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Nanoparticulate Drug Delivery Systems in Oncological Treatment

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Abstract

Cancer is one of the most deadly global diseases, with over 10 million new cases annually. Despite progress in comprehending tumor biology and treatment modalities, obstacles such as multidrug resistance (MDR), aberrant tumor vasculature, and elevated interstitial fluid pressure impede therapeutic effectiveness. Multidrug resistance (MDR), marked by the overexpression of drug-efflux proteins in neoplastic cells, considerably diminishes drug efficacy. Nanotechnology has emerged as a promising approach to overcome these limitations by enabling targeted drug delivery and minimizing side effects. Nanoparticles (NPs), ranging in size from 10 to 1000 nm, improve drug solubility, enhance circulation time, and facilitate tumor accumulation via the Enhanced Permeability and Retention (EPR) effect. They allow controlled drug release, intracellular targeting through endocytosis, and resistance to efflux-mediated drug resistance. Various nanoparticle types include lipid-based systems like liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and non-lipid systems like ceramic and magnetic nanoparticles. Liposomes are approved for cancer therapy and encapsulate drugs, reducing toxicity and increasing efficacy. Nanocapsules offer high drug-loading capacity and stability, making them suitable for theranostic applications. Developing biocompatible, biodegradable materials such as PLGA (poly-lactide-co-glycolide) enhances the potential of nanoparticulate systems. These systems enable targeted delivery of novel chemotherapeutics, such as pyridine-based compounds, optimizing efficacy while minimizing side effects. Nanotechnology-driven therapies are revolutionizing cancer treatment by addressing critical challenges in drug delivery, offering hope for improved therapeutic outcomes and reduced patient burden.

Keywords: Nanocapsules; Nanoparticulate Drug Delivery Systems; Cancer Therapy.

1. Introduction

Cancer is considered one of the world's most devastating diseases, with more than 10 million new cases every year. (Stewart and Kleihues, 2003). However, the mortality rate has decreased in the past two years owing to a better understanding of tumor biology and improved diagnostic devices and treatments. Current cancer treatments include surgical intervention, radiation, and chemotherapeutic drugs, which often also kill healthy cells and cause toxicity to the patient. In addition, several difficulties are faced in anticancer drug delivery and actions. First, there are interstitial matrix structural changes, abnormal tumor vasculature, and increased tumor vasculature permeability. Lack of lymphatic drainage also occurs in cancer, high interstitial fluid pressure, and multidrug resistance (MDR) - a situation where chemotherapy treatments fail patients owing to resistance of tumor cells towards one or more drugs. MDR occurs because transporter proteins that expel drugs from cells are over-expressed on the surface of tumor cells (Willers et al., 2019). Expelling drugs inevitably lowers the therapeutic effect, and cancer cells soon develop resistance to various drugs.

It would, therefore, be desirable to develop chemotherapeutics that can either passively or actively target cancerous cells. Passive targeting exploits the characteristic features of tumor biology that allow nanocarriers to accumulate in the tumor by the Enhanced Permeability and Retention (EPR) effect. Passively targeting nanocarriers first reached clinical trials in the mid-1980s, and the first products, based on liposomes and polymer–protein conjugates, were marketed in the mid-1990s. Later, therapeutic nanocarriers based on this strategy were approved for broader use (Table II), and methods of further enhancing the targeting of drugs to cancer cells were investigated. (Kumari et al., 2016).

Drugs' acute and chronic toxicity could severely hinder their anticancer efficacy. In addition, poor pharmacokinetic performance, biodistribution, and membrane transport properties could hamper their therapeutic efficacy, leading to poor tumor tissue internalization. (Duan et al., 2017)Therefore, improving drugs' physicochemical properties and anticancer efficacy while limiting their side effects is essential. In this regard, nanoparticles may be used to circumvent problems associated with drug delivery and improve pharmacokinetic parameters. (Ramasamy et al., 2017). In particular, lipid polymer hybrid nanoparticles (LPN) are developing platforms for drug delivery applications. (Tahir et al., 2017) And offer many attractive features for improving the anticancer efficacy of chemotherapeutic drugs. LPN offers high systemic stability, drug loading, protection of encapsulated compounds, and prolonged blood circulation. Nanosized particles will preferentially accumulate in tumor tissues via the enhanced permeation and retention (EPR) effect. (Zhang et al., 2015).

(Chen, 2010) The advantages of nanoparticles for delivering small molecular anticancer agents were reported as follows:-.

