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OVERVIEW OF SOLID LIPID NANOPARTICLES FOR IMPROVED ANTI-CANCER DRUG DELIVERY

Gajendra Prasad Pradhan and Snehamayee Mohapatra *

Department of Pharmaceutics, School of Pharmaceutical Sciences, Siksha 'O' Anusandhan University, Bhubaneswar - 751003, Odisha, India.

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Solid lipid nanoparticles (SLNs), Chemotherapeutics, Multidrug resistance (MDR), Non- small cell lung cancer (NSCLC)

Correspondence to Author:
Dr. Snehamayee Mohapatra

Associate professor,
Department of Pharmaceutics,
School of Pharmaceutical Sciences,
Siksha 'O' Anusandhan University,
Bhubaneswar - 751003, Odisha, India.

E-mail: snehamayeemohanpatra@soa.ac.in

ABSTRACT: Nanoparticles with lipids as a constituent are called "solid lipid nanoparticles" (SLNs). Based on the most recent trends, SLNS is a promising approach for overcoming multiple barriers in drug delivery. Through SLNs, maximized drug payload to the site of action for different pharmaceutical drugs can be achieved. They range in size from 10nm to 1000nm and possess a solid lipid core matrix that aids in the solubilization of lipophilic compounds. The evolution of multidrug resistance therapy against various chemotherapeutic agents, tissue toxicity, and a high prevalence of drug-resistant tumors are the most common impediments in the clinical management of cancer. For more than a decade, SLNs have been widely used as drug delivery systems in the treatment of various cancers due to their low toxicity, high drug bioavailability, and usefulness with hydrophilic and lipophilic drugs. In this review, we discussed the incorporation and controlled delivery of different cytotoxic anti-cancer drugs to target sites using SLNs to treat various malignancies.

INTRODUCTION: Cancer is a disease characterized by aberrant cell proliferation, and it is by far the most lethal disease in terms of mortality. Unfortunately, conventional anti-cancer medications are ineffective in improving the quality of life [1]. The reasons behind this are poor drug delivery and toxicities accompanied by high doses [2]. Drugs classified as class II in biopharmaceutical classification have low solubility and high lipophilicity. By developing a particular cargo carrier system, the low solubility may be increased [3]. When medications have low penetration through the cell membrane, a higher dose is frequently given, resulting in drug toxicity and adverse effects.

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As a result, the method for delivering the medicament could selectively absorb the appropriate drug concentration to targeted sites, increasing its bioavailability while reducing the associated side effects with higher doses. Nanotechnology has effectively distributed therapeutic components to targeted areas while limiting high dosages and toxicities. This has led to significant medical advancements and the emergence of new medical professions such as nanomedicines [4].

