Effective Luteinizing Hormone Drug Delivery by Nanocarriers in Hormonal Cancer Treatment

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Abstract

The luteinizing hormone (LH) secretes mainly two types of hormone, that is, LH and follicle-stimulating hormone (FSH). The receptors of luteinizing hormone-releasing hormone (LHRH) are overexpression in the majority of different types of cancers, while their expression in healthy tissues, apart from pituitary cells, is limited. In the current scenario, modern research studies recommended that LHRH peptides can be employed to efficiently guide anticancer and imaging agent means visualizing the internal organs directly to cancerous cells. As a result, the number of these compounds in tumour tissue increases, while normal cells are spared unneeded exposure. Nanoparticles can be employed for targeting anticancer drugs in which it is anticipated that nanocarriers would deliver the drug at the unhealthy cancerous tissues via two mechanisms, i.e., passive or active mechanism. However, several nano-medicines have been formulated to improve

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the anticancer effect. Hence, synthesized nanoparticles could serve as a potential carrier with an advantage of improved biodegradability, biocompatibility, improved loading capacity, targeting ability, scalability, and stability.

Keywords

Receptors · Nanocarriers · Biodegradability · Biocompatibility · Improved loading · Targeting ability

16.1 Introduction

Cancer is one of the contemporary medicine's most difficult challenges, and it is still the top cause of mortality globally (WHO: Cancer 2012). The limited accessibility of available therapeutic and imaging agents to cancer cells, their lack of selectivity, rapid clearance from the blood circulation, and toxicity on healthy organs are the main causes for the high mortality rate among cancer patients (Allen et al. 1995; Minko et al. 2013; Torchilin VP Passive and active drug targeting 2010). As a result, a medication delivery strategy that is focused and selective to cancer cells has enormous potential to increase the efficacy of cancer detection and treatment (Allen et al. 1995; Torchilin VP Passive and active drug targeting 2010).

It is commonly acknowledged that two major techniques, passive and active targeting, can be used to deliver anticancer medicines to specific cancer areas (Bae and Park 2011; Allen et al. 1995). The ability of large molecules and nanoparticles ranging in size from 10 nanometers to several hundred nanometers to accumulate specifically in the tumour microenvironment by escaping from systemic circulation into the tumor interstitium through leaky tumour blood vessels is the basis for passive targeting (Bae and Park 2011; Torchilin VP Passive and active drug targeting 2010). Furthermore, the retention of penetrated macromolecules inside cancer tissues is due to a lack of lymphatic outflow. Another strategy based on the modification of anticancer agents and/or drug-loaded nanoparticles with targeting ligands that bind specifically to the receptors preferentially expressed or highly overexpressed by cancer cells is active targeting of cancer cells (Bae and Park 2011; Torchilin VP Passive and active drug targeting 2010; Maeda et al. 2000). Many cancer cells have overexpressed cell surface receptors for peptides, hormones, and vital nutrients as a result of their changed cellular nature, giving a large number of target options for active drug targeting to cancer cells (Minko et al. 2013; Torchilin VP Passive and active drug targeting 2010). The goal of this research is to look into current drug delivery system improvements and advancements. Whereas the active targeting characteristics that utilize the luteinizing hormone-releasing hormone (LHRH) receptor.

16.1.1 Hormonal Cancer

Cancer is found in different parts of the body but not all types of cancer are affected by hormones. But some types of cancer such as ovarian cancer, breast cancer, and prostate cancer, uterine or endometrial cancer need hormones as estrogen and progesterone to grow. Hormone can influence your weight, your internal body temperature level, and surprisingly your mindset. (Garrett 2008) They can likewise affect your disease hazard. Estrogens, a female sex hormone, are known as human cancer-causing agents. Albeit these hormones play fundamental physiological parts in the two: females and male, they have additionally been related with an expanded danger of cancer. For example, taking joined menopausal hormone treatment (estrogen in addition to progestin, which is an engineered adaptation of the female hormone progesterone) can build a female breast cancer. In cancer cells, LHRH controls the cell multiplication and abnormal growth of cancer cell. (Pike et al. 1983; Collaborative Group on Hormonal Factors in Breast Cancer 1996).

Types of Hormone-Sensitive Cancer.

