



# REVIEW ON LIPID NANOPARTICLES FOR ANTICANCER DRUG THERAPY

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*Abstract:* Cancer is the second leading cause of death worldwide and its treatment still represents a major challenge as cases continue to increase. Since the earliest medical records were kept, cancer as a disease has been described in the history of medicine. "Edwin Smith" and "George Ebers" papyri, contain descriptions of cancer written around 1600 B.C. Neoplasia (neo = new, plasia = tissue or cells) or neoplasm literally means new tissue in Greek. Lipid based nanoparticles provide the prospect of developing novel treatments owing to their unique size related characteristics. The process of integrating medicines into nanomedicines provides a novel drug discovery concept that might be used for therapeutic targeting. LBNPs advantages include high temporal and thermal stability, high loading capacity, ease of preparation, low production costs, and large-scale industrial production since they can be prepared from natural sources.

LNPs (Lipid nanoparticles) are legitimate particulates (approx. 100 nm in size) gathered from various lipid as well as other biochemical compounds which overall functionality to resolve biological barriers (biobarriers), allowing LNPs to selectively collect somewhere outside of disease-target cells again for responsive therapeutics. Most pharmaceutically important compounds were insoluble throughout water solutions, were chemical & physiologically unstable, or have toxicities. Moreover, the association of chemotherapeutic agents with lipid nanoparticles reduces active therapeutic dose and toxicity, decreases drug resistance and increases drug levels in tumor tissue by decreasing them in healthy tissue. LBNPs have been extensively assayed in in vitro cancer therapy but also in vivo, with promising results in some clinical trials. LBNPs were widely studied in cancer treatment, both in vitro and in vivo, with encouraging outcomes in certain clinical trials. This study provides an overview of the many types of LBNPs which have been created in latest years and their applications and contributions in different types of cancers

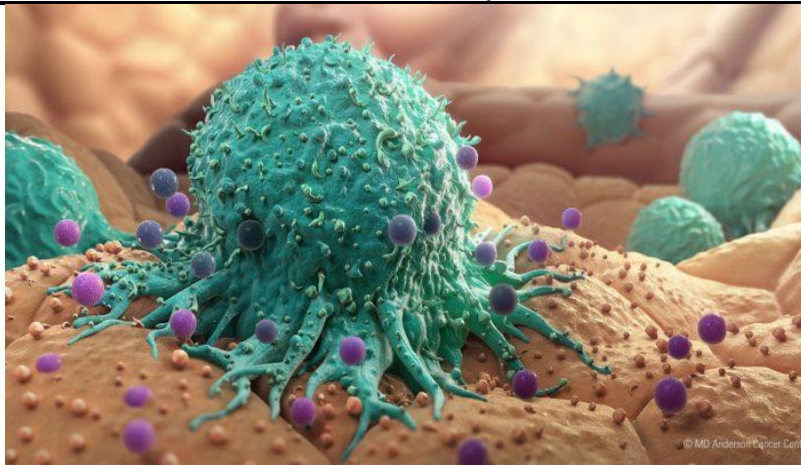
*Index Terms* - Oral; Delivery; Nanoparticles; Size; Controlled Release

## I. INTRODUCTION

Cancer is the second leading cause of death worldwide and its treatment still represents a major challenge as cases continue to increase. Since the earliest medical records were kept, cancer as a disease has been described in the history of medicine. "Edwin Smith" and "George Ebers" papyri, contain descriptions of cancer written around 1600 B.C. (4) The Smith papyrus describes surgery, while the Ebers' papyrus outlines pharmacological, mechanical, and magical treatments. Hippocrates and Galen defined disease as a natural process, and based treatment on observation and experience. Cancers were identified, with warnings against treatment of the more severe forms. Hippocrates is credited with naming "cancer" as "karkinoma" (carcinoma) because a tumor looked like a "crab" ("karkinoma" is Greek for "crab") in that there is a central body to a tumor and the tumor extension appeared as the legs of the "crab". (6,8)