(a) NPs improve the solubility of anticancer agents; (b) NPs enhance the circulation time of anticancer agents in the blood vessels; (c) NPs facilitate the accumulation of anticancer agents in targeted tumor tissues; (d) the targeting features of NPs allow drug uptake by tumor cells through endocytosis, resulting in increased intracellular drug concentrations; (e) NPs achieve controlled and stable drug release; and (f) NPs are not substrates for ATP-binding cassette proteins, thereby minimizing efflux pump-mediated drug-resistance.

To avoid high cancer mortality, developing nanotechnology treatments, especially developing novel carriers for cancer chemotherapy, has generated widespread interest. (Chen et al., 2013). In the last decades, the development of nanoparticle formulations has become a popular strategy for treating cancerous tumors. (Stirland et al., 2016)In this study, some new compounds, pyridine derivatives incorporated into nanoparticles, were synthesized to evaluate their potential cytotoxicity against cancer.

Another definition of nanoparticles is that they are submicron-sized, colloidal particles with diameters ranging from 10 to 1000 nm. (Peer et al., 2007). Many types of nanoparticles can be used as drug-delivery systems (Table 1). These can be formulated from diverse materials with unique architectures to serve as a possible drug-delivery vehicle to treat a particular disease. Drugs can be loaded onto nanoparticles by various methods, such as encapsulation, surface attachment, or entrapment.

Due to their small size, nanoparticles can efficiently penetrate across barriers through tiny capillaries into individual cells, thus allowing efficient drug accumulation at the target site. Therefore, the therapeutic agent's unwanted side effects and toxicity are reduced, enhancing therapeutic efficacy. (Bahrami et al., 2017).
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Nanoparticles in the pharmaceutical biotechnology sector serve to improve the therapeutic index of drugs and provide solutions to future delivery problems for new and upcoming classes of biotechnological products such as recombinant proteins and oligonucleotides. They are opening new therapeutic opportunities for therapeutic agents that cannot be used effectively as conventional drug formulations due to poor bioavailability or drug instability. Because of the various advantages, diverse types of nanoparticles can be used to deliver active therapeutics to the site of action.

2. Rational design of nanocarriers for cancer therapy

Nanocarriers can offer many advantages over free drugs. They protect the drug from premature degradation, prevent drugs from prematurely interacting with the biological environment, enhance its absorption into a selected tissue (for example, a solid tumor), and control the pharmacokinetic and drug tissue distribution profile, improving intracellular penetration.

The nanocarrier should be made from a biocompatible, well-characterized, and easily functionalized material for rapid and effective clinical translation. It should also exhibit high differential uptake efficiency in the target cells over normal cells (or tissue), be either soluble or colloidal under aqueous conditions for increased effectiveness, and have an extended circulating half-life, a low aggregation rate, and a long shelf life. **(Sun et al., 2017)**.

3. Types of Nanoparticles drug delivery system

Different types of nanoparticles are used as drug delivery carriers in which active ingredients can be incorporated. These nanoparticles can be classified as lipid-based nanoparticles and non-lipid-based nanoparticles.

3.1. Non-Lipid based nanoparticles

3.1.1. Ceramic nanoparticles

The use of inorganic (ceramic) particles for drug delivery, especially macromolecular therapeutics, is emerging as a new area. Ceramic nanoparticles are becoming important drug-delivery vehicles because of their ultra-low size (less than 50 nm) and porous nature. One example is *Silica nanoparticles*, which have also been tested as a nonviral vector for gene delivery. **(Roy et al., 2005)**.

3.1.2. Magnetic nanoparticles

Magnetic nanoparticles may immensely benefit drug delivery because these particles can target a specific site, such as a tumor. Thus, they reduce the systemic distribution of cytotoxic compounds in vivo and enhance uptake at the target site, resulting in effective treatment at lower doses. **(Dobson, 2006)**.

3.1.3. Metal nanoparticles

Metal nanoparticles can be synthesized in tiny sizes of around 50 nm; thus, their large surface area allows them to carry a relatively higher dose of drugs. Gold nanoparticles (AuNPs) are most commonly used as they offer manifest advantages. **(Sahoo et al., 2017)**.