Few types of cancer powered by hormone:

- Ovarian cancer: Ovarian cancer beginning in female is more difficult to treat. It can be affected by estrogen. For a long time, scientists have accepted that in the case of female ovarian cancer, the stage of metastasizes through a passive cell mechanism system by which ovarian malignant growth cells are shed from the essential cancer and conveyed by the physiological development of peritoneal liquid to the peritoneum and omentum. Ovarian cancer is a hormone-based cancer with estrogen receptor.
- Breast cancer: Breast cancer also begins in female organ and affected by progesterone and estrogen. HER2 or HER2/Neu receptor of breast cell is responsible for the development of cancer cell, whereas HER2 receptor works with cancer cell and develops cancer fast.
- Prostate cancer: Prostate cancer begins in male organ. Some male sex hormones such as testosterone and other male sex hormones that help to grow for cancer. The male prostate malignant growth is essentially portrayed on the hub of androgen hormone and its intellectual receptor, the nuclear receptor (NR) and androgen receptor (AR), which assumes parts in carcinogenesis, malignancy advancement, illness movement, and treatment obstruction in the male prostate cancer. Prostate cancer progresses with androgen level.
- Uterine or endometrial cancer: Uterine cancer also begins in female organ and some female sex hormones such as estrogen and progesterone that help to grow for cancer. In the case of female uterine cancer, both estrogen and progesterone female sex hormone apply their impact through intra- and extra-nuclear receptors mechanism. The estrogen receptor and progesterone receptor are decidedly connected with the anticipation of endometrial malignant growth, including the endurance rate and endurance time.

16.2 Nanoparticles (NPs)

The term "nano" is derived from the Greek word meaning "Dwarf" which implies that nanoparticles size is generally in the range from 1 to 500 nm. NPs are of great scientific interest as they serve as a bridge between bulk materials and atomic molecules/structures. Properties of the substance vary completely when it is converted from bulk matter to nanomaterial. Bulk gold, for example, is a brilliant yellow colour, whereas nanogold seems red. Silver nanoparticles have a great deal of potential.

Different Types of Nanoparticles for Drug Delivery.

Nanoparticles in the size ranging from 1 to 500 nm are well known for their applications in various sectors, and specifically, healthcare system is increasing and replacing conventional systems. Various nanoparticles are involved in drug delivery systems.

1. Polymeric nanoparticles
2. Dendrimers
3. Carbon nanotubes
4. Nanocapsules
5. Liposomes
6. Solid lipid nanoparticles
7. Self-nanoemulsifying drug delivery system
8. Silica nanoparticles
9. Fullerenes
10. Metallic nanoparticles

16.2.1 Drug Delivery System

Drug delivery is an interesting field of pharmaceutical research which mainly encompasses the process of releasing the drug/pay loads at the specified cite and at a specific rate. Recent advances have proved that the research in targeted drug delivery is very crucial to improve therapeutic efficacy and reduce drug toxicity. It also attracts the attention of pharmaceutical industry to expand commercial drug markets. TDDS serves various advantages such as (Jing-Liang et al. 2009; Sperling et al. 2008; Kim et al. 2004):

1. Improved patience compliance
2. Improved product shelf life
3. Reduced costing
4. Reduced drug toxicity
5. Better therapeutic efficacy

Therefore, developments of techniques which are focused on TDDS are on rise in the present pharmaceutical drug delivery research. Emergence of nanotechnology in