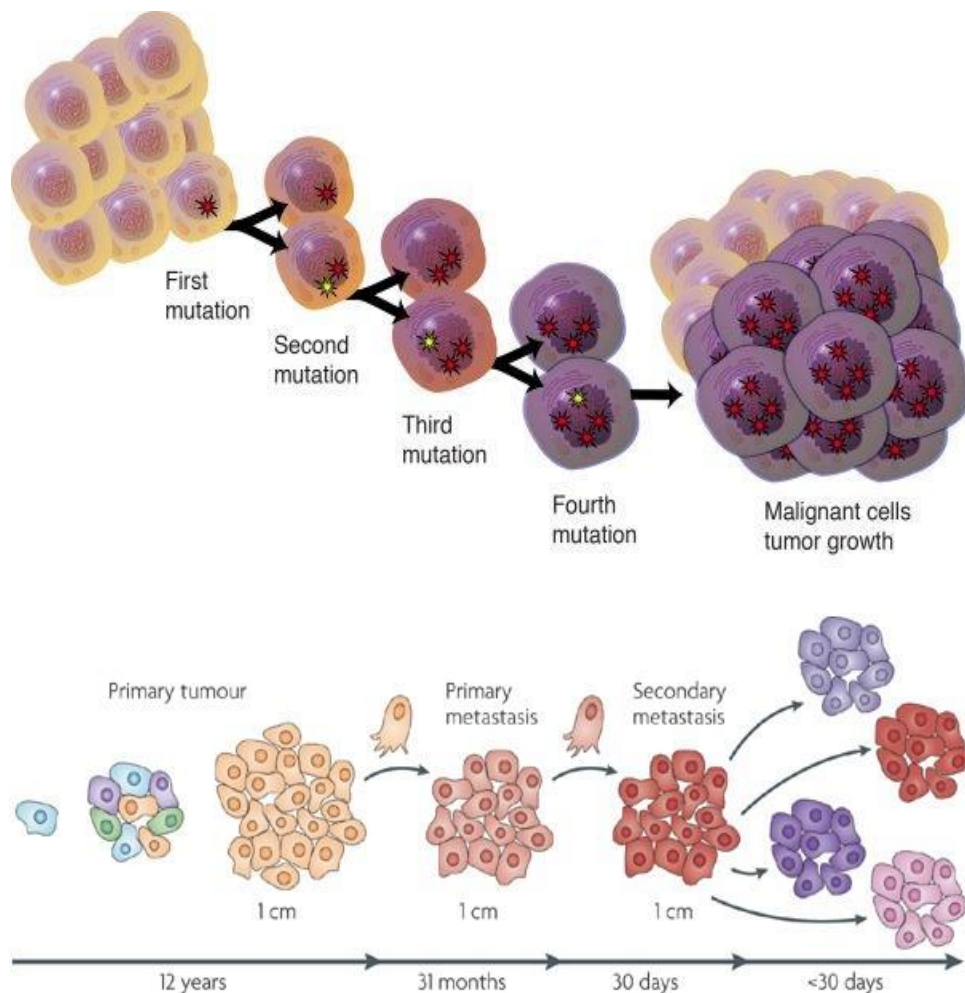
Cancer is a group of diseases characterized by uncontrolled growth (proliferation) and spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer is a non-infectious disease. It starts at the molecular level of the cell and, ultimately affects the cellular behavior. Neoplasia (neo = new, plasia = tissue or cells) or neoplasm literally means new tissue in Greek. This indicates that cancers are actually new growths of cells in the body. (11,12)

Another term for cancer is "malignant tumor." Tumor literally means "swelling" or "mass." In this case, it refers to a mass of non-structured new cells, which have no known purpose in the physiological function of the body.



### Development of Cancer:

The development of cancer is a multistep process in which cells gradually become malignant through a progressive series of alternations.(15)The first step in the process is when a single cell within a tissue of the organ concerned is genetically modified. The modified cell divides rapidly, although surrounding cells do not— and a mass of tumour cells forms. This process is known as clonal selection. Clonal selection continues throughout tumour development and consequently, tumour become more and more rapid, growing and increasingly malignant. The tumour cell, by their rapid proliferation, invades the basal lamina that surrounds the tissue.(11) Then tumour cells spread into blood vessels that will distribute them to other sites in the body. This is known as metastasis. If the tumour cells can exit from the blood vessels and grow at distant site, they are considered malignant.(13,17)



### CELL CYCLE

Cell division is the process by which cells reproduce (mitosis). The cell cycle is a series of changes the cell goes through from the time it is first formed until it divides into two daughter cells. It starts at mitosis (M-phase) and ends with mitosis. In between are the G-1, S, and G-2 phases. The duration of S, M and G-2 are relatively constant in different tissues.(8)

Between the M-phase and the S-phase is a gap (G-1) where production of RNA, proteins, and enzymes needed for DNA synthesis occurs. The duration of G-1 varies and determines the length of the cell cycle.

