Cassette (ABC) Transporter Superfamily. J Lipid Res 2001;42:1007–17.

[16] Yallapu MM, Othman SF, Curtis ET, Bauer NA, Chauhan N, Kumar D, Et Al. Curcumin-Loaded Magnetic Nanoparticles For Breast Cancer Therapeutics And Imaging Applications. Int J Nanomedicine 2012;7:1761–79.

[17] Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MDP, Acosta-Torres LS, Et Al. Nano Based Drug Delivery Systems: Recent Developments And Future Prospects. Journal Of Nanobiotechnology 2018 16:1 2018;16:1–33.

[18] Edis Z, Wang J, Waqas MK, Ijaz M, Ijaz M. Nanocarriers-Mediated Drug Delivery Systems For Anticancer Agents: An Overview And Perspectives. Int J Nanomedicine 2021;16:1313–30.

[19] Ekambaram P, Abdul A, Sathali H, Priyanka K. SOLID LIPID NANOPARTICLES: A REVIEW. Sci Revs Chem Commun 2012;2:80–102.

[20] Mukherjee S, Ray S, Thakur RS. Solid Lipid Nanoparticles: A Modern Formulation Approach In Drug Delivery System. Indian J Pharm Sci 2009;71:349–58.

[21] Kumar, R., Saha, P., Kumar, Y., Sahana, S., Dubey, A., & Prakash, O. (2020). A review on diabetes mellitus: type1 & Type2. World Journal of Pharmacy and Pharmaceutical Sciences, 9(10), 838-850.

[22] Campos JR, Severino P, Santini A, Silva AM, Shegokar R, Souto SB, Et Al. Solid Lipid Nanoparticles (SLN): Prediction Of Toxicity, Metabolism, Fate And Physicochemical Properties. Nanopharmaceuticals: Volume 1: Expectations And Realities Of Multifunctional Drug Delivery Systems 2020:1–15.

[23] Harde H, Das M, Jain S. Solid Lipid Nanoparticles: An Oral Bioavailability Enhancer Vehicle. Expert Opin Drug Deliv 2011;8:1407–24.

[24] Rostami E, Kashanian S, Azandaryani AH, Faramarzi H, Dolatabadi JEN, Omidfar K. Drug Targeting Using Solid Lipid Nanoparticles. Chem Phys Lipids 2014;181:56–61.

[25] Nguyen T-T-L, Duong V-A. Solid Lipid Nanoparticles. Encyclopedia 2022, Vol 2, Pages 952-973 2022;2:952–73.

[26] Madkhali OA. Perspectives And Prospective On Solid Lipid Nanoparticles As Drug Delivery Systems. Molecules 2022;27.

[27] Üner M, Yener G. Importance Of Solid Lipid Nanoparticles (SLN) In Various Administration Routes And Future Perspectives. Int J Nanomedicine 2007;2:289.

[28] Dhiman N, Awasthi R, Sharma B, Kharkwal H, Kulkarni GT. Lipid Nanoparticles As Carriers For Bioactive Delivery. Front Chem 2021;9:580118.

[29] Paliwal R, Paliwal SR, Kenwat R, Kurmi B Das, Sahu MK. Solid Lipid Nanoparticles: A Review On Recent Perspectives And Patents. Expert Opin Ther Pat 2020;30:179–94.

[30] Jenning V, Gohla SH. Encapsulation Of Retinoids In Solid Lipid Nanoparticles (SLN). J Microencapsul 2001;18:149–58.

[31] Mukherjee S, Ray S, Thakur RS. Solid Lipid Nanoparticles: A Modern Formulation Approach In Drug Delivery System. Indian J Pharm Sci 2009;71:349.

[32] Shegokar R, Singh KK, Müller RH. Production & Stability Of Stavudine Solid Lipid Nanoparticles—From Lab To Industrial Scale. Int J Pharm 2011;416:461–70.

[33] Trotta M, Debernardi F, Caputo O. Preparation Of Solid Lipid Nanoparticles By A Solvent Emulsification–Diffusion Technique. Int J Pharm 2003;257:153–60.

[34] Khairnar S V., Pagare P, Thakre A, Nambiar AR, Junnuthula V, Abraham MC, Et Al. Review On The Scale-Up Methods For The Preparation Of Solid Lipid Nanoparticles. Pharmaceutics 2022;14:1886.