3.1.4. Dendrimers

Dendrimers derive their name from the Greek word dendra, meaning reminiscent of a tree. They are polymeric molecules composed of multiple perfectly branched monomers that emanate radially from a central core. **(Dwivedi et al., 2016)**One of the earliest examples of antitumor drug delivery using dendrimers was achieved by complexing the

Table 1. Examples of nanocarrier-based drugs in the market **(Peer et al., 2007).**

Compound	Commercial name	Nanocarrier	Indications
Styrene maleic anhydride-neocarzinostatin (SMANCS)	Zinostatin/Stimalmer	Polymer–protein conjugate	Hepatocellular carcinoma
PEG-L-asparaginase	Oncaspar	Polymer–protein conjugate	Acute lymphoblastic leukemia
PEG-granulocyte colony-stimulating factor (G-CSF)	Neulasta/PEGfilgrastim	Polymer–protein conjugate	Prevention of chemotherapy-associated neutropenia
IL2 fused to diphtheria toxin	Ontak (Denilelukin diftitox)	Immunotoxin (fusion protein)	Cutaneous T-cell lymphoma
Anti-CD33 antibody conjugated to calicheamicin	Mylotarg	Chemo-immunoconjugate	Acute myelogenous leukemia
Anti-CD20 conjugated to yttrium-90 or indium-111	Zevalin	Radio-immunoconjugate	Relapsed or refractory, low-grade, follicular, transformed non-Hodgkin's lymphoma
Anti-CD20 conjugated to iodine-131	Bexxar	Radio-immunoconjugate	Relapsed or refractory, low-grade, follicular, transformed non-Hodgkin's lymphoma
Daunorubicin	DaunoXome	Liposomes	Kaposi's sarcoma
Doxorubicin	Myocet	Liposomes	Combinational therapy of recurrent breast cancer, ovarian cancer, Kaposi's sarcoma
Doxorubicin	Doxil/Caelyx	PEG-liposomes	Refractory Kaposi's sarcoma, recurrent brea cancer, ovarian cancer
Vincristine	Onco TCS	Liposomes	Relapsed aggressive non-Hodgkin's lymphoma (NHL)
Paclitaxel	Abraxane	Albumin-bound paclitaxel nanoparticles	Metastatic breast cancer

anticancer drug cisplatin to the surface groups of a G-4carboxylate-terminated polyamidoamines-dendrimer. These conjugates exhibited slower release, higher accumulation in solid tumors, and lower toxicity than free cisplatin. **(Malik et al., 1999)**.

3.2. Lipid-based nanoparticles

This section will discuss all lipid-based nanoparticle drug delivery systems in detail, starting from the first developed type, liposomes. A clear advantage of using lipid particles as drug carrier systems is that the matrix is composed of physiological components, that is, excipients generally recognized as safe for oral and topical administration, decreasing cytotoxicity. **(Severino et al., 2012)**Due to the enormous amount of information in the literature about these widely used delivery systems, our review will focus only on anticancer substances.

3.2.1. Liposomes

Liposomes represent the first generation of novel colloidal carriers, revolutionizing parenteral drug delivery. Liposomes offered several advantages, such as encapsulation of hydrophobic and hydrophilic drugs, controlled drug release and reduction in toxicity, and increased therapeutic efficacy of drugs, most of which were not offered by submicronic-emulsions **(Joshi et al., 2009)**.

Liposomal anticancer drugs were the first nano-based formulations approved by the FDA for cancer therapy. The liposomal anticancer drugs approved and marketed for clinical oncology use in the US include Doxil® (doxorubicin), DauoXome® (daunorubicin), and DepoCyt® (cytarabine).

3.2.2. Solid lipid nanoparticles (SLN)

SLN is a relatively new colloidal drug delivery system introduced in the early 1990s. SLNs are biocompatible, biodegradable, and have been used for controlled drug delivery and specific targeting.

These colloidal carriers comprise a lipid matrix that should be solid at room and body temperatures, with a mean particle size between 50 and 1000 nm. **(Poovi et al., 2019)**. SLN can be obtained by exchanging the liquid lipid (oil) of the o/w nanoemulsions for a solid lipid **(Lingayat et al., 2017)**.

3.2.3. Nanostructured Lipid Carriers (NLC)

NLC is considered the type of generation of lipid nanoparticles with a solid matrix. At the turn of the millennium, NLC was developed (98) based on the controlled nanostructuring of the particle matrix. In the generation technology of the nanostructured lipid carriers (NLC), the particles are produced by blending a solid lipid with a liquid lipid, which is also solid at body temperature.**(Joshi et al., 2019)**.

When particles are prepared from solid lipids, especially highly purified solid lipids, the particle matrix tends to form a relatively perfect crystal lattice, leaving limited space to accommodate the active (Figure 1, left). This limits the loading capacity and can lead to the expulsion of activity from the lipid matrix during storage. **(Pornputtapitak et al., 2018)**.

In contrast, using a lipid mixture with very differently structured (sized) molecules distorts the formation of a perfect crystal. The particle-matrix contains many imperfections, providing space to accommodate the active in molecular form or as amorphous clusters (Figure 1, right). One could state that the NLC system's "perfectness" is its "imperfectness" in its crystalline structure. **(Müller et al., 2007)**.