The S-phase is when DNA synthesis occurs.(10,11)

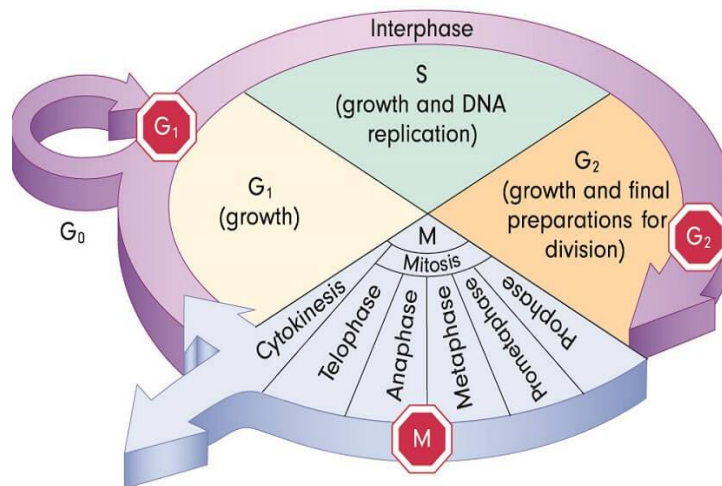
Between the S-phase and M-phase is a second gap (G-2). Cells are thought to prepare for mitosis in G-2 when specialized proteins and RNA are produced. G-0 is a dormant phase.

The four phases of mitosis are:

1. Prophase a. Centrioles separate and migrate to opposite poles.
- b. Centrioles separate.
- c. Chromatin is transformed into chromosomes composed of pairs of filaments called chromatids (each is a complete genetic copy of its chromosome).
- d. The nuclear membrane disappears.
2. Metaphase a. Paired chromosomes become lined up between the centrioles.
3. Anaphase
4. Telophase (divided into parts I and II)

Chromatids are pulled toward the centrioles. One chromatid from each pair goes to each daughter cell.

- a. Telophase I
  - i. Chromosomes become more polarized and transformed into thread-like structures.
  - ii. A nuclear membrane forms around each set of chromosomes forming a new nucleus with a nucleolus.
  - iii. The centrioles duplicate.
- b. Telophase II
  - i. Actual dividing of the cell occurs (cytokinesis).
  - ii. Cytoplasm splits and two daughter cells are formed.



Types of Cancer(15)

(i) Carcinomas:

It includes approximately 90% of human cancer. This type is principally derived from epithelial cells of ectoderm and Endoderm.

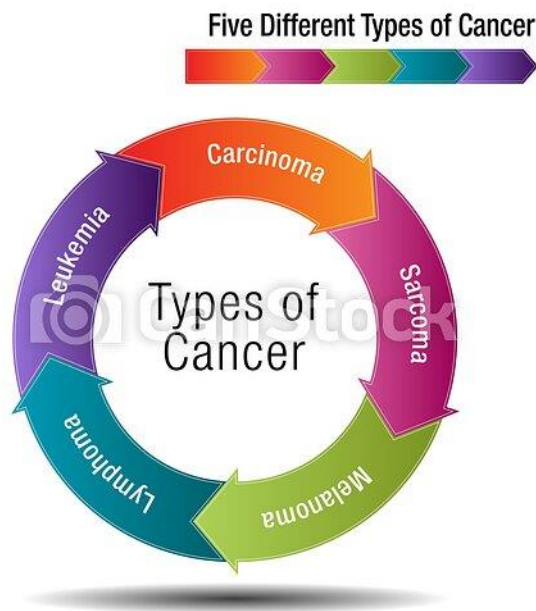
(ii) Sarcomas:

Sarcomas are solid tumors of connective tissues such as muscle, bone, cartilage and fibrous tissue.

(iii) Lymphomas:

It is a type of malignancy in which there is excessive production of lymphocytes by the lymph nodes and spleen.

(iv) Leukemia's: This type of malignancy arises from the blood forming cell. Leukemia's are commonly known as blood cancer.



#### Most Common Cancers

Breast Cancer  
Lung Cancer  
Prostate Cancer  
Colorectal Cancer  
Skin Cancer

#### Less Common Cancers

Multiple Myeloma  
Brain Cancer  
Ovarian Cancer  
Leukemia  
Stomach Cancer

#### Children's Cancers

Childhood Leukemia  
Acute Lymphoblastic Leukemia  
Osteosarcoma  
Retinoblastoma  
Neuroblastoma

#### CANCER TREATMENT(21)

Cancer treatment is the use of surgery, radiation, medications and other therapies to cure a cancer, shrink a cancer or stop the progression of a cancer.