[35] Battaglia L, Gallarate M, Panciani PP, Ugazio E, Sapino S, Peira E, Et Al. Techniques For The Preparation

Of Solid Lipid Nano And Microparticles. Application Of Nanotechnology In Drug Delivery 2014.

[36] Shah RM, Eldridge DS, Palombo EA, Harding IH. Microwave-Assisted Formulation Of Solid Lipid Nanoparticles Loaded With Non-Steroidal Anti-Inflammatory Drugs. Int J Pharm 2016;515:543–54.

[37] Khairnar S V., Pagare P, Thakre A, Nambiar AR, Junnuthula V, Abraham MC, Et Al. Review On The Scale-Up Methods For The Preparation Of Solid Lipid Nanoparticles. Pharmaceutics 2022;14.

[38] Duong VA, Nguyen TTL, Maeng HJ. Preparation Of Solid Lipid Nanoparticles And Nanostructured Lipid Carriers For Drug Delivery And The Effects Of Preparation Parameters Of Solvent Injection Method. Molecules 2020;25.

[39] Schubert MA, Müller-Goymann CC. Solvent Injection As A New Approach For Manufacturing Lipid Nanoparticles – Evaluation Of The Method And Process Parameters. European Journal Of Pharmaceutics And Biopharmaceutics 2003;55:125–31.

[40] Hielscher T. Ultrasonic Production Of Nano-Size Dispersions And Emulsions 2007:14–6.

[41] Kumar R, Singh A, Garg N, Siril PF. Solid Lipid Nanoparticles For The Controlled Delivery Of Poorly Water Soluble Non-Steroidal Anti-Inflammatory Drugs. Ultrason Sonochem 2018;40:686–96.

[42] Dong X, Mattingly CA, Tseng MT, Cho MJ, Liu Y, Adams VR, Et Al. Doxorubicin And Paclitaxel-Loaded Lipid-Based Nanoparticles Overcome Multidrug Resistance By Inhibiting P-Glycoprotein And Depleting ATP. Cancer Res 2009;69:3918–26.

[43] Rajoriya V, Gupta R, Vengurlekar S, Jain SK. Folate Conjugated Nano-Lipid Construct Of Paclitaxel For Site-Specific Lung Squamous Carcinoma Targeting. Int J Pharm 2025;672:125312.

[44] 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. Nanomedicine 2010;6:210–3.

[45] Gabizon AA, Gabizon-Peretz S, Modaresahmadi S, La-Beck NM. Thirty Years From FDA Approval Of Pegylated Liposomal Doxorubicin (Doxil/Caelyx): An Updated Analysis And Future Perspective. BMJ Oncology 2025;4.

[46] Da Rocha MCO, Da Silva PB, Radicchi MA, Andrade BYG, De Oliveira JV, Venus T, Et Al. Docetaxel-Loaded Solid Lipid Nanoparticles Prevent Tumor Growth And Lung Metastasis Of 4T1 Murine Mammary Carcinoma Cells. J Nanobiotechnology 2020;18.

[47] Al-Nemrawi NK, Altawabeyeh RM, Darweesh RS. Preparation And Characterization Of Docetaxel-PLGA Nanoparticles Coated With Folic Acid-Chitosan Conjugate For Cancer Treatment. J Pharm Sci 2022;111:485–94.

[48] Dong X, Mumper RJ. Nanomedicinal Strategies To Treat Multidrug-Resistant Tumors: Current Progress. Nanomedicine (Lond) 2010;5:597.

[49] Viegas C, Patrício AB, Prata JM, Nadhman A, Chintamaneni PK, Fonte P. Solid Lipid Nanoparticles Vs. Nanostructured Lipid Carriers: A Comparative Review. Pharmaceutics 2023;15:1593.

[50] Lee MK, Lim SJ, Kim CK. Preparation, Characterization And In Vitro Cytotoxicity Of Paclitaxel-Loaded Sterically Stabilized Solid Lipid Nanoparticles. Biomaterials 2007;28:2137–46.

[51] Patil YB, Swaminathan SK, Sadhukha T, Ma L, Panyam J. The Use Of Nanoparticle-Mediated Targeted Gene Silencing And Drug Delivery To Overcome Tumor Drug Resistance. Biomaterials 2010;31:358–65.

[52] Yu YH, Kim E, Park DE, Shim G, Lee S, Kim YB, Et Al. Cationic Solid Lipid Nanoparticles For Co-Delivery Of Paclitaxel And Sirna. European Journal Of Pharmaceutics And Biopharmaceutics 2012;80:268–73.

[53] Lv H, Zhang S, Wang B, Cui S, Yan J. Toxicity Of Cationic Lipids And Cationic Polymers In Gene Delivery. Journal Of Controlled Release 2006;114:100–9.

[54] Gao L, Meng F, Yang Z, Lafuente-Merchan M, Fernández LM, Cao Y, Et Al. Nano-Drug Delivery System For The Treatment Of Multidrug-Resistant Breast Cancer: Current Status And Future Perspectives. Biomedicine & Pharmacotherapy 2024;179:117327.

[55] Han Y, Zhang P, Chen Y, Sun J, Kong F. Co-Delivery Of Plasmid DNA And Doxorubicin By Solid Lipid Nanoparticles For Lung Cancer Therapy. Int J Mol Med 2014;34:191–6.

[56] Sadhukha T, Wiedmann TS, Panyam J. Inhalable Magnetic Nanoparticles For Targeted Hyperthermia In Lung Cancer Therapy. Biomaterials 2013;34:5163–71.

[57] Bayón-Cordero L, Alkorta I, Arana L. Application Of Solid Lipid Nanoparticles To Improve The Efficiency Of Anticancer Drugs. Nanomaterials 2019, Vol 9, Page 474 2019;9:474.

[58] Duan Y, Dhar A, Patel C, Khimani M, Neogi S, Sharma P, Et Al. A Brief Review On Solid Lipid Nanoparticles: Part And Parcel Of Contemporary Drug Delivery Systems. RSC Adv 2020;10:26777–91.

[59] Patel P, Garala K, Singh S, Prajapati BG, Chittasupho C. Lipid-Based Nanoparticles In Delivering Bioactive Compounds For Improving Therapeutic Efficacy. Pharmaceuticals 2024;17:329.

[60] Beloqui A, Solinís MÁ, Rodríguez-Gascón A, Almeida AJ, Préat V. Nanostructured Lipid Carriers: Promising Drug Delivery Systems For Future Clinics. Nanomedicine 2016;12:143–61.

[61] Mall J, Naseem N, Haider Mdf, Rahman MA, Khan S, Siddiqui SN. Nanostructured Lipid Carriers As A Drug Delivery System: A Comprehensive Review With Therapeutic Applications. Intelligent Pharmacy 2024.

[62] Duong VA, Nguyen TTL, Maeng HJ. Preparation Of Solid Lipid Nanoparticles And Nanostructured Lipid Carriers For Drug Delivery And The Effects Of Preparation Parameters Of Solvent Injection Method. Molecules 2020;25.

[63] Arpicco S, Battaglia L, Brusa P, Cavalli R, Chirio D, Dosio F, Et Al. Recent Studies On The Delivery Of Hydrophilic Drugs In Nanoparticulate Systems. J Drug Deliv Sci Technol 2016;32:298–312.

[64] Mahor AK, Singh PP, Gupta R, Bhardwaj P, Rathore P, Kishore A, Et Al. Nanostructured Lipid Carriers For Improved Delivery Of Therapeutics Via The Oral Route. J Nanotechnol 2023;2023:4687959.

[65] Badawi N, El-Say K, Attia D, El-Nabarawi M, Elmazar M, Teaima M. Development Of Pomegranate Extract-Loaded Solid Lipid Nanoparticles: Quality By Design Approach To Screen The Variables Affecting The Quality Attributes And Characterization. ACS Omega 2020;5:21712–21.

[66] Musielak E, Feliczak-Guzik A, Nowak I. Optimization Of The Conditions Of Solid Lipid Nanoparticles (SLN) Synthesis. Molecules 2022;27:2202.

[67] Fatima F, Aleemuddin M, Ahmed MM, Anwer MK, Aldawsari MF, Soliman GA, Et Al. Design And Evaluation Of Solid Lipid Nanoparticles Loaded Topical Gels: Repurpose Of Fluoxetine In Diabetic Wound Healing. Gels 2023, Vol 9, Page 21 2022;9:21.

[68] Ebrahimi HA, Javadzadeh Y, Hamidi M, Jalali MB. Repaglinide-Loaded Solid Lipid Nanoparticles: Effect Of Using Different Surfactants/Stabilizers On Physicochemical Properties Of Nanoparticles. DARU, Journal Of Pharmaceutical Sciences 2015;23:1–11.

[69] International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use Impurities: Guideline For Residual Solvents Q3c(R8)