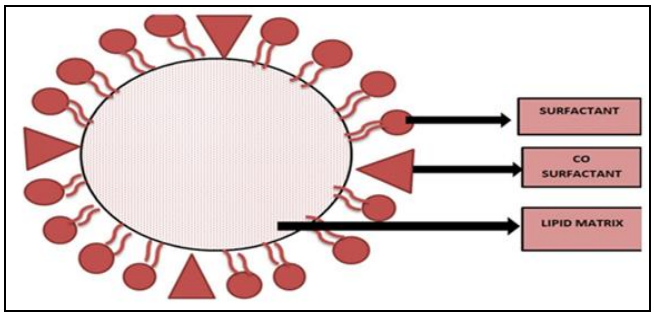

FIG. 1: STRUCTURAL MODEL OF SOLID LIPID NANOPARTICLE

Solid lipid nanoparticles (SLNs) are one of these types of nanomedicines. Solid lipid nanoparticles are formulated using a solid lipid matrix at physiological temperature with surfactants and co-surfactants [5] **Fig. 1**. Its particle size ranges between 10 and 1000 nm. SLN has been accounted to be a substitute for emulsions, liposomes, and microparticles since the mid-1990s because of their different benefits. They're made from custom-made polymers designed to improve drug delivery while lowering toxicity. SLN has a variety of qualities, including smaller size, a greater surface area, increased drug stacking, and stage interaction at the interfaces, and is well noted for its ability to improve pharmaceutical delivery. The most important aspects of nanotechnology research in drug development include toxicity reduction while ensuring therapeutic efficacy, specific drug targeting mechanisms, and biocompatibility and safety. Likewise, various studies have been conducted to improve the stability of SLNs in physiological fluids following administration-using particles coated with hydrophilic moieties, such as PEG subsidiaries [6]. Enclosing SLN with hydrophilic moieties changes the surface properties, increasing the drug half-life in plasma and hence the bioavailability of encapsulated drugs [7]. Drug release from SLNs includes four general principles: drug release is inversely proportional to the partition coefficient of the drugs; drugs with more surface area result in increased drug release; drug release can be slower due to homogeneous mixing of the lipid matrix and crystallizing characteristics of the lipid matrix; and higher drug mobilization results in faster drug release.

- **Advantages of SLNs over Various Delivery Systems:**

- Under optimizing attributes, SLNs can encapsulate lipophilic or hydrophilic medications.
- Their colloidal dimensions & controlled release mechanism can be able to provide protection & administration by parenteral & non-parenteral administration.
- SLNs have greater permeability through BBB (Blood-Brain Barrier) *i.e.,* beneficial in targeting medications to the brain.
- SLNs confers enhanced stabilization of proteins & restrict proteolytic degradation.
- Long-term storage stability & amendable to lyophilization as well as steam sterilization.
- Liposomes are a widely used lipid drug delivery system despite their poor physical& chemical stability.
- To increase their stability, a substitute can be used, made of biocompatible &biodegradable lipids and solid at body temperature.

Role of SLNs in Cancer & Cancer Therapy: The most advanced approach in cancer is the use of chemotherapeutics through conventional drug administration. Yet, it has some drawbacks, including low drug solubilization, low specificity, increased toxicity, and a lower therapeutic index [2]. Drug resistance, which refers to disease resistance towards pharmacological therapy, is another barrier to cancer treatment [8]. Novel drug delivery systems, such as SLNs, can help overcome conventional cancer therapy's constraints [9]. This delivery mechanism's nanometric size range, combined with a few changes, makes it suitable for overcoming biological barriers and delivering drugs to the site of action with minimal toxicity [10]. In contrast to other administration techniques, the use of SLNs in cancer treatment can also be permitted for drug administration, extending the time of exposure of tumor cells to medications [11]. Given the global effect of cancer and the need for enhanced delivery systems, SLNs can be viewed as an emerging drug delivery mechanism for advancing cancer chemotherapeutic therapies [12].

Barriers to Achieving Maximum Chemotherapeutic Effect:

Physiological Barriers: For efficient chemotherapeutic treatments, the medications must bypass the biological barriers to reach the site. Due to the limited bioavailability of drugs, the oral route of administration is not effectively employed in chemotherapeutics [10]. To achieve maximum absorption, drugs should be digested in the stomach and absorbed in the small intestine during oral delivery [13]. Compounds are absorbed in blood capillaries and transported through the liver before they enter the systemic blood circulation, exposing

them to metabolizing enzymes [14]. Because of their lipophilic character, SLNs and other lipid formulations have been shown to protect medicines against presystemic metabolization while improving membrane absorption and uptake [15]. In this process, SLNs can help bypass the barriers and enhance the administration of medications, especially lipophilic drugs [16]. For instance, SLNs have the potential to enhance the penetration of drugs through the skin, particularly for those having small sizes [17]. On the other hand, the blood-brain barrier prevents drug administration to the central nervous system (CNS) for treating brain tumors [18]. For enhancement of delivery of medications to the brain, the medications are being incorporated into SLNs, which can stabilize the drug molecules, thus enhancing their permeation capacity and bioavailability [19].