Many cancer treatments exist. Depending on patient particular situation, you may receive one treatment or you may receive a combination of treatments.

Cancer treatments may be used as:

##### **Primary treatment.**

The goal of a primary treatment is to completely remove the cancer from patient body or kill all the cancer cells.

**Adjuvant treatment.** The goal of adjuvant therapy is to kill any cancer cells that may remain after primary treatment in order to reduce the chance that the cancer will recur.

**Palliative treatment.** Palliative treatments may help relieve side effects of treatment or signs and symptoms caused by cancer itself. Surgery, radiation, chemotherapy and hormone therapy can all be used to relieve symptoms.

### Antineoplastic Agents(25)

- Alkylating Agents- Altretamine
- Platinum Coordination Complexes-Carboplatin, Cisplatin
- Antibiotics, Cytotoxic- Bleomycin, Dactinomycin

### Antimetabolites

- Antifolates: Methotrexate
- Purine Analogues: Azathioprine
- Pyrimidine Analogues: Azacitidine

### Biologic Response Modifiers-Interferon Gamma

### Hormonal Agents

- Antiandrogens:- Cyproterone
- Antiestrogens (including Aromatase Inhibitors): Anastrozole
- Gonadotropin Releasing Hormone Analogues: Degarelix

### Monoclonal Antibodies

### Protein Kinase Inhibitors-Ceritinib

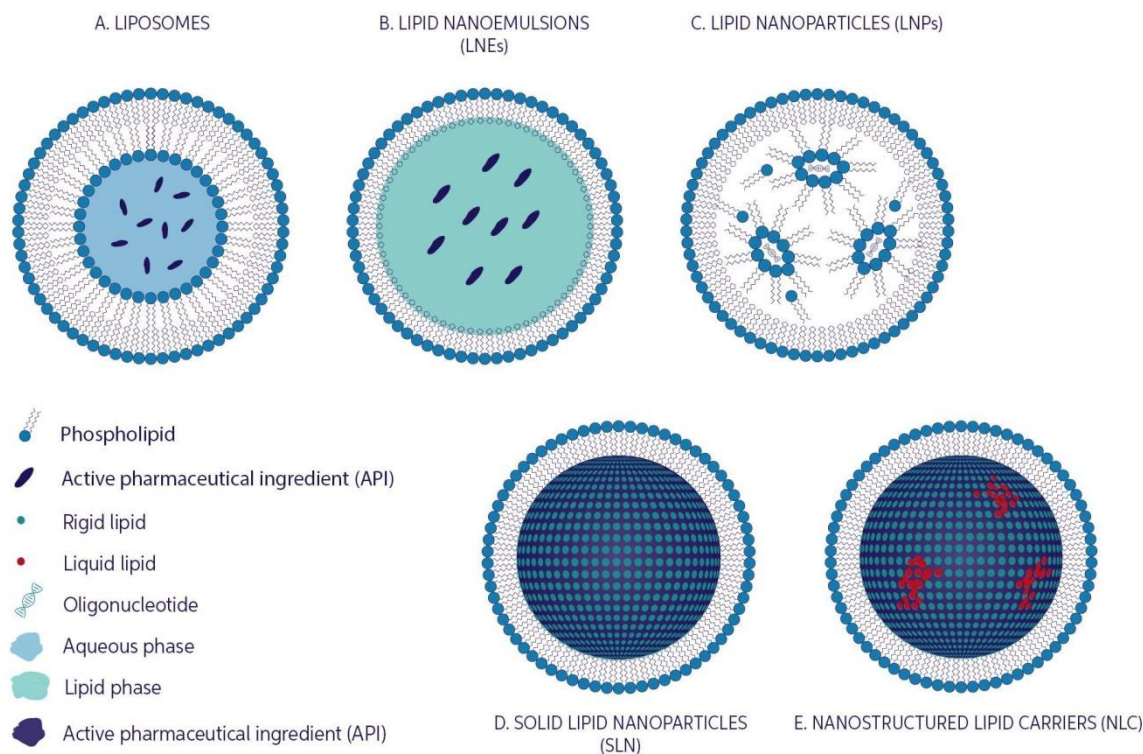
### Vinca Alkaloids-Vinblastine, Vincristine