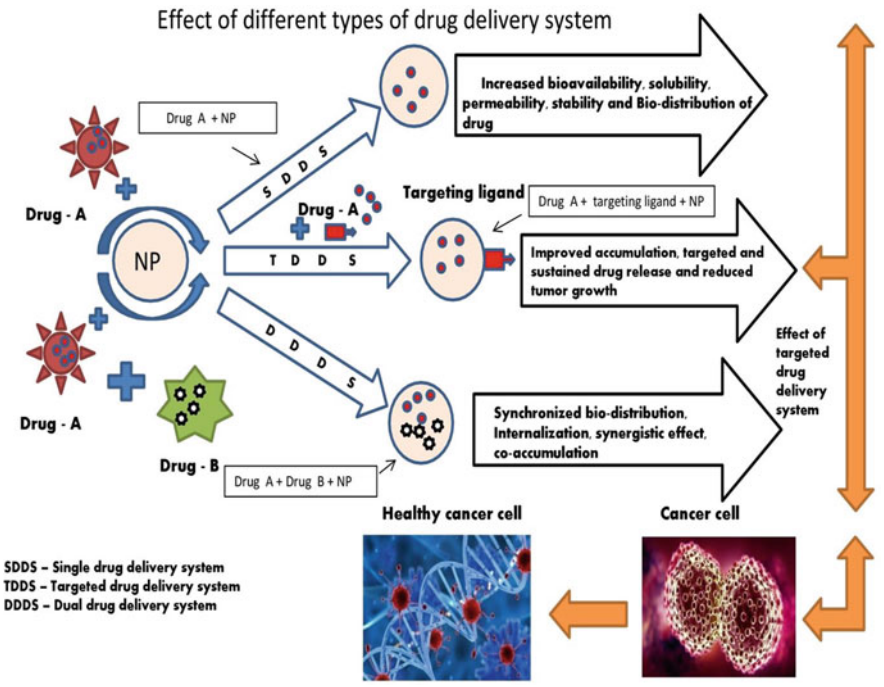

Fig. 16.1 Schematic representation of different types of drug delivery system by nano carriers

the field of drug delivery is well known for its potential to effectively deliver the drug at targeted cites and is well proved for its improved therapeutic and diagnostic potential.

16.2.1.1 Single Drug Delivery System (SDDS)

Fig. 16.1 represents that the SDDF increased bioavailability, solubility, permeability, stability, and bio-distribution of drug.

16.2.1.2 Targeted Drug Delivery System (TDDS)

The aim of TDDS is to reach at the desired site after administration of it. Improved accumulation targeted and sustained drug release and reduced tumor growth (Fig. 16.1).

The two approaches explaining targeting mechanisms are as follows:

1. Active targeting
2. Passive targeting

Active targeting involves active ligands (drug molecule, peptides, proteins, and genes, DNA or RNA) loaded on the carrier surface for exact recognition by cell surface receptors. On the other hand, passive targeting depends on the concentration

of the drug molecules in unhealthy cancerous tissues due to extravasation via leaky gaps (approx. 600 nm) in blood vessels (Raghunandan et al. 2009; Naik et al. 2002).

16.2.1.3 Dual Drug Delivery System (DDDS)

Dual drug delivery system stacked nanoparticles showed essentially improved cancer cell inhibitory impact. Figure 16.1 shows that the DDDS synchronized bio-distribution, internalization, synergistic effect, and co-accumulation of drug.

16.3 LHRH Drug Delivery by Nano Carriers

Gonadotropin-releasing hormone (GnRH) LHRH stimulates the pituitary to release LH and FSH, which regulate gonadal sex steroid synthesis in both males and females. LHRH binding to its receptors (LHRH-R) appears to cause receptor micro aggregation and peptide internalization (Keller et al. 2005a; Emons et al. 1996). It is well known that LRHR-R is expressed not only in the pituitary but also in cancer tissues. Although the precise biological role of LHRH-R in cancer tumours has yet to be determined, many studies show that LHRH peptides may act as local tumour growth regulators. The binding of LHRH activates mitogenic signal transduction pathways involving growth factor receptors and tyrosine kinase activity, as well as antimetastatic signal transduction (Emons et al. 1996; Moretti et al. 1996). Overexpression of the LHRH-R gene was found in hormone-dependent cancer tissues such as breast cancer, endometrial cancer, ovarian cancer, and prostate cancer, as well as hormone-independent cancer tissues like pancreatic cancer, lung cancer, melanoma, and glioblastoma. Furthermore, LHRH-R expression has been observed to be common in a variety of malignancies. LHRH-R is expressed in 86% of prostate cancers, 80% of human endometrial and ovarian cancers, 80% of renal malignancies, 50% of breast cancers, and 32–50% of pancreatic cancers. LHRH-R expression is much higher in several malignancies than in normal tissues, including tissues of the reproductive organs. Previous research also found that LHRH-R expression in lymph node metastases was comparable to or even greater than that in original cancer tumours (Keller et al. 2005a; Emons et al. 1996). The patients who received neo adjuvant LHRH agonist therapy, there was no substantial influence on receptor expression on cancer cells when pituitary LHRH receptors were down regulated (Keller et al. 2005b; Minko 2013). With the maximum effectiveness, nanoparticles conjugated with LHRH. These qualities have the potential to usher in a new era of tailored imaging and treatment, as well as expand nanoparticle uses in the future (Moretti et al. 1996; Needham et al. 2000).