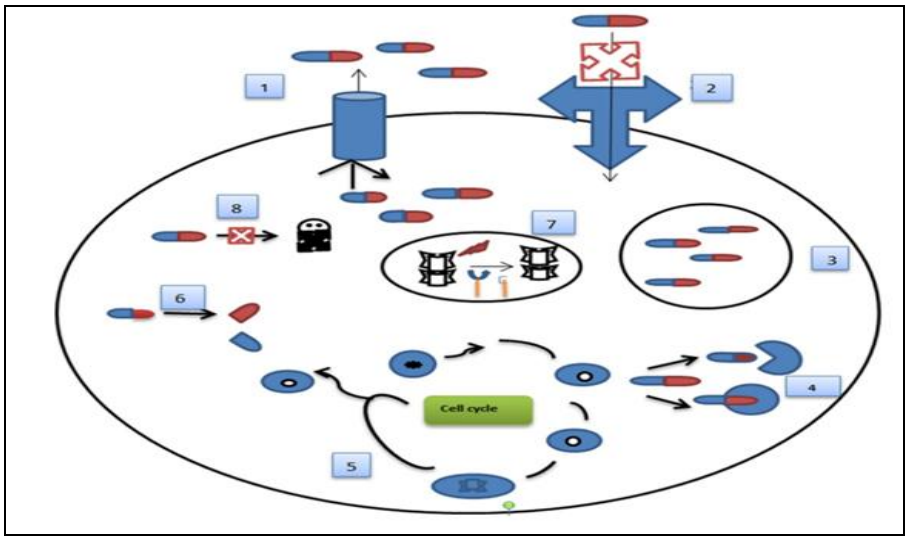

FIG. 2: MDR MODE OF ACTION IN CANCER CELLS. MULTIDRUG RESISTANCE IS RELATED TO VARIOUS BIOCHEMICAL PROCESSES 1) ACTIVE INFLUX OF COMPOUNDS,2) LOSS OF SURFACE RECEPTORS OR ALTERATIONS IN THE CELL MEMBRANE, 3) DRUG COMPARTMENTALIZATION, 4) ALTERATION OF DRUG TARGETS, 5) CHANGES IN THE LIFE CYCLE, 6) ELEVATED DRUG MECHANISM,7) ACTIVATION OF DNA DAMAGE REPAIR SYSTEM AND 8) INHIBITION OF APOPTOSIS

Multidrug Resistance (MDR)-: Efficacy of antitumor chemotherapeutics limits the MDR, which is achieved by being exposed to certain compounds [20] **Fig. 2**. SLNs can be beneficial in overcoming these barrier mechanisms due to two relative characteristics: one is it permits the co-transportation of drugs that restrict the MDR mechanism & other is, it can avoid the efflux mechanism by exporters such as p-glycoproteins because of the drug incorporation mechanism [21].

Drugs for Antitumor Treatments

- SLNs permit the encapsulation of various medications viz., both hydrophilic & lipophilic ones. In the case of chemotherapeutics, the medications such as alkylating agents, antimetabolites, or natural compounds [22].
- One of the alkylating agents such as temozolomide can be made more efficacious when administrating by incorporating into SLNs for treating melanomas, presenting a significant cytotoxic effect in JR8, A2058 human & B16 –F10 mice melanoma cells in contrast to the free temozolomide. SLN-loaded temozolomide has been administered to mice having melanoma tumors and showed that the utilization of these Nanocarrier systems minimized the size of cancer cells by up to 50% whereas the drug solution showed insignificant results [23].
- Another example of an anti-cancer drug is capecitabine, an antimetabolite that can be converted to fluorouracil, *i.e.*, beneficial against a variety of tumors such as breast or colon cancer, but there are certain adverse effects related to it, viz., cardiotoxicity. Capecitabine could be efficiently loaded. Cytotoxicity is being analyzed with HT-29 human colon cancerous cells, while Capecitabine- loaded with SLNs represented a better cytotoxic effect

than that of free drug. Therefore, SLN delivery of drug leads to improved drug bioavailability & minimized variations in rats having 1,2-dimethylhydrazine induced colon cancer [24].