### Miscellaneous- Asparaginase

## **Nanotechnology**

Due to drug instability, low solubility, the presence of efflux pumps, and biological barriers that must be overcome, many anticancer agents cannot be administered orally.(27) Additionally, gastrointestinal (GI) metabolism and absorption can vary greatly between patients and depend on their unique pathophysiological states. A biological barrier is an ensemble of tissues and molecules designed to keep toxic substances out of the body. Cancer nanotechnology has been developed as a possible cancer treatment that delivers anticancer drugs. Nanoparticles have diameters ranging from 1 to 1000 nm, and they increase the anticancer drug's selectivity and bioavailability(19) We highlight the lipid-based nanoformulations among the many others utilised in oncology since significant improvements in production and alternate compositions have been made recently. They can prolong the biological half-life of chemotherapeutic drugs by preventing early degradation [12]. These systems are made to efficiently penetrate tumour tissues and, while reducing systemic side effects, selectively increase drug concentration in tumour cells. Nanomedicine also enables the coencapsulation of drugs for combined therapy in order to simultaneously inhibit complementary molecular targets

The first nanomedicines to be sold for use in cancer therapy historically were liposomes for parenteral delivery, but in the early 1990s, certain research organisations began to investigate a new generation of solid lipid nanovectors. Lipid nanoparticles (LNPs) now have a significant position in oral delivery.(30) Additionally, nanotechnology has significantly improved drug delivery across the body through improvements in drug stability, hydrophobic molecule entrapment efficiency, and oral drug absorption.



Other biological lipids and biocompatible and biodegradable fatty acids make up the majority of LNP composition. Compared to polymeric nanoparticles or liposomes, the production method is repeatable and typically does not strictly require the use of organic solvents. (24) Although various hybrid forms might be explored, the three basic types of LNPs are SLNs, nanostructured lipid carriers (NLCs), and lipid-drug conjugates (LDCs).

### Liposomes

*Liposomes* in the form of 'uni-lamellar vesicles'. Due to their biocompatibility and biodegradability, liposomes are the delivery technology that has been investigated the most. (28) These nanoparticles mostly consist of phospholipids, which are arranged in a bilayer form as a result of their amphipathic characteristics. They create vesicles when there is water present been put into their structure, increasing the anticancer medicines' solubility and stability.

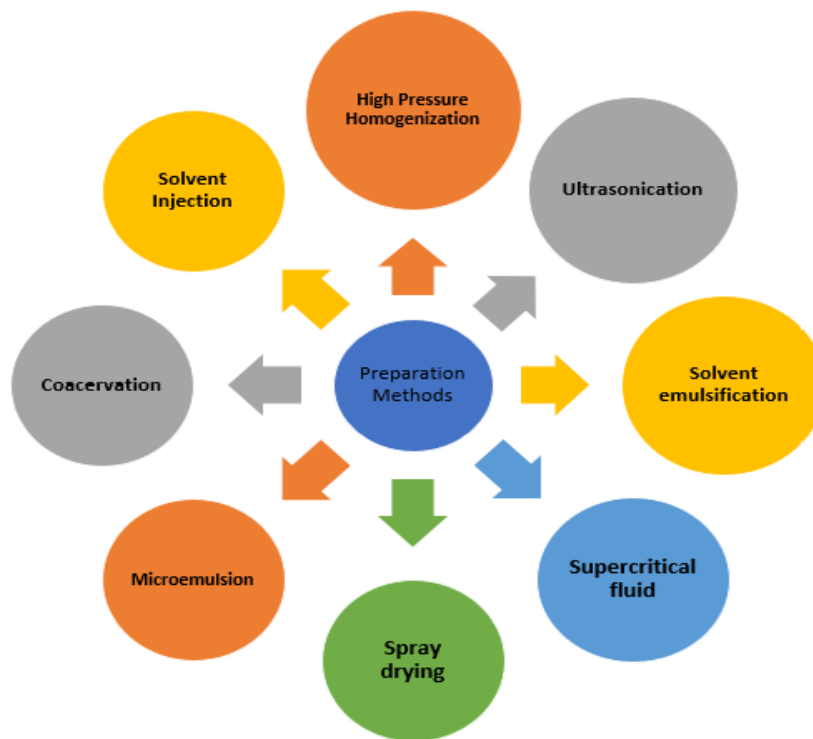
They can encapsulate hydrophobic or hydrophilic medications. Other substances, such as cholesterol, can be added to their formulations in addition to phospholipids. (25) Cholesterol reduces the fluidity of the nanoparticle and increases the permeability of hydrophobic drugs through the bilayer membrane, improving the stability of these nanoparticles in blood and the solubility and stability of anticancer drugs once they are loaded into their structure.