16.3.1 Inorganic-Based Nano Carrier in Drug Delivery

For LHRH-targeted DDS, inorganic nanocarriers have also been developed. The production of nanocarriers from metallic and semimetallic materials for the possible application of medication delivery is referred to as inorganic nanomedicine. Due to

Table 16.1 Advantages and disadvantages of different types of nanocarrier in drug delivery

S. No.	Drug carrier nanomaterials	Targeted drug delivery therapy	
		Advantage	Disadvantages
1.	Inorganic based nano carrier in drug delivery	• Nontoxic in nature • Hydrophilic in nature • Highly stable biocompatible	• Toxicity
2.	Dendrimers nano carrier in drug delivery	• Incorporate both hydrophobic and hydrophilic molecules • High drugs carriage	• Low hydro solubility • Cytotoxic
3.	Liposomes and lipid-based nano carrier in drug delivery	• Wide range of drug delivery system	• Cationic lipids cause toxicity
4.	Polymers nano carrier in drug delivery	• Biocompatibility, biodegradability • Non-toxicity • Hydrophilicity	• Toxic degradation • Toxic monomers aggregation
5.	Carbon nanotubes Nano carrier in drug delivery (CNTs)	• Better flow • Improved hydrophilic properties	• Potential material toxicity • Lack of solubility in aqueous media

their diverse features, chemically modified inorganic nanoparticles are given as another choice for cellular delivery breakthrough. 39 Controlled release, various functions, good biocompatibility, and the ability to facilitate targeted drug delivery with imaging capabilities are among these qualities (Xu et al. 2006; Bauer et al. 2004). LHRH-targeted inorganic nanoparticles have also been investigated as PET and MRI contrast agents. By encapsulating hydrophobic Mn_3O_4 nanocrystals with lipid-PEG molecules, water soluble manganese oxide (Mn_3O_4) nanoparticles were created. Nano carrier of face-centered cubic (fcc) FePt NPs with an LHRH peptide were found to bind and highly toxic to the human ovarian cancer cell line. Nanocarrier of LHRH-targeted super paramagnetic iron oxide nanoparticles (SPION) increased accumulation of SPION in cancer cells (Table 16.2). The inorganic-based nano carrier has advantages such as high stability, biocompatibility, nontoxic in nature, and hydrophilic in nature and disadvantage of toxic in nature sometimes (Table 16.1).

16.3.2 Dendrimers Nano Carrier in Drug Delivery

Dendrimers are nanometer-sized drug delivery devices made from synthetic polymeric macromolecules. They are made up of several conspicuously branching monomers that protrude outwards from a central core. Because of their changeable surfaces, monodisperse size, hydrophilic interior chambers, and multivalences, dendrimer-based drug delivery devices have a lot of unique qualities (Li et al. 2018). Scaffold systems made on poly(amidoamine) dendrimers coupled with cisplatin are well-known. (Wang et al. 2009) Dendrimers are unique multifunctional

Table 16.2 Summary of LHRH-targeted nano drug delivery system

Drug delivery system	Carrier composition of nano drug	Type of cancer	Reference
Inorganic based nano carrier in drug delivery	Face-centered cubic nanoparticles (FCC-FEPT-NPs)	Ovarian	Xu et al. (2009)
	Super paramagnetic iron oxide (SPION-NPs)	Ovarian	Li et al. (2018)
Dendrimers nano carrier in drug delivery	Poly propylene imine (PPI-NPs)	`	`
	Poly-amido-amine (PAMAM-NPs)	Ovarian	Wang et al. (2009); Luo et al. (2019)
Liposomes and lipid-based nano carrier in drug delivery	Liposome-NPs	Breast	Schurmann et al. (1994)
Polymers nano carrier in drug delivery	Poly(ethylene glycol) (PEG-NPs)	Ovarian	Gasco (1997, 1993)
	Poly(ethylene glycol)-poly (methyl methacrylate) (PEGG-PMAA-NPs)	Ovarian	Vauthier and Bouchemal (2009)
	Dextran-NPs	Breast	Qiu and Bae (2006)
	Human serum albumin (HAS-NPs)	Breast	Qiu and Bae (2006)
Carbon nanotubes (CNTs) nano carrier in drug delivery	Cisplatin (CDDP—NPs)	Breast	Qiu and Bae (2006); Prakash et al. (2021)
	Multiwalled carbon nanotubes cisplatin (MWCNT-COOH-CDDP—NPs)	Breast	Prodana et al. (2011)
	Multiwalled carbon nanotubes (MWCNTs-NPs)	Breast	Shaffer and Koziol (2002)