- One of the lipophilic natural drugs, docetaxel has antimitotic activity & poor dissolution in water; therefore, incorporating it into SLNs might enhance its activity. Studies of pK were done by evaluating the plasma concentration in rats and results showed that SLN increased the absorption rate and minimized elimination. Further, this mechanism could enhance the cytotoxic effect in MCF-7 breast cancer cells relative to medications in their marketed form & their free forms [25].

- Retinoic acid has low aqueous solubility and is increased by loading with the SLNs [26].

SLNs & Anticancer Drug Delivery:

- SLNs are being broadly studied for delivering anti-cancer drugs by incorporating them into an SLN formulation to improve oral bioavailability of drugs, protecting them from labile environment & also helpful in reducing adverse effects by minimizing the dosage by effective targeting to site of action [27]. There is various drugs approved by FDA **Table 1.**

- Niclosamide-loaded SLNs were formulated by Pindiprolu *et al.*, in the year 2018. This formulation led to an increase in cellular uptake and effective anti-cancer activity against the triple-negative breast [28]. Esklier developed talazoparib-loaded SLNs in 2018, which improved the therapeutic activity of triple-negative breast cancer cells. These developments resulted in reducing toxicity & overcoming homologous recombinant–mediated resistance.

- The first in-vivo study of SLN containing anti-cancer compound was carried out by Yang et al. in 1999; they utilized a chemically reactive compound, Campothecin, which is having ant carcinogenic properties. Among all anti-cancer drugs, researchers examine paclitaxel to evaluate the potentiality of SLNs. In this study, researchers demonstrated that paclitaxel loaded with SLNs has cytotoxic effects on various cancer cells (HCT-15, U-118, A-549, etc.) & explained the potentiality of SLN for therapeutic targeting of cancer cells [29].

- In another experiment, the cellular uptake & cytotoxic effect of Doxorubicin or Paclitaxel loaded SLN by utilizing two different cell lines (MCF-7 & HL-60) [30]. It was found that the cytotoxic effect of Dox -SLN & PTX-SLN were more than free drug concentrations in both cell lines.

- Tamoxifen is an anti-cancer drug used to treat breast cancer (MCF-7) in SLN. It was observed that the efficacy of tamoxifen-loaded SLN was contrasted with the free drug, but the beneficial effects of these SLNs in cancer therapy were due to their prolonged drug release. Reddy *et al.* demonstrated that tamoxifen citrate of these SLN contrasted to free drugs that showed the prolonged circulation of SLN, which is beneficial for the treatment of breast cancer [31].

- Lu & colleagues analyzed that the therapeutic efficacy of mitoxantrone -SLN (MTO-SLN) had potentiality concerning either the breast tumor weight or the tumor inhibition percentage.

- Etoposide is another anti-cancer agent utilized for treating various malignancies such as lymphoma. To surpass the drawbacks of etoposide, it has been incorporated into SLN & it was being examined for its biodistribution & efficacy in Dalton's lymphoma tumor-bearing mice. These studies demonstrated that etoposide-loaded SLN had significantly higher apoptosis induction for a prolonged period and a further increase in survival in tumor-bearing mice when contrasted with the free drug [32].

- Another *in-vitro* cellular taken-up study was carried out using Vinrorelbine bitartrate. Encapsulation of this drug product into PEG-modified SLN resulted in potential uptake in MCF-7 & A-549 cell lines. The antitumor effect of this drug was improved after being encapsulated into SLN & PEG-modified SLN [33].

- Xiang *et al.* showed that dexamethasone acetate loaded with SLNs being analyzed for lung-

targeting delivery & evaluated them in contrast to DXM-sol, DXM-SLNs having poor taken up by liver & spleen macrophages after IV administration hence, better taken up by the lung [34].

- SLNs have been explored as a pharmaceutical carrier replacement for lipid-soluble drugs such as CUR. The bioavailability of class two drugs or lipophilic medicines could be improved when encapsulated into SLNs, according to evidence gathered from the literature [35].

- SLNs improve the photo stabilization of CUR and make it easier to target specific tissues. Mulik *et al.*, for example, enhanced photo stabilization and boosted the anti-cancer effect of Transferrin-mediated CUR-SLNs [36].

- Formulation & evaluation of CUR-SLN with P-gp modulator excipients, TPGS & BRijj78, was estimated by Ji *et al.* CUR-SLNs had a relative bioavailability of 942.53 percent, according to an *in-vivo* pharmacokinetic study.

  The AUC0-t for CUR-SLNs was 12.27 times that of CUR suspension. In human cancer cell lines, CUR-SLNs increased CUR bioavailability by 32-155 times and enhanced apoptosis. PC3 (HL-60, A549, and HL-60).

- Additional medical study on lipid nanoparticles for releasing mRNA to solid cancer cells or lymphoma is presently underway (NCT03739931). In this scenario, nanoparticles are being used to deliver mRNA-2752, which encodes intratumorally OX40L, IL-23 and IL-36G.

  The administration of interleukins together with other anti-cancer drugs is believed to improve the anti-cancer impact by triggering the inflammatory response at the tumor site [37].

- Herceptin is a drug that targets human EGF receptor 2(HER2) i.e., over expressed in breast tumor cell lines [38].

  HER 2 targeted PEGylated liposomal nanoparticles doxorubicin has been formulated to minimize the cardiotoxic effect, a common adverse effect of anthracyclines.

- SLN is also used as a vehicle. Studies of floxuridine showed that SLN as a vehicle increased the cellular uptake and floxuridine efficacy at specific sites. This mechanism can be used in increasing the poor efficacious drug [28]. Methotrexate-loaded SLNs, formulated using coacervation, showed an enhanced cytotoxic effect towards MCF-7 & Mat B-III cell lines in contrast to free drug [39].

TABLE: 1 FDA –APPROVED NANOPARTICLE-BASED DRUGS

Trade name	Drug	Delivery mechanism	Indication
Abraxane [40]	Paclitaxel	Bound with albumin	Metastatic breast cancer, NSCLC
General-PM [41]	Paclitaxel	Polymeric micelle	Breast & nonsmall cell lung cancer
Marqibo [42]	Vincristine	Liposome	Acute lymphoblastic leukemia
Mepact [43]	Mifamurtide	Liposome	Nonmetastatic osteosarcoma
Oncaspar [44]	Pegaspargase	PEG conjugate of L- asparaginase	Acute lymphoblastic leukemia
DaunoXome [45]	Daunorubicin	Liposome	Kaposi's sarcoma
Onivyde [46]	Irinotecan	Liposome	Pancreatic cancer
Doxil [47]	Doxorubicin	Liposome-PEG	MBC,metastatic ovarian cancer
Eligard [48]	Leuprolide acetate	PLGA	Prostate cancer

TABLE 2: LIPID-BASED NANOPARTICLES UTILIZED IN CANCER THERAPY [28]

Type of cancer	Nanoparticle type	Target organ	Medication/cargo	Clinical status
Gastric cancer	SLN	TopiII	Etoposide (VP16)	IVT
A wide variety of cancers	SLN	AEG-1, Ras/Raf/Mek/Erk cascade pathway & ReA receptors	miR-542-3p & Sorafenib	IVT
A wide variety of cancers	SLN	Tubulin & Hsp90	Paclitaxel	IVT+IVV
Colorectal cancer	SLN	--	Omega-3 PUFA-DHA & Linoleic acid	IVT
A wide variety of cancers	SLN	TopII	DOX	IVT+IVV
GBM	SLN	LRP-1	Docetaxel	IVT+IVV

Lung cancer	SLN	Tubulin	Paclitaxel	IVT+IVV
A wide variety of cancers	SLN	Tubulin & Tf receptors	Docetaxel & Baicalin	IVT+IVV
Breast cancer	SLN	--	PTX & DNA	IVT+IVV
A wide variety of cancers	SLN	--	Methotrexate	IVT+IVV

Use of SLNs in Different Cancer Therapies: Table 2:

Breast Cancer: Breast cancer is the most commonly occurring malignancy in females. Since 1989, its death rate has decreased to 1.8% because of the enhancement in preventive technology and treatment process [49]. A prominent barrier in cancer therapy is multidrug resistance. Chemotherapeutics resistance has resulted from two means: impairment of tumor delivery through physical means (i.e., poor absorption, enhanced metabolism or excretion, or slow diffusion of medications into tumor cells) or by the intracellular mechanism which raises threshold of cell death [50]. SLNs are known to be effective in the targeting of tumors because of their passive targeting mechanism by improving permeability & retention effect along with the advantage of the stealth shielding effect of particles having polyethylene glycol or oxide modification of surface restricts taken up by the reticuloendothelial system, thus enhancing circulation time of the nanoparticles [51].

Colorectal Cancer: Colorectal cancer is the most commonly occurring malignancy in western countries. Hyaluronic acid-coupled chitosan nanoparticles containing Oxaliplatin encapsulated into Eudragit S100 – coated pellets were formulated for potential delivery to colon tumors [52]. SLN is being proposed as a new approach for drug carrier mechanisms. SLN containing cholesteryl butyrate, doxorubicin & paclitaxel had been formulated. However, doxorubicin is not so effective against these types of cancers [53]. SLN is present in the colloidal range, so both hydrophilic & lipophilic medications are based on their preparation method. The constitution of warm microemulsions through which SLN are formulated is considered flexible thus, can be varied for type of drug products & route of administration [54].

Lung Cancer: Adenocarcinoma, squamous cell carcinoma & large-cell carcinoma, altogether constitute various lung cancers, commonly known as 'non-small cell lung cancers (NSCLCs) [55]. Recent treatments for these types of tumors showed less effectiveness as they could not treat disseminated tumors with an acceptable level of toxicity & mutations reason these in the p53 gene that is resulted in the loss of tumor-suppressing action, enhancement of resistance of drug, increase in tumor angiogenesis, inhibition of apoptosis. Therefore, an alternate method that showed a promising effect in treating these types of tumors is gene therapy which constitutes vectors, viz., viral & non-viral. Amongst all the non-viral vectors, biodegradable nanoparticles proved advantageous over other carrier mechanisms due to their enhanced stability & controlled release mechanism. Nanoparticles in gene delivery mechanisms are categorized into two types, *i.e.*, cationic & anionic nanoparticles. Cationic lipid formulations and SLNs have been proven promising colloidal carrier mechanisms [56].

Gastrointestinal Cancer: In the case of GIT, drugs in SLP are administered through the oral route.SLN had been presented as a novel carrier system for oral delivery in the mid-1990s [57]. Nanoparticles' adhesive properties have been reported to enhance bioavailability & minimizing erratic absorption. Absorption of nanoparticles occurred through intestinal mucosa through various mechanisms such as Peyer's patches, intracellular uptake, or the Paracellular pathway. Pinto & Muller (1999) encapsulated SLN into spherical pellets and further analyzed the release mechanism of SLN for administrating orally. Granulates/powder particles can be incorporated into capsules, compressed into tablets, or encapsulated into pellets. Due to a few of these applications, transforming the liquid dispersion into the dry product through spray drying. Thus, analyzing the stabilization of colloidal carriers in GI fluids is essential to foresee their effectiveness for administrating orally.

Brain Cancer: This type of cancer greatly impacts patients, causing severe health problems. There are several instances where SLNs, are effective in improving the treatment process of this kind of tumor [10]. One of the experiments studied the use of SLNs for delivering indirubin against human U87MG glioblastoma –astrocytoma cells [58]. Solid lipid nanoparticles enhanced the drug's cytotoxic

effect, especially in an acidic medium, representing that these SLNs have the potential for treating brain tumor cells. As it is difficult to treat brain tumors due to the presence of the blood-brain barrier, therefore for enhanced delivery of drugs in these types of therapies, the surface of SLNs is being altered by using molecules that help in targeting receptors that are highly expressed in BBB.

For example, SLNs can be incorporated with apolipoprotein E (ApoE), a molecule specifically recognized through the receptors of low or very low-density lipoproteins (LDL or VLDL). These receptors are being expressed in BBB cells, further targeting them with ApoE, which permits an active cellular taken up of ApoE-SLN. Therefore, this perspective could enhance the accumulation of nanoparticles in the brain [59].

Other Malignancies: Such leukemia studies showed the introduction of lignin AP9-cd into SLNs to achieve their anti-cancer effect. With incorporation with SLNs AP9-cd showed improved cytotoxic activity in contrast to AP9-cd individually against human leukemia Molt-4 cell lines [10].

6. Challenges Associated with Cancer Therapy: A wide range of studies has been conveyed by lipid nanoparticles in improving the population's well-being through appropriate diagnosis, prevention & treatment of ailments. Nano bio-interaction is a major obstacle for the transferal of lipidic cancer theranostic nanomedicines to clinics.

Various side effects such as inflammation, immunoreactions etc., can rise when a comparative agent in lipidic theranostic nanomedicines meets the biological matter due to its incompatibility or toxicity. Another obstacle relative to the clinical translation of lipidic theranostic nanomedicines is their complexity in producing a reproducible & controlled synthesis mechanism. Lipid nanoparticle synthesis on a large scale has faced challenges such as varied physical & chemical properties, low yield, & insufficient batch-to-batch reproducibility [60].

7. Future Aspects: SLNs are nanocarriers that are beneficial in administering and delivering bioactive components. SLNs have been considered a better choice for targeted drug delivery. SLNs as medication carriers provide advantages in administrating and delivering synthetic and natural bioactive components. Despite the advancement in the field of lipid nanoparticle research, there is yet to go before making the clinical progress of lipid nanoparticle formulations.

However, a great deal of exploration and studies are done on the production, storage conditions, and toxicity of the SLNs, still, major issues are there *viz.,* the scale-up issues, long-term storage stability, and toxicity in the advancement of lipid nanoparticles. The study of SLN is right now among the most engaging field of exploration. Many types of research in this field over the most recent 5 years have effectively prompted filling <2,000 patents and completing a few clinical trials across the world.

In this way, nanotechnology is relied upon to present new vistas in biomedical science using the benefit of its smaller size. SLNs have served as a promising colloidal drug carrier mechanism because of their improved encapsulation of active constituents & their effectiveness. Though various technologies have been used to deliver single chemotherapeutic agents to the tumor cells.

The nanotechnology field has emerged by enabling multimodal delivery using a single application. Even though SLNs have been utilized for targeting drugs to the specific diseased tissue in the body. Thus, for effective delivery of the drug, biodegradable nanoparticle formulations are essential as these are intended for the transportation & release mechanism of the drug effectively. Before cancer therapies, the ability of SLNs to surpass the MDR mechanism effectively has been reported [61].

Therefore, it might show that nanoparticles will not benefit any kind of tumor. These will be dependent upon the resistance mechanism of cancerous cells. Since then, various studies have shown better results by incorporating various drugs into SLNs & utilizing them against tumor cells' resistance to medications. All these studies explained that nanocarriers have the potential for effectively altering resistance mechanisms.

CONCLUSION: SLN is a biocompatible drug delivery system that can be used to encapsulate a

variety of drugs and treat a wide variety of cancers by evading tumor cell resistance mechanisms. Furthermore, SLNs have been shown to improve the cellular absorption of encapsulated drugs by bypassing multiple biological barriers through multiple transport pathways.

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CONFLICTS OF INTEREST: NIL

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