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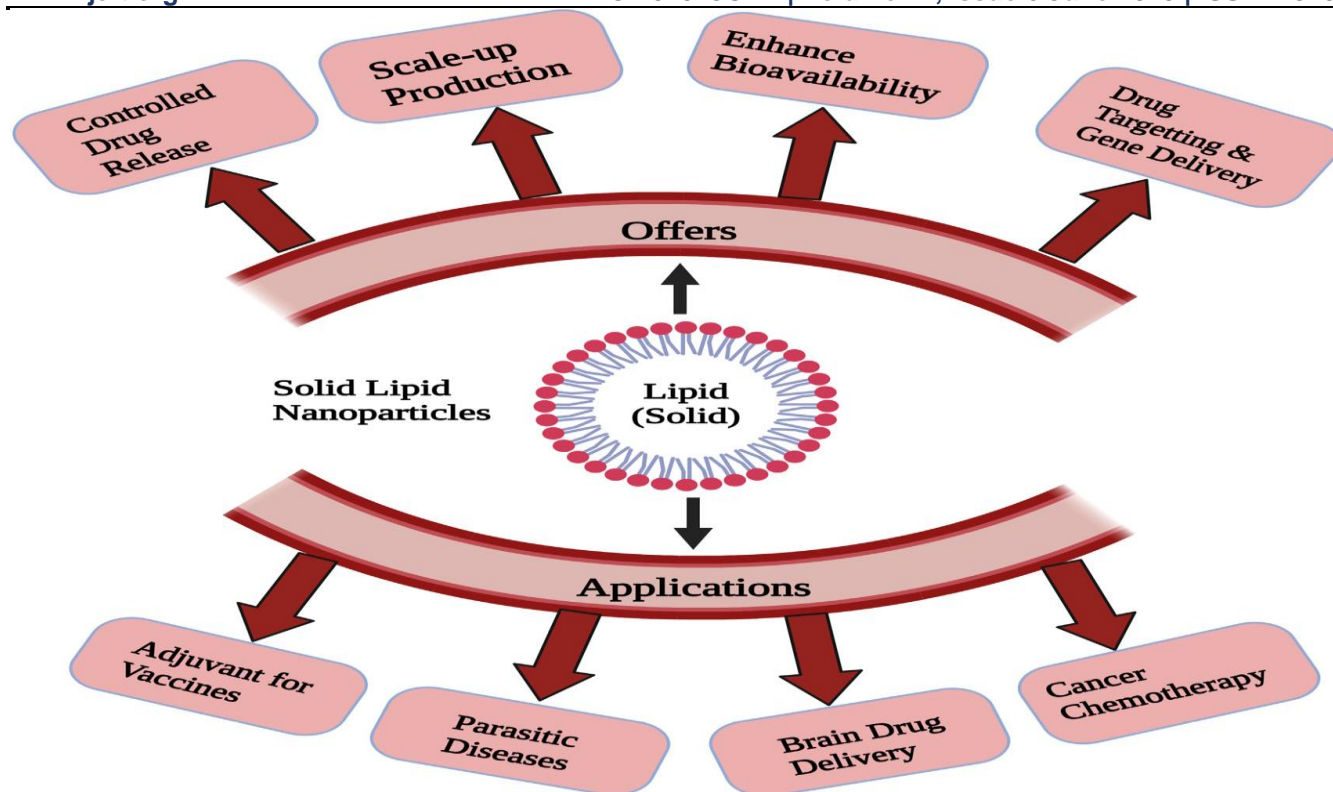
### Solid lipid nanoparticles

These have rigid sizes that range from 1 to 1000 nanometers. Particles are typically between 150 and 300 nanometers in size. The size range of solid, submicronic colloidal nanocarriers (SLNs) is 1–1000 nm. (12) Most of the particles are between 150 and 300 nm in size. Such drug delivery techniques, such as polymeric nanoparticles, offer a framework for controlled releases. They can combine the advantages of polymeric nanoparticles, liposomes, and micronized emulsifiers thanks to their solid matrix of SLNs, which also allows them to restrict medicine motility and provide superior stabilisation. (18) They can combine the advantages of polymeric nanoparticles, liposomes, and micronized emulsifiers thanks to the solid matrix of SLNs in their formulation, which also helps to limit medicine motility and provide greater stabilisation. A blend of polymers or surfactants stabilises this matrix. Site-specific targeting, physical stability over an extended duration, potential for regulated release of both hydrophilic and lipophilic pharmaceuticals, protection of labile chemicals, low cost, simplicity in manufacturing, and nontoxicity are just a few of the many benefits of SLNs medicines that are hydrophilic, protect labile pharmaceuticals, are inexpensive, simple to prepare, and are nontoxic. (15) One key characteristic of SLNs is that they have been solid at both room temperature as well as body temperature. SLNs are produced by substituting a solid lipid or even a combination of solid lipids for the liquid lipid (oil) in the structure of an oil in water emulsion. (20)

Drug	Method of Preparation	Characterization	References
$\alpha$ -tocopherol acetate (ATA)	Solvent injection-homogenization	Size, zeta potential, entrapment efficiency	16
Temazepam	Solvent injection Method	zeta potential, and polydispersity index	17
Enrofloxacin	Ultrasonication and hot homogenization method	Zeta potential	18



Drug	Type	Tumor	Lipid(s)	Surface decoration	Study	Refs
Doxorubicin	SLN	Not specified	Monostearin	PEG2000	in vivo gut sacs and pharmacokinetic studies	19
Gemcitabine	SLN	Lung cancer	GMS	DSPE-PEG2000	In vitro release and stability in GI fluids and in vivo pharmacokinetics and efficacy studies	20
Sorafenib	SLN	Hepatic cancer	GMS	PEGylated galactose conjugate	in vivo pharmacokinetic and biodistribution studies	21
Doxorubicin-SPION	SLN	Colon cancer	Trilaurin	Folic acid-TPGS	in vivo GI tract distribution, efficacy and systemic toxicity studies	22
Gemcitabine-DHA		Melanoma	GMS	TPGS	In vitro stability and release in GI fluids studies and in vivo pharmacokinetic and efficacy studies	23



## Nanoparticles

The variety of applications that are being created for them demonstrates the flexibility and versatility of nanoparticles, which are nano-sized carriers (5-200 nm) [30]. They are an excellent tool for the treatment of many diseases, including cancer, due to their ability to control aspects like shape, size, surface charge, and composition at the atomic level as well as properties like biocompatibility or the ability to transport insoluble substances. Currently, surgical resection, when possible, as well as chemotherapy, radiation, and hormonal therapies, are the mainstays of cancer treatment. The many side effects of commonly prescribed chemotherapy drugs (such as insomnia, fatigue, cognitive decline, nausea, vomiting, anaemia, and weight loss) reduce patients' quality of life and are frequently ineffective because of the high relapse rate, which leads to low survival rates in the majority of cases. Currently, NPs have a dual role, providing tailored and precise illness therapy (teragnosis) in addition to aiding in disease diagnosis. (26)

### Applications in cancer therapy

A significant role for lipid-based nanoparticles (LBNPs), a large and diverse class of nanoparticles, is played in BreC therapy. In addition to their variety, liposomes are used widely due to their excellent biocompatibility and capacity to encapsulate a variety of cargos. (5) LBNPs are now being used in several studies, and some of them (such as Doxil® or Abraxane®) have already been granted a licence for BreC therapy. The most recent significant developments in the use of LBNPs in the management of the most prevalent types of cancer are presented in this section. (6)

### Bowel cancer

Due to its high mortality rate (second-leading cause of death) and recent increase in incidence, bowel cancer is a serious health concern. In advanced colorectal cancer where chemotherapy is used, LBNPs offer a potential strategy for enhancing current treatments or monoclonal antibodies (such as bevacizumab, trastuzumab, and cetuximab) fail to work. (11) A thermosensitive gel-mediated 5-FU microemulsion (ME) was superior to a 5-FU thermosensitive gel-mediated microemulsion (ME) in increasing Caco-2 permeability, cell uptake, and accumulation in rectal tissue in living organisms. employing high-intensity focused ultrasonic waves and lipopolysaccharide (LPS) from attenuated Salmonella bacteria coated with DOX-thermosensitive liposomes to activate macrophages in the tumour environment. This strategy improved DOX internalisation and inhibited cancer formation in vivo via altering membrane fluidity. Additionally, liposome characterization is used to improve CRC treatment.