drug delivery devices because their single adjustable exterior property allows them to be conjugated with many molecules at the same time. LHRH-designated poly propyleneimine(PPI) dendrimers stacked with the CD44siRNA that have been additionally used to beat the cancer prevention agent protection instrument in ovarian malignancy cells, which thus essentially upgraded the remedial impact of photodynamic therapy. In option to the PPI dendrimers, an siRNA conveyance framework dependent on the LHRH focused on polyamidoamine (PAMAM) dendrimer was likewise evolved. The subsequent LHRHPAMAM forms proficiently complexed siRNA into circular nanoparticles and just the designated edifices essentially downregulated the designated quality in LHRH positive malignant growth cells (Table 16.2) (Luo et al. 2019). Advantages of dendrimers nano carriers are incorporate both hydrophobic and hydrophilic molecules, high drugs carriage with disadvantage of low hydro solubility, sometimes cytotoxic in nature. The impact of dendrimers loaded nanocarrier on cancer cell results good as shown in Fig. 16.2.

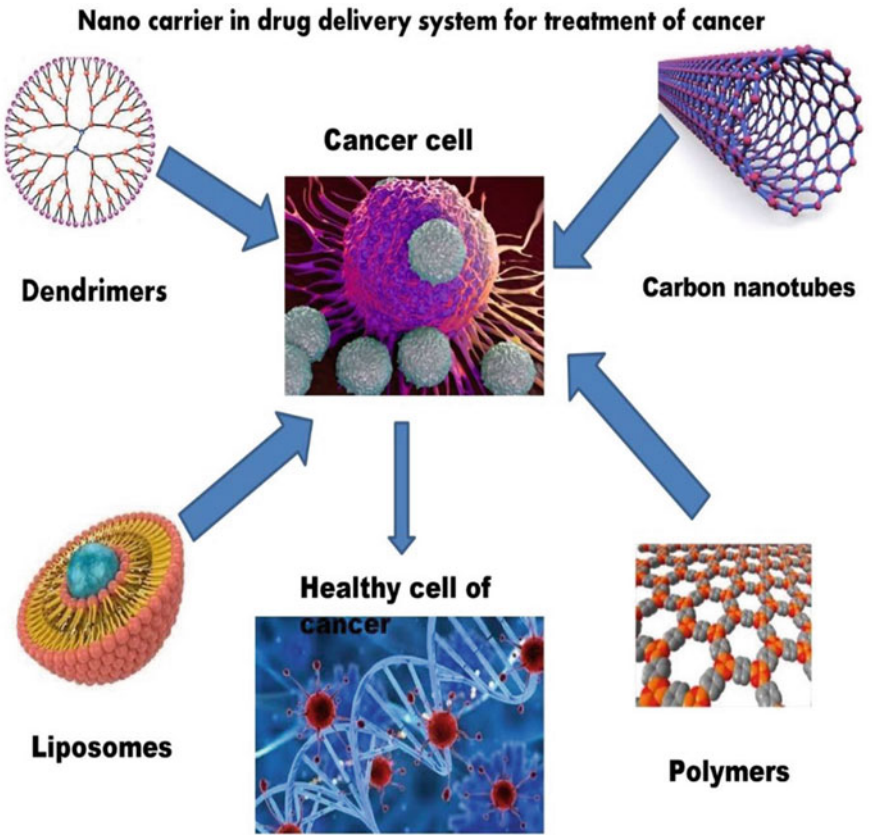

Fig. 16.2 Schematic representations of different types of nano carrier in drug delivery system

16.3.3 Liposomes and Lipid-Based Nano Carrier in Drug Delivery

Liposomes have a wide range of features in terms of size, surface charge, and lipid content, and their ability to incorporate practically any medication regardless of its water solubility making them suitable for drug administration. Song and colleagues developed an LHRH-targeted liposome method to deliver the anticancer medication mitoxantrone (Mit). A thioether bond was used to link gonadorelin, a peptide homolog of LHRH, to PEGylated liposomes. At a dosage of 1.0 mg/mL, the loading of MIT was 98%. Targeted liposomes showed increased uptake and cytotoxicity than non-targeted liposomes in in vitro tests on LHRH-R high expressing MCF-7 cells (Gasco 1997). This increased performance, however, was Mit dose-dependent, and the difference between targeted and non-targeted liposomes may not be significant at some dosage ranges. This study also discovered that the tested formulations of targeted liposomