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REVIEW ARTICLE

SOLID LIPID NANOPARTICLES AS A PROMISING APPROACH FOR DELIVERY OF ANTICANCER AGENTS: REVIEW ARTICLE

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Summary

Cancer disease has a complicated pathophysiology and is one of the major causes of death and morbidity. Classical cancer therapies include chemotherapy, radiation therapy, and immunotherapy. A typical treatment is chemotherapy, which delivers cytotoxic medications to patients to suppress the uncontrolled growth of cancerous cells. Conventional oral medication has a number of drawbacks, including a lack of selectivity, cytotoxicity, and multi-drug resistance, all of which offer significant obstacles to effective cancer treatment. Multidrug resistance (MDR) remains a major challenge for effective cancer chemotherapeutic interventions. The advent of nanotechnology approach has developed the field of tumor diagnosis and treatment. Cancer nanotechnology enables direct access to tumor cells, resulting in enhanced drug localization and cellular uptake. Since the early 1990's, several solid lipid nanoparticle (SLN) or SLN-based systems for the delivery of cytotoxic drugs have been manufactured and tested with success. High shear homogenization, microemulsion-based SLN, Supercritical fluid technology, spray drying, and solvent emulsification/evaporation methods can all be used to successfully formulate SLN.There is great potential to enhance cancer chemotherapy by incorporating it into a solid lipid nanoparticle (SLN) drug delivery system. Improving tumor diffusivity, improvement of body distribution, and inhibiting MDR are the main attributes. This type of review article discusses advantages and disadvantages of SLNs, their production techniques, and their potential usage in the treatment of various cancers.

Key words: Cancer; Chemotherapy; Multiple drug resistance; Solid lipid nanoparticles; Cytotoxic drugs

1. Introduction

Cancer is considering one of the major causes of death around the world .According to World Health Organization (WHO), cancer is responsible for 1.9 million death in 2021 (1). Female patients are most likely to develop thyroid, lung, and breast cancers, whereas male patients are most likely to develop lung, colon, liver, and prostate cancers (2). The early diagnosis of cancer disease is considered the critical step in improving cancer therapy. When cancer is diagnosed at an early stage, the effective therapy could be more effective and successful. Cancer treatment regimen includes surgical removal, chemotherapy, radiation, and hormone therapy. Conventional chemotherapy

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is the most frequently used systemic treatment for suppressing cancer cell proliferation and metastasis. However systemic administration of chemotherapeutic agents for cancer patients produces severe side-effects due to their non-specific targeting and cytotoxic effects even on non- target normal cells. The common side effects caused by conventional chemotherapy are alopecia, depression, anemia, mouth sores, nausea, vomiting, neutropenia, thrombocytopenia etc. These side effects could be cute or chronic and may lead to discomfort and inconvenience and even cause death in some cases (3). Therefore a significant efforts have been devoted to develop Nano carrier system that can show higher specificity to tumor cells with no/minimal effects on healthy cells.

Nanotechnology approach has ushered in a new era of specific tumor targeting. It has been widely used over the last decade as it offers multiple advantages to overwhelm the limitations of classical chemotherapies. Nanoparticles (NP) are colloidal carriers ranging from 1 to 1000 nm in size with natural or synthetic origins. Colloidal drug delivery is regarded a promising strategy for cancer treatment due to the high loading capacity, excellent stability, high specificity and low over all toxicity for the patients. These advantages stem not only from their ability to be manufactured at nanoscales, but also from their flexibility to be synthesized from a variety of components such as lipids, surfactants, and polymers. Solid lipid nanoparticles (SLN) have emerged as an unique colloidal carrier system in the last years due to their ability to combine multiple advantages while avoiding the drawbacks of existing colloidal carriers (4).

1.1 Methods

A coherent and detailed search was done by the Authors using specific terms "Anticancer agents" , "solid lipid nanoaparticles", "SLNs preparation techniques", "Novel drug delivery approach" from PubMed, google scholar, Ohio link electronic database conducted till October 2021. Following that, all of the publications were exhaustively investigated and well presented in the manuscript.

2. Obstacles to Conventional chemotherapy

MDR is defined as the cross resistance of cancer cells to the therapeutic actions of anticancer drugs. MDR mechanisms can be categorized into non-cellular and cellular mechanism. Non –transport Cellular MDR mechanisms involve series of detoxifying enzymes such as glutathione-S- transferase(GST) that catalyzes the biotransformation of organic molecules into more polar compounds to facilitate their excretion. high levels of GSTs enzymes have been reported in a large number of cancer types. The overexpressed GST leads to an accelerated detoxification of cancer drugs thus limiting them from reaching to desired concentration inside tumor cells. The transport based cellular MDR mechanism involves active efflux of a broad range of cytotoxic molecules by some membrane transporters (5). Breast Cancer Resistant Protein (BCRP) and P-glycoprotein (PGP)) are two prominent members of the ABC transporters. These efflux transporters are responsible for transport multiple chemical classes of compounds and act as barriers to tissue permeability. P-glycoprotein and BCRP are overexpressed on the surface of malignant cells, preventing drug accumulation within the tumor and thereby mediating the development of anticancer treatment resistance (6, 7). Non-cellular MDR mechanisms involve factors that are extracellular such as poor vasculature of solid tumor and lack of oxygen and nutrients that lead to confer resistance to chemotherapy and may further limit the clinical outcome. Gene mutations, are also considered one of the main causes of MDR. Researchers frequently discovered mutations in the TP53 gene in tumors. Normally, anticancer drugs that cause DNA damage trigger cell death via the TP53 genome's activity. In contrast, when it is depleted in cancer cells, it allows for continuous replication regardless of the type or extent of DNA damage, making them more resistant to cytotoxic drugs (8). Conclusively, The abnormal vasculature of solid tumor ,elevated metabolism of drugs, increase efflux of genotoxic drugs and genetic factors could be considered the main factors associated with development of MDR.Therfore a lot of novel strategies were designed by scientists to treat cancers through diminishing development of MDR in cancer cells.

Recently the nanotechnology has attracted increasing attention for more specific tumor targeting. Nanoparticle (NP)-based drug delivery systems have shown many advantages in chemotherapy, such as good pharmacokinetics, precise tumor targeting and reduction of drug resistance. In particular, SLNs are capable of circumventing the drug resistance mechanisms as a result of two critical characteristics : (i)Ability of SLN to avoid efflux transporter such as P-glycoprotein(ii) Drug loaded SLN can specially transport of many compounds that inhibit MDR mechanism.

It was demonstrated that the tamoxifen loaded SLN reversed the Tamoxifen resistance by inducing apoptosis in MCF7 and MCF7-TamR cells without damaging control cells (9). Thus, approaches based on the special features of SLNs formulations could be key for future antitumor therapy utilizing novel drug delivery systems.

3. Solid lipid nanoparticles

Solid Lipid Nanoparticles (SLN) are newest class of drug carrier which have size in between 10 and 1000 nm. These colloidal lipid carriers designed to be solid at room temperature and also in body temperature. SLN is consist of solid lipid, surfactant, co-surfactant and deionized water. A wide variety of lipids were used in preparing of SLN such as fatty acids, steroids, waxes, triglycerides, acyl glycerols and their combinations. The incorporation of drugs in solid lipids instead of liquid lipids improves the stability of incorporated chemically sensitive lipophilic ingredients and has been shown to increase control release kinetic of incorporated drugs. In addition the rate of degradation reactions could be reduced because the mobility of the compounds in a solid matrix is lower than a liquid matrix. Müller *et al*. found that SLN made from glyceryl palmitostearate was stable for up to thirty six months and had an average diameter of 160 to 220 nm (10). Other major excipients of SLNs are surfactants. The Most commonly used surfactants in the production of SLN are lecithin, bile acid, Polysorbates, and polaxamer They are primarily used as an emulsifier in the creation of o/w type emulsions and as a stabilizer in SLN preparations. The choice of the suitable surfactant and their concentration have great impact on the quality of prepared SLN. It was found that 1.5% of Polyglyceryl-3 Methylglucose Distearate (TegoCare1450) was the most effective stabilizer for SLN dispersion compared to Tween80, and Pluronic F68. The efficacy of drug entrapment in SLNs products is dependent on several factors, including the molecular weight of the drug loaded, the polymorphism of the lipid matrix, and the solubility of the drug molecule in lipids (11). SLNs prepared using lipids of less ordered crystal lattices such as glycerylmonostearate show high drug loading capacity, compared to those prepared using highly ordered crystal lipids such as solid paraffin, and beeswax. The glyceride's lipophilicity increases in proportion to the length of the hydrocarbon chain. As a result, hydrophobic compounds dissolve more readily in fatty acid chain-length-longer lipid melts. Solubility of the drug molecule in the molten lipid is more than in the solid lipid and this is the critical element that determine maximum amount of drug loaded and entrapment efficiency. In addition, using of high amount of surfactants used in preparation of SLN should be avoided to prevent decrease in entrapment efficiency (12). The release of drug from SLNs depends on matrix type and location of the drug in the colloidal formulation. In SLN, the drug is either adhered to the core or to the surface, and such a system can exhibit flexible release characteristics, including immediate or sustained release, or a combination of both. Drug embedded on the surface of SLN will show an immediate release effect due to partitioning of drug in aqueous phase , thereafter the matrix can erode and release the drug in a controlled manner. Burst drug release from the SLN can occur as a result of applying high temperature or usage of a significant amount of surfactant during SLN preparation. Therfore, the SLN is normally synthesized at room temperature in order to prevent burst release and possibility of drug partitioning into the aqueous phase. This can lead to partitioning a considerable amount of the drug into the lipid phase, resulting in a controlled release of the medication from SLNs formulations (13, 14).

3.1 Advantages of SLNs

- Utilization of physiological lipids may mitigate the risk of acute and chronic toxicity.
- Improved solubility and bioavailability of molecules that are poorly soluble in water.
- Site-specific targeting of the drugs, increased drug permeation across the blood-brain barrier (BBB).
- Chemically labile agents are protected from degradation, and moisture sensitive molecules are protected from the outside environment.
- SLNs exhibit high stability and lower production costs compared to liposomes.
- Lyophilization is possible.
- Much easier to formulate than polymeric nanoparticles.
- Avoidance use of toxic additives such as organic solvents.
- They are suitable to be sterilized by different methods such as autoclaving ,filtration and irradiation.
- Excellent long-term stability.
- They can be administered by parenteral or non-parenteral routes (15).
- Good carrier for lipophilic and hydrophilic molecules (16).

3.2 Disadvantages of SLNs

- Poor drug loading capacity due to crystalline structure of the lipids used.
- Possibility of drug expulsion following polymeric change of solid lipid during storage (17).
- Particle growth could occur (18).
- Un expected gelation tendency (19).

3.3 Preparation methods of SLNs

SLNs are made from lipid, emulsifier, and water/solvent in a variety of techniques, which are mentioned below:

3.3.1 High pressure homogenization (HPH)

It is a dependable and effective strategy which is used for manufacturing of nanoemulsion and SLNs. The technique is based on particle size reduction under intense pressure settings .High pressure homogenizers use high pressure (100–2000 bar) to force a liquid through a narrow gap (in the range of a few microns). Pressure causes fluids to accelerate and move at a very high velocity (above 1000 km/h) for a short distance. Shearing stress and cavitation forces produced as a result might disrupt the particles, decreasing their sizes to the required nanometer scale. This process is cycled until ideal size is obtained (20). Hot and cold homogenization are the two approaches often used prepare SLNs using the high shear technique. These approaches work on same concept of dissolving and dispersing drug in the bulk melted lipid. In hot homogenization technique the active ingredient is dissolved in the melted lipid and mixed homogenously (21). A coarse pre-emulsion is prepared by dispersing the lipid melt in a hot surfactant solution that has been heated to a high temperature above the lipid's melting point while stirring. The resultant hot pre-emulsion is then passed through a high pressure homogenizer for 3 to 5 cycles until the fluid droplets are gradually broken down to the required particle size in the submicron range.The obtained oil in water ME is then allowed to cooldown to room temperature or lesser which result in recrystallization of lipid and formation of SLNs (22). This method is suitable for drugs that are lipophilic or insoluble in water, but is insufficient for drugs that are hydrophilic. Additionally, the use of high temperatures in the aforementioned technique may result in the degradation of heat-sensitive drugs (23). Cold HPH was developed to combat the limitations associated with hot homogenization method such as faster degradation of active ingredient due to use of high temperatures and distribution of drug during homogenization into the water phase.In this technique the drug initially dissolved in molten lipids then the mixtures are rapidly cooled with aid of gas nitrogen or dry ice. The solid material is ground by a Ball mill or mortar.The typical particle size attained in the range of 50-1000 micron.The lipid micro-particles produced are then dispersed in a chilled emulsifier solution yielding a pre-suspension. The dispersion is homogenized under cold conditions over five to ten cycles at a pressure of five hundreds bar where the cavitation force is sufficient to break the micro-particles into SLNs (24). The cold homogenization approach reduce the sample's thermal exposure, but it does not eliminate it due to the melting of the lipid/drug mixture in the first step. On the other hand, cold homogenization samples have larger particle sizes and a wider size distribution than homogenization samples (20).

3.3.2 Ultrasonication and /or high speed homogenization

High speed stirring has been one of the simplest and most cost-effective methods of manufacturing SLNs. The feature of this technique is that the required equipment is readily available in every single laboratory. According to this method, the drug is first added to the previously melted lipid at temperatures 5–10 ºC above the melting point of solid lipids. At the same temperature, an aqueous surfactant solution is made, then added to the molten lipid-drug, and the whole mixture is uniformly dispersed with using of high shear mixing apparatus. The obtained pre emulsion is ultrasonicated using probe sonicator with a water bath at 0 ºC.The resultant nanoemulsion is then filtered through a 0.45 μm membrane filter. Finally, by allowing the heated nanoemulsion to cool to ambient temperature, SLN are obtained. and stored properly at 4 ºC to increase stability of the produced SLNs (25). However, there are some disadvantages related with this technique such as significant physical instability ,bulky size particle growth upon storage and contamination with impurities by high speed stirring homogenizer and probe sonicator used in production of SLNs (26).

3.3.3 Microemulsion

SLN formulation were first developed by Gasco on the basis of dilution microemulsion (27). Microemulsions (MEs) are transparent isotropic mixtures that are typically made up of lipid or oil, surfactant and/or co-emulsifier and water. In this method the lipids are melted above their melting temperature and a combinations of surfactant, co-surfactant and water are added at the same temperature to produce oil in water ME while gentle stirring (28, 29). SLNs with a reduced mean particle size and narrow size distribution can be obtained after dilution of the hot ME in cold water at temperature of 2-10°C. The volume ratio of hot ME to cold water should be between 1:25 and 1:50 (30). When diluted, a nanoemulsion (NE) is generated and the lipids droplets rapidly crystallize to produce SLN. The main advantage of this technique is that no additional energy is required to reach the submicron range.

3.3.4 Spray drying method

It is an alternative method to the freeze-drying procedure for modifying the aqueous dispersion of the drug. This recommends the use of lipids with a boiling point more than 70ºC selected for spray drying. There are several techniques to manufacturing drug-incorporated SLNs by spray drying method. The first method involves converting a drug-loaded nan suspension into free powder . In the second method, drug-loaded SLN is suspended in a polymer solution to form SLN polymer composites that can be dissolved later to release SLN . The third approach involves converting a lipid, drug, and polymer solution to SLN-incorporated polymer particles that may then be dissolved in water to produce SLNs. The best result was achieved by trehalose in ethanol–water mixtures (10/90 v/v (31).

3.3.5 Solvent evaporation method

This method is based on precipitation of the lipids from O/W emulsion preparation. The lipid is dissolved in a water-insolube organic solvent (such as cyclohexane , chloroform) which is then emulsified in an aqueous phase to generate a nanodispersion. The organic solvent is evaporated under reduced pressure using a rotary evaporator with simple mechanical agitation. Following evaporation of the organic solvent, the lipid in the aqueous medium precipitates to create the SLNs loaded drug .This method has the benefit of avoiding heat during the preparation process, makings it suitable for the incorporation of highly thermo-sensitive drugs. Problems might arise due to presence of organic solvent residues in the final formulation which may cause toxicological issues (32).

3.3.6 Solvent injection method

In this technique , the drug and lipid are dissolved in a water- miscible organic solvent (ethanol). Under continuous stirring, the organic mixture is injected through syringe needle into aqueous phase containing surfactantsThe resulting dispersion is then filtered via filter paper to eliminate any remaining lipid . Addition of an emulsifier to the liquid phase aids in formation of lipid droplets at the injection site and stabilization of SLNs until the full diffusion of solvent is completed by lowering the surface tension between solvent and water. The advantages of this technology include ease of handling and quick production process that does not require technically sophisticated equipments (e.g., high-pressure homogenizer) (33).

3.3.7 Supercritical fluid method

In recent years, there has been a surge of interest in supercritical fluid (SCF) technology for the production of nanoparticles . It is solvent-free process that uses of supercritical fluids such as supercritical CO_2. Supercritical CO_2 is the most popular SCF, because of non-toxicity, non-flammability, high diffusity,low viscosity, and easily accessible in critical condition such as Tc=304.25K and Pc=73.7 bar (34). Various supercritical fluid technique are being developed to design particles for multiple purposes in the drug delivery system. The main techniques used for produce nanoparticles by SCF are the rapid expansion of supercritical solutions (RESS), the supercritical anti-solvent process (SAS) gas anti-solvent process (GAS), and Supercritical Fluid Extraction of Emulsions (SFEE). Of these techniques, SFEE is the simplest method in which lipid nanoparticles are manufactured by supercritical fluid extraction of the organic solvent from oil in water emulsions. Water-immiscible and water-partially miscible solvents are used to make the o/w emulsions type. Typically, the emulsion is introduced from the top of an extraction column, while supercritical carbon dioxide is given counter-currently from the bottom.

Due to higher extraction efficiency of SFEE, the solvent is rapidly and fully eliminated, resulting in lipid precipitation. Additionally, the generated SLNs exhibit a homogeneous particle size distribution and narrow polydispersity index (35).

3.4 SLNs as potential carriers for anticancer compounds

SLN has been represented as valuable as medication carriers for treatment neoplasms. Tumor targeting was achieved with drug-stacked SLNs, for example, camptothecin and methotrexate. It was founded that SLNs have "enhanced permeation and retention" (EPR) effect. Various macromolecules, protein, polymeric conjugates, and nanoparticles, accumulate preferentially in solid malignant cells.This process, which is exploited to target cancerous cells, is termed as the EPR phenomena (36). Malignant cells have an unique vasculature in relative to healthy tissue cells. Tumor cells are characterized by irregularly shaped, dilated, and leaky blood vessels. Additionally, they have disordered endothelial cells with numerous fenestrations, as well as a lack of or irregularity of microvascular cells and smooth-muscle layers. Tumor tissues are distinguished by a large lumen and poor lymphatic drainage. These properties facilitate the flow of blood plasma constituents into tumor sites, including macromolecules, lipid nanoparticles, and other molecules. Due to the sluggish venous return to tumor tissue and inadequate lymphatic clearance, these molecules are trapped in the tumor, results in an EPR effect.In addition, SLNs provide an additional advantage, they can be phagocytosed, enhancing the cellular internalization of the drug and leading to drug delivery closer to the site of action (37).

Recently, SLNs have been widely studied as anticancer drug carriers. They have been demonstrated to be a viable carrier system for a range of tumor types, including breast, lung, colon, hepatic, and brain cancer.

3.4.1 Breast cancer

Breast cancer (BC) is one of the most popularly diagnosed solid tumor in women around the world. The rate of prevalence of carcinoma is steady increasing because of enhancements in multiple risk factors namely, environment, hormonal and lifestyle. Metastasis to other organs such as the liver, lungs, lymph nodes, bones, and the brain has been documented as a leading cause of death in patients diagnosed with BC (38).

Paclitaxel (PTX) is an active antineoplastic agent that is widely used for the treatment of wide variety of human malignancies including breast, ovarian, and other cancers.it has been reported that PTX loading SLNs showed significantly higher anticancer potential against Resistant breast cancer cells MCF7/ADR as compared to marketed PTX formulation and significantly improved cell penetration in MCF7/ADR with different endocytosis mechanisms (39). Kumar *et al*. developed the Paclitaxel and Embelin loaded PEGylated SLNs as combination therapy to target tumor cells.Embellin is non-peptide small-molecule isolated from dried berries of *Embelia ribes* plants. Embelin played an important role in upregulation of the Tumor necrosis factor (TNFα) induced apoptosis of paclitaxel. Hot homogenization method was used to prepare PTX-EMB. loaded PEGylated SLNs. The optimized formulation (Paclitaxel and Embelin loaded PEGylated SLNs) exerts synergistic anticancer activity due to anti-cancer effect of PTX and embedin compound (40).

Docetaxel (DTX) is a lipophilic anticancer agent that has been approved by FDA for the treatment various types of tumors such as breast cancer.The clinical effectiveness of Intravenous DTX is limited due to its acquired drug resistant, side effects, poor aqueous solubility and higher toxicity. Therfore, the development of SLNs provides an excellent alternative carrier for prolonging the half-life of DTX in the plasma, avoiding drug toxicity, and increasing DTX distribution to cancerous tissues. Da Rocha *et al.* designed DTX SLNs with Compritol 888 ATO as lipid and Pluronic F127 and Span 80 as emulsifiers to improve stability of nanoparticles dispersion. The dispersion size of the SLN formulation was 128 nm. The half-maximal inhibitory concentration (IC50) of DTX SLN against murine mammary cancer cells (4T1) was greater than 100 times lower than that of free docetaxel after Twenty-Four hours treatment. These findings suggest that SLNs containing DTX may be a suitable colloidal carrier for the treatment of BC patients (41).

Guney Eskiler *et al*. was synthesized tamoxifen SLNs using stearic acid and Tween 80 and tested the SLNs formulations on the breast cancer cells (MCF-7) and Tam-resistant breast cancer cells (MCF-7-TamR) .Cytotoxicity

studies showed the tamoxifen loaded SLN reversed the Tamoxifen resistance by inducing apoptosis in MCF7 and MCF7-TamR cells without damaging control cells (42).

S. Nayek *et al*. was successfully prepared Gifitinib SLNs using novel lipids (Lipoid S PC-3) by hot homogenization method. In vitro cytotoxicity studies showed that optimized SLNs have higher anti-tumor activity (cell viability >65%) compared to free drug (43).

3.4.2 Lung cancer

Lung carcinoma is the most prevalent type of cancer and is the leading cause of death worldwide. Lung cancer (LC) is histologically divided into two types: small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Current available treatment Options are highly dependent on the type of diagnosed tumor and its stage but they frequently include a combination of surgery, chemotherapy, and/or radiation therapy. Chemotherapy is often given intravenously as a first-line treatment for advanced-stage LC. Chemotherapeutic agents such as Cisplatin, carboplatin, paclitaxel, gemcitabine, etoposide, and vinblastine, are used in first-line regimens for treatment LC. The primary disadvantage of these drugs is lack of tumor tissue specificity which results in increased tissue toxicity and hence low therapeutic effectiveness (44).

The delivery of cytotoxic agents into the lungs through lipid nanoparticle is a rapidly emerging and growing topic of research. This method of drug delivery eliminates the need for needles, improving patient compliance. It can be utilized to alleviate the limitations associated with the intravenous(I.V) or oral routes including significant systemic toxicity, low drug solubility in water, low rate of drugs accumulation within the cancer tissue, and increased rate of tumor relapse (45).

Erlotinib (ETB) is a potent reversible kinase inhibitor which is highly overexpressed in lung cancer of NSCLC type. ETB-loaded SLNs were successfully synthesized using hot homogenization method. As a dry powder formulation, ETB-loaded SLNs showed high efficiency of drug encapsulation and great potential of cytotoxicity against human alveolar adenocarcinoma epithelial A549 as compared to drug alone (46).

Gefitinib is another tyrosine kinase inhibitor used in treatment of lung tumor. Nazafarin *et al*. developed glucosamine-conjugated gefitinib SLNs using emulsion-solvent diffusion and evaporation methods. The prepared formulation showed excellent anticancer effect compared to free gefitinib drug through high cellular uptake by A549 cells (47).

A novel oleic acid based SLN s was found to be as an effective nano-carrier for delivery of chemotherapeutic agent such as gemcitabine(GM) and oxaliplatin(OXA).The formulation has been optimized and characterized *in vitro*. The (GM+OXA) oleic acid-SLN formulation had effectively inhibited the proliferation of lung carcinoma cells (A549) in a dose-dependent pattern within twenty-four hours of treatment. Additionally, The (GM+OXA) oleic acid-SLNs had greater effect on apoptosis (326.38 ± 4.21 pg/ml) than the untreated control cells (206.2 ± 6.69 pg/ml) (48).

Recently, it was revealed that compounds derived from natural sources inhibited the proliferation of abnormally divided cells. Silymarin is a bioactive component of Silybum marianum that has significant chemosensitizing, antioxidant, and anti-cancer activity. The cytoprotective and anticancer properties have been studied in breast, prostate, cervical, and lung malignancies. C.V. Sezer developed silymarin SLNs to circumvent the compound's low water solubility and hence enhance its bioavailability. Hot homogenization technique was used to prepare silymarin SLNs. The particle size of the silymarin-incorporated SLNs formulation was measured with Malvern Zetasizer Nano ZS instrument and found to be around 92.5 nm. It has been established that silymarin- SLNs greatly suppress the proliferation of MCF-7 and A549 cells when compared to silymarin solution (49).

3.4.3 Brain cancer

Glioma is the most prevalent encountered malignant brain cancers .Glioblastoma multiforme (GBM) is one of the most aggressive and incurable human cancers, accounting for half of all gliomas. Glioma is an insidious

and destructive types of brain tumor that have poor prognosis, common recurrence and an exceptionally high mortality rate despite the use of a combination of radiotherapy, surgery, and chemotherapy. Poor prognosis can still be problematic as it is the result of limited delivery of therapeutic agents through the blood-brain barrier (BBB), drug resistance, and a high probability of relapse. The use of lipids as matrix for the preparation of SLNs provides numerous benefits over other materials, including: Excellent biocompatibility, minimal cytotoxicity, and controlled drug release (50).

Many studies have demonstrated both in in vivo and *in vitro* the efficacy of nanocarriers for the treatment of GBM. The addition of a hydrophilic or flexible polymer (such as polyethylene glycol, PEG) and/or a surfactant (such as Polysorbate 80 and Poloxamer 188) on the SLN surface may prevent opsonization and facilitates crossing of many therapeutic agents through BBB (51). Albumin, a cationic polymer, has also been frequently used to carry drugs to the brain. Cationic bovine serum albumin (CBSA) was linked to PEG-poly(lactide) (PEG-PLA) nanoparticles. The permeability of CBSA NPs across BBB was about 7.76 folds higher than free bovine serum albumin(BSA), whereas transcytosis was blocked in the presence of abundant free CBSA, confirming that CBSA NPs selectively and specifically penetrate the BBB and targeting brain tumor (52). Tween 80 is not only useful as an emulsifying agent but also has the advantage of increasing the permeability of numerous drugs through BBB (53).