3.2.4. Micelles

Micelles are the most straightforward colloidal systems formed spontaneously by amphiphilic molecules. Depending on the types of amphiphilic molecules, micelles can be divided into lipid micelles, polymeric micelles, and lipid-polymeric hybrid micelles. For lipid micelles, the amphiphilic molecules are usually small molecular surfactants. Different from the lipid bilayer structure of liposomes, the structure of lipid micelles is a monolayer structure with hydrophilic heads facing the outside aqueous environment and lipophilic tails forming the inner core. **(Mu et al., 2005)**.

3.2.5. Nano and microemulsions

As a thermodynamic equilibrium system, micro-emulsion is formed spontaneously within the ''micro-emulsion window'' by mixing oil, water, and surfactant(s); therefore, no energy is needed. On the contrary, nano-emulsion is in a non-equilibrium state and is generally formulated through ''high-energy'' methods such as high-pressure homogenization and ultrasonication to recruit high energy to break the large droplets to submicron size. **(Helgeson and science, 2016)**.

3.2.6. Nanocapsules

Nanocapsules are nano-scaled particles with an oil core surrounded by a rigid shell. With the liquid oil core as a drug reservoir and rigid shell as a drug leaking barrier, nanocapsules are expected to have high drug encapsulation capacity, good drug retention, and high stability. Nanocapsules are

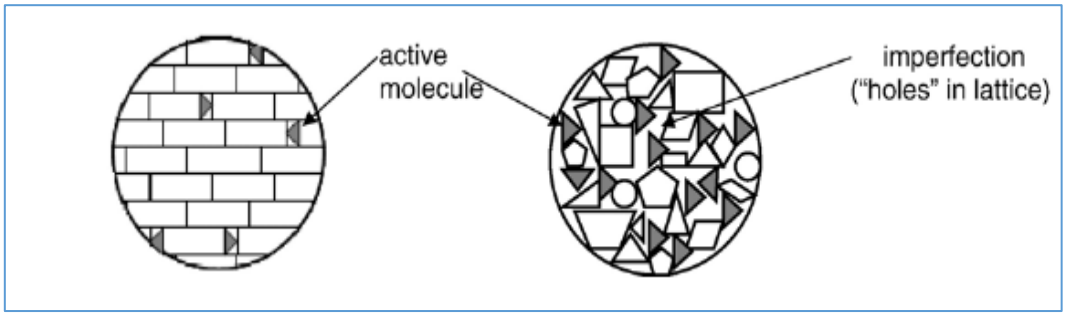

Figure 1. Left: Formation of perfect crystalline structure in SLN by identical molecules similar to a brick wall made from identically shaped bricks with limited loading possibilities for actives. Right: Formation of a crystalline particle matrix with many imperfections comparable to building a wall from very differently shaped stones **(Müller et al., 2007).**

generally stable over a year. There are two types of nanocapsules based on the structure and components of the shells: polymer-shelled nanocapsules and surfactant-shelled nanocapsules. **(Mehrotra and Pandit, 2015)**.

The preparation of both types is closely related to nano-emulsion/micro-emulsion. Polymer-shelled nanocapsules can be prepared by interfacial polymerization, salting out, emulsification–diffusion, and nanoprecipitation (Helgeson and Science). Surfactant-shelled nanocapsules are prepared using the phase inversion temperature (PIT) method, which is based on the changes in solubility of the polyoxyethylene-type non-ionic surfactant with temperature.

Nanocapsules, defined by the interaction of molecular and macromolecular materials, are relevant to the formulation's pharmacological effect. **(Antonow et al., 2017).** Polymeric nanocapsules may be promising approaches to tumor treatment, increasing drug availability in the tumor microenvironment. **(Mahapatro and Singh, 2011)&(Huynh et al., 2012)**.

Nanocapsules are vesicular systems in which the drug is confined to a cavity of an inner liquid core surrounded by a polymeric membrane. The active substances are usually dissolved in the inner core but may be adsorbed to the capsule surface. **(Reis et al., 2017).**

Polymeric nanocapsules show significant advantages over microcapsules. Some investigations show that oral administration of nanocapsules containing insulin prepared by interfacial polymerization can cross the intestinal mucosa into the blood system. **(Kumar et al., 2014)**.

Nanocapsules have attracted increased attention among the different drug delivery methods (e.g., microemulsions, functional micelles, dendrimers, nanospheres). **(Bazylińska et al., 2016)**They have advantages over conventional drug delivery systems, as they can increase the bioavailability, solubility, and sustained release of many potent drugs that are otherwise difficult to deliver orally. **(Szczepanowicz et al., 2015)**Therefore, poorly water-soluble nanoparticles can be used in many encapsulation technologies to improve their several good biological properties. **(Zhang, 2003)**.

Additionally, due to the high interior loading capacity, nanocapsules could allow simultaneous multi-cargo encapsulation, i.e., a hydrophobic drug creating multifunctional nanocarriers dedicated to theranostic applications. **(Chen et al., 2014)**. Furthermore,-nanocapsules can be found in specific drug delivery systems, as they can penetrate the cell membrane and increase its permeability for many potent drugs that are otherwise difficult to deliver to the target tissues. **(Nicolas et al., 2013)**. Correspondingly, in each nanocarrier preparation method, particular importance has to be placed on determining the container features responsible for the best attainment of the final goal. For example, if one mainly needs to provide high long-term stability of the colloidal system and to protect it from aggregation, either charged or sterically branched container shells are necessary. **(Bazylińska et al., 2012)**.

The nanoprecipitation technique, solvent displacement or interfacial deposition, is the most applicable method for polymeric nanocapsule preparation. Nanoprecipitation is based on spontaneous emulsification of the organic internal phase with the dissolved polymer and oil (in the case of nanocapsules fabrication) into the aqueous external phase in the presence of a surfactant. **(Mora-Huertas et al., 2011)**.

Nanoprecipitation is a straightforward and quick methodology that does not require high shearing/stirring rates, sonication, or very high temperatures. It often enables the production of small nanoparticles (100–200 nm) with a narrow unimodal distribution and exhibits a high drug-loading capacity and long-term stability. **(Bazylińska et al., 2014b)**. Additionally, it has been successfully applied to encapsulate different hydrophobic drugs and other bioactive molecules. **(Mora-Huertas et al., 2010)**The polymeric nanocapsule shell generally consists of a polymer, while its core commonly employs oil to dissolve the drug. Therefore, applying the appropriate biodegradable oil phase is essential for achieving the multifunctional cargo's high loading capacity and physical stability. **(Bazylińska et al., 2014a)**. Furthermore, besides its nanoscale size, high loading capacity of active molecules, and long-term stability, an ideal drug delivery system should also have high biocompatibility to enhance the active

load bioactivity and reduce its side effects. **(Kowalczuk et al., 2014)**. Therefore, efforts to produce pure and highly biocompatible polymers have allowed scientists to apply them in several scientific areas, including tissue engineering and drug delivery. **(Nicolas et al., 2013).**

Biocompatible polyester containing biodegradable natural units such as poly (lactide-co-glycolide) (PLGA) has emerged as a fascinating class of biomedical materials. The polyester bonds are sufficiently stable in blood circulation and extracellular fluid. However, after cell internalization, they will be cleaved rapidly under intracellular reductive conditions. **(Gaucher et al., 2010)**.

The present study is focused on delivering novel syntheses of pyridine compounds with anti-tumor potential by using PLGA nanocapsules with one of the different oil phase, i.e., Caprylic/capric triglyceride (CCT), olive oil (V.O) or oleic acid (O.A) and prepared according to the interfacial precipitation technique, in terms of their physicochemical characteristics, investigation and biopharmaceutical evaluate potential chemotherapeutic anti-tumor novel compounds were used as drug design for development and to optimize the effectiveness of antitumor therapeutics.

4. Conclusion

Nanotechnology presents a transformative approach to addressing the persistent challenges of cancer treatment. By enabling targeted drug delivery, nanoparticles enhance the therapeutic index of anticancer agents while minimizing systemic toxicity and adverse effects. Their ability to exploit tumor-specific characteristics, such as the Enhanced Permeability and Retention (EPR) effect, improves drug accumulation in tumor tissues. Additionally, nanoparticles overcome multidrug resistance and poor pharmacokinetics by facilitating controlled release, intracellular delivery, and resistance to efflux-mediated drug elimination.

Diverse nanoparticulate systems, including liposomes, solid lipid nanoparticles, nanocapsules, and metallic or ceramic nanoparticles, demonstrate versatility in improving drug solubility, stability, and efficacy. Recent advances in biocompatible and biodegradable materials, like PLGA, further optimize these systems for clinical application.

Integrating pyridine derivatives into nanoparticulate platforms highlights the potential of combining novel chemotherapeutic agents with cutting-edge delivery technologies.

While substantial progress has been made, continued research into nanoparticle-based therapies holds the promise of revolutionizing cancer treatment. By overcoming conventional therapies' limitations and enhancing anticancer strategies' precision and effectiveness, nanotechnology offers a path toward more personalized, less invasive, and highly efficient cancer care.

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