### Stomach cancer

Only stomach cancer that has not metastasized to the lymph nodes can be treated surgically. Combination chemotherapy should be used to treat severe stomach cancer because it has many drawbacks. (27) In GC treatment, liposomes were widely used, either alone or in conjunction with substances such the Arg-Gly-Asp peptides SATB1 siRNA/CD44 antibodies [67] or in the production of DNA complexes. (25)

### Breast tumour

It is the number one cause of death for women [6] and has seen major changes as a result of the invention of NPs, particularly in the management of metastatic cancer. NEs preloaded with DOX and bromo tetra trandrine (W198, P-glycoprotein (Pgp) inhibitor) have been studied throughout the tolerant MCF-7/ADR cancer cell. This caused cancer cells to absorb and accumulate DOX more quickly. On the other hand, DOX lessened cardiac and gastrointestinal damage (27). Contrarily, clinical investigations investigated DOX-liposome-based compositions.

### Glandular carcinoma

Presently, NEs, liposomes, and solid-lipid NPs (SLNs) (PrC) are the main LBNPs being researched as prospective prostate cancer therapeutic options. A toxoid medicinal drug connected to an omega-3 fatty acid is present in a recently developed oil-in-water



NE. By reducing the toxic IC50 of PPT2 cell types by a factor of 12, NE is more effective than Abraxane™ at shrinking tumour size in tumor-bearing rats. Similar antitumor effects were observed in PC-3 cells when NE was supplemented with catechin extract (a flavanol with anticancer properties). Regarding liposomes, PEG-folate-targeted-oleuropein-liposomes were used to treat 22Rv1 PrC cells.

#### New generation anticancer agents

These anticancer medications have been developed during the past 20 years as a result of extensive study into the cellular mechanisms behind cancer in order to provide new therapeutic opportunities(4). They are believed to bypass the intrinsic toxicity of conventional chemotherapy and target molecular pathways specific to tumours. Tyrosine-kinase inhibitors, short peptides, immunomodulators, and hormone inhibitors are a few of the compounds categorised under this general category. They can serve as adjuvant treatments to complement traditional chemotherapy, and they occasionally take the place of traditional chemotherapy when it is ineffective. As a result, they are becoming particularly important in oral chronic anticancer therapy. Unfortunately, some of them also have poor GI stability and bioavailability, therefore lipid nanotechnology may help them.

The histone deacetylase inhibitor chemical vorinostat, which is marketed and used orally to treat cutaneous T-cell lymphoma, is also being researched for use in treating various cancers (5). Its low water solubility, brief half-life, and rapid first pass metabolism, however, limit its effectiveness. These factors led to the recent suggestion of this medication for lipid nanoencapsulation [106]. In vitro, when vorinostat loaded SLNs were compared to pure vorinostat in MCF-7 and MDA-MB-231 breast cancer cell lines, as well as A-549 human non-small lung cancer cells, the cytotoxic activity was reduced. When compared to the usual medicine given orally and intravenously in rats, vorinostat-SLNs also achieved higher plasma concentration and prolonged systemic circulation over time. It is still unknown whether the innovative formulation is more effective in vivo than the commercial version.

#### Conclusion and future challenges

Lipid-based nanoparticles are a diverse and extensive class of substances that have been used to treat a number of illnesses, most notably cancer. Because of their great biocompatibility and flexibility, liposomes are currently the most widely used lipid-based nanoparticles, however SLNs and NLCs have recently grown in popularity.

However, research aren't just concentrating on these Nanoparticles; there are a number of papers highlighting cutting-edge methods for employing lipid-based Nanoparticles to treat various types of cancer. Some of it has already advanced to the following step and started new professions in clinical trials. In the past ten years, SLNs and nanostructured lipid carriers have drawn a lot of attention as potential drug delivery (nano)systems. The use of biomaterial, environmentally friendly materials, and production methods can be one's key advantage. But it must be emphasized that before large production & distribution of through clinical and environmental safety studies must be performed on these plans. It is deemed vital to establish standardised procedures for evaluating potential risks associated with consuming nanomaterials, as well as the requisite regulatory framework. Melanoma therapy is a crucial research area in which SLNs can be used, similar to other nanosized drug carriers. This may also indicate the importance of the field's funding as well as the suitability of nanostructures for the delivery of cytotoxic drugs due to the direct and indirect attacking caused by malignant cellular level. Nevertheless, the use of lipid nanoparticles is beneficial in several medicinal fields. Regrettably, more study, more work, and working cash resources need to be made available for SLN/NLC to be proven therapeutically helpful in actual situations.

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