Koziara *et al*. investigated the use of paclitaxel SLNs in the treatment of gliomas and other brain metastases. PTX was incorporated into SLN formula containing cetyl alcohol/polysorbate, as emulsifying wax and Brij 72 as the oil phase and Tween 80 as the surfactants. The researchers used an in vivo rats brain models to determine nanoparticle uptake by the brain. Following the incorporation of paclitaxel in nanoparticles, it was discovered that the drug's brain uptake increased considerably (54). In another study, PTX SLN was developed and conjugated with PEG AND Tyr-3-octreotide (TOC) .TOC act as ligand for Somatostatin receptors (SSTRs) as these receptors is highly expressed in brain tumors. Survival experiment studies confirmed the improved anti-glioma efficacy and Anti-angiogenic activity of prepared TOC SLN formulation without observable accompanied toxicity (55).

Natural compounds such as silymarin, quercetin, silymarin curcumin, quinine, colchicum, resveratrol and rutin have been identified as promising therapies due to their broad biological effects, large safety margins, and cheaper cost. Rutin is flavonoid compound has which has significant pharmacological properties, high antitumor, good antibacterial and antiviral activity. Because of its large macromolecular size and high metabolic activity of the liver, the rutin molecule does not reach the brain in large quantities. Rutin-incorporated SLN was prepared by the ME technique using high-speed homogenizer combined with ultra-sonication method. *In vivo* animal investigations of Rutin SLN revealed that rutin compound was found in the brain tissue at a concentration of 15.23 ± 0.32% after fifty-four hours after injection (56). Trans resveratrol (RSV) is another naturally occurring non flavonoid polyphenolic compound found in abundance in grapes, red wine, peanuts, berries, and a variety of other food. Numerous studies have demonstrated that resveratrol has good anti-glioma action. Due to the resveratrol molecule's short half-life, it is difficult to reach the effective concentration at targeted site. Resveratrol SLNs were successfully designed using Compritol 888 ATO as oil and tween 80 as surfactant. The substantial accumulation of resveratrol compound in the brain of experimental rats when supplied in SLN formulation implies that this type of nanocarrier may be beneficial for delivering resveratrol directly to the brain (57).

In another study resveratrol SLNs was loaded with D-α-tocopheryl polyethylene glycol succinate (TPGS). TPGS has been used in a range of pharmaceutical applications, including bioavailability enhancement, emulsification, and P-glycoprotein (P-gp) inhibition. It has been established that. The area under the curve (AUC) and half-life of RSV-TPGS-SLN were 11.12 and 9.37 times greater than those of RSV solution respectively. Additionally, the brain dispersion of RSV incorporated in TPGS-SLN was shown to be 9.23 times greater than that of RSV alone. These findings strongly suggest that RSV-TPGS-SLNs could be the most effective technique for increasing brain tumor targeting and prolonging RSV circulation (58). Neves *et al*. was also developed RSV SLNs but functionalized with specific type of protein called apolipoprotein E (ApoE). ApoE can be identified by the low density lipoprotein (LDL) receptors that are highly expressed on the BBB. The permeability through hCMEC/D3 monolayers increased significantly (1.8-times higher) for RSV SLNs modified with ApoE when compared to un functionalized one suggesting the potential role of apolipoprotein in enhancing delivery of drugs through BBB (59).

4. Conclusion

SLNs-based drug delivery carries many chemotherapy-enhancing features by enhancing cell uptake of many cancer cells and altering MDR, thereby reducing the dose-related toxicity of anticancer drugs. The ability of SLNs to target the CNS would have implications for enhancing chemotherapy of cancers. The diversity of synthesis method and the simplicity with which SLN may be manufactured on a large scale may contribute to the broad usage of SLN in general, and specifically for cancer treatment.

Conflict of Interest

The authors state that there are no conflicts of interest regarding the publication of this article.

Adherence to Ethical Standards

This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the author.

References

1. Gavas S, Quazi S & Karpiński T. (2021). Nanoparticles for Cancer Therapy: Current Progress and Challenges
2. WHO. Available online: https://www.who.int/news-room/fact-sheets/detail/cancer (accessed on September 2018).
3. Lowenthal RM & Eaton K. Toxicity of chemotherapy. Hematology/Oncology Clinics. 1996;10(4):967-990
4. Wong HL, Bendayan R, Rauth A, et al. Chemotherapy with anticancer drugs encapsulated in solid lipid nanoparticles. Advanced drug delivery reviews. 2007;59(6):491-504.
5. Ullah, M. F. Cancer multidrug resistance (MDR): a major impediment to effective chemotherapy. Asian Pac J Cancer Prev. 2008;9(1):1-6.
6. Luqmani YA. Mechanisms of drug resistance in cancer chemotherapy. Medical principles and practice. 2005;14(Suppl. 1):35-48.
7. Wu CP, Hsiao SH, Huang YH, et al. Sitravatinib sensitizes ABCB1-and ABCG2-overexpressing multidrug-resistant cancer cells to chemotherapeutic drugs. Cancers. 2020;12(1):195.
8. Mantovani F, Collavin L & Del Sal G. Mutant p53 as a guardian of the cancer cell. Cell Death & Differentiation. 2019;26(2):199-212.
9. Javid S, Ziamajidi N, Foroughi S, et al. (2017). Effects of tamoxifen-loaded solid lipid nanoparticles on the estrogen receptor-α (ER-α) and vascular endothelial growth factor-A (VEGF-A) genes expression in the endometrial tissue of ovariectomized female Sprague-Dawley rats. International journal of biological macromolecules. 2017;96:706-712.
10. Wissing SA, Kayser O & Müller RH. Solid lipid nanoparticles for parenteral drug delivery. Advanced drug delivery reviews. 2004;56(9):1257-1272.
11. Kamel AE, Fadel M & Louis D. Curcumin-loaded nanostructured lipid carriers prepared using Peceol™ and olive oil in photodynamic therapy: development and application in breast cancer cell line. International journal of nanomedicine, 2019;14:5073.
12. Manjunath K, Reddy JS & Venkateswarlu V. (2005). Solid lipid nanoparticles as drug delivery systems. Methods Find Exp Clin Pharmacol. 2005;27(2):127-144.
13. Parhi R & Suresh P. Production of solid lipid nanoparticles-drug loading and release mechanism. J Chem Pharm Res. 2010;2(1):211-27.
14. Mishra V, Bansal KK, Verma A, et al. Solid lipid nanoparticles: Emerging colloidal nano drug delivery systems. Pharmaceutics. 2018;10(4):191.
15. Dolatabadi JEN, Valizadeh H & Hamishehkar H. Solid lipid nanoparticles as efficient drug and gene delivery systems: recent breakthroughs. Advanced pharmaceutical bulletin. 2015;5(2):151.
16. Mirchandani Y, Patravale VB & Brijesh S. (2021). Solid lipid nanoparticles for hydrophilic drugs. Journal of Controlled Release.
17. Bunjes H, Westesen K & Koch MH. Crystallization tendency and polymorphic transitions in triglyceride nanoparticles. International journal of pharmaceutics. 1996;129(1-2):159-173.

18. Schubert MA, Müller-Goymann CC. Characterisation of surface-modified solid lipid nanoparticles (SLN): influence of lecithin and nonionic emulsifier. European journal of pharmaceutics and biopharmaceutics. 2005 Sep 1;61(1-2):77-86
19. Rashidi, L. (2021). Different nano-delivery systems for delivery of nutraceuticals. Food Bioscience. 101258.
20. Mehnert W & Mäder K. Solid lipid nanoparticles: production, characterization and applications. Advanced drug delivery reviews. 2012;64:83-101.
21. Suter F, Schmid D, Wandrey F et al. Heptapeptide-loaded solid lipid nanoparticles for cosmetic anti-aging applications. European Journal of Pharmaceutics and Biopharmaceutics. 2016;108:304-309.
22. Gupta S, Kesarla R, Chotai N, et al. (2017). Systematic approach for the formulation and optimization of solid lipid nanoparticles of efavirenz by high pressure homogenization using design of experiments for brain targeting and enhanced bioavailability. Biomed research international, 2017.
23. Das S & Chaudhury A. (2011). Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. Aaps Pharmscitech. 2011;12(1):62-76.
24. Duan Y, Dhar A, Patel C, et al. A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. RSC Advances. 2020;10(45):26777-26791.
25. Ganesan P & Narayanasamy D. (2017). Lipid nanoparticles: Different preparation techniques, characterization, hurdles, and strategies for the production of solid lipid nanoparticles and nanostructured lipid carriers for oral drug delivery. Sustainable Chemistry and Pharmacy. 2017;6:37-56.
26. Silva AC, González-Mira E, García ML, et al. Preparation, characterization and biocompatibility studies on risperidone-loaded solid lipid nanoparticles (SLN): high pressure homogenization versus ultrasound. Colloids and Surfaces B: Biointerfaces. 2011;86(1):158-165
27. Gasco MR. (1993). U.S. Patent No. 5,250,236. Washington, DC: U.S. Patent and Trademark Office.
28. Yasir M, Gaur PK, Puri D, et al. Solid lipid nanoparticles approach for lymphatic targeting through intraduodenal delivery of quetiapine fumarate. Current drug delivery. 2018;15(6):818-828.
29. Masiiwa WL & Gadaga LL. (2018). Intestinal permeability of artesunate-loaded solid lipid nanoparticles using the everted gut method. Journal of drug delivery. 2018.
30. de Souza Guedes L, Martinez RM, Bou-Chacra NA, et al. An Overview on Topical Administration of Carotenoids and Coenzyme Q10 Loaded in Lipid Nanoparticles. Antioxidants. 2021;10(7):1034.
31. Sastri KT, Radha GV, Pidikiti S, et al. (2020). Solid lipid nanoparticles: Preparation techniques, their characterization, and an update on recent studies. J. Appl. Pharm. Sci. 2020;10:126-141.
32. Pooja D, Tunki L, Kulhari H, et al. (2016). Optimization of solid lipid nanoparticles prepared by a single emulsification-solvent evaporation method. Data in brief. 2016;6:15-19.
33. 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(1):125-131.
34. Ting SS, Tomasko DL, Foster NR, et al. Solubility of naproxen in supercritical carbon dioxide with and without cosolvents. Industrial & engineering chemistry research. 1993;32(7):1471-1481.
35. Chattopadhyay P, Shekunov BY, Yim D, et al. Production of solid lipid nanoparticle suspensions using supercritical fluid extraction of emulsions (SFEE) for pulmonary delivery using the AERx system. Advanced drug delivery reviews. 2007;59(6):444-453.
36. Maeda H, Wu J, Sawa T, et al. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. Journal of controlled release. 2000;65(1-2):271-284.
37. Iyer AK, Khaled G, Fang J, et al. Exploiting the enhanced permeability and retention effect for tumor targeting. Drug discovery today. 2006;11(17-18):812-818.
38. Parker B, Sukumar S. Distant metastasis in breast cancer: molecular mechanisms and therapeutic targets. Cancer biology & therapy. 2003;2(1):13-22.
39. 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.
40. Kumar A, Kaur V, Singh A, et al. Development and characterization of paclitaxel and embelin loaded solid lipid nanoparticles for breast cancer. Journal of Drug Delivery and Therapeutics. 2020;10(1):60-68.
41. da Rocha MCO, da Silva PB, Radicchi MA, et al. Docetaxel-loaded solid lipid nanoparticles prevent tumor growth and lung metastasis of 4T1 murine mammary carcinoma cells. Journal of nanobiotechnology. 2020;18(1):1-20.
42. Eskiler GG, Cecener G, Dikmen G, et al. Solid lipid nanoparticles: Reversal of tamoxifen resistance in breast cancer. European Journal of Pharmaceutical Sciences. 2018;120:73-88.

43. Nayek S, Raghavendra NM, Kumar BS. Development of novel S PC-3 gefitinib lipid nanoparticles for effective drug delivery in breast cancer. Tissue distribution studies and cell cytotoxicity analysis. Journal of Drug Delivery Science and Technology. 2021;61:102073.
44. Babu A, Templeton AK, Munshi A, et al. (2013). Nanoparticle-based drug delivery for therapy of lung cancer: progress and challenges. Journal of Nanomaterials, 2013.
45. Amararathna M, Goralski K, Hoskin DW, & et al. Pulmonary nano-drug delivery systems for lung cancer: current knowledge and prospects. Journal of Lung Health and Diseases. 2019;3(2):11-28.
46, Bakhtiary Z, Barar J, Aghanejad A, et al. Microparticles containing erlotinib-loaded solid lipid nanoparticles for treatment of non-small cell lung cancer. Drug development and industrial pharmacy. 2017;43(8):1244-1253.
47. Satari N, Taymouri S, Varshosaz J, et al. Preparation and evaluation of inhalable dry powder containing glucosamine-conjugated gefitinib SLNs for lung cancer therapy. Drug Development and Industrial Pharmacy. 2020;46(8):1265-1277.
48. Al-Mutairi AA, Alkhatib MH, Gashlan HM. (2021). Antitumor Activities of Co-loading Gemcitabine and Oxaliplatin into Oleic Acid-Based Solid Lipid Nanoparticle against Non-Small Cell Lung Cancer Cells.
49. Sezer CV. (2021). An *In Vitro* Assessment of the Cytotoxic and Apoptotic Potency of Silymarin and Silymarin Loaded Solid Lipid Nanoparticles. Pakistan Journal of Zoology, 53(4).
50. Zhang F, Xu CL, Liu CM. Drug delivery strategies to enhance the permeability of the blood–brain barrier for treatment of glioma. Drug Design, Development and Therapy. 2015;9:2089.
51. Kulkarni SA, Feng SS. Effects of surface modification on delivery efficiency of biodegradable nanoparticles across the blood–brain barrier. Nanomedicine. 2011;6(2):377-394.
52. Lu W, Tan YZ, Hu KL, et al. Cationic albumin conjugated pegylated nanoparticle with its transcytosis ability and little toxicity against blood–brain barrier. International journal of pharmaceutics, 2005;295(1-2):247-260.
53. Prabhakar K, Afzal SM, Surender G, et al. Tween 80 containing lipid nanoemulsions for delivery of indinavir to brain. Acta Pharmaceutica Sinica B. 2013;3(5):345-353.
54. Koziara JM, Lockman PR, Allen DD, et al. Paclitaxel nanoparticles for the potential treatment of brain tumors. Journal of controlled release. 2004;99(2):259-269.
55. Banerjee I, De K, Mukherjee D, et al. Paclitaxel-loaded solid lipid nanoparticles modified with Tyr-3-octreotide for enhanced anti-angiogenic and anti-glioma therapy. Acta biomaterialia. 2016;38:69-81.
56. Pandian SRK, Pavadai P, Vellaisamy S, et al. Formulation and evaluation of rutin-loaded solid lipid nanoparticles for the treatment of brain tumor. Naunyn-Schmiedeberg's Archives of Pharmacology. 2021;394(4):735-749.
57. Jose S, Anju SS, Cinu TA, et al. *In vivo* pharmacokinetics and biodistribution of resveratrol-loaded solid lipid nanoparticles for brain delivery. International journal of pharmaceutics. 2014;474(1-2):6-13.
58. Vijayakumar MR, Kumar, L, Patel KK, et al. Intravenous administration of trans-resveratrol-loaded TPGS-coated solid lipid nanoparticles for prolonged systemic circulation, passive brain targeting and improved *in vitro* cytotoxicity against C6 glioma cell lines. RSC advances. 2016;6(55):50336-50348.
59. Neves AR, Queiroz JF, Reis S. Brain-targeted delivery of resveratrol using solid lipid nanoparticles functionalized with apolipoprotein E. Journal of nanobiotechnology. 2016;14(1):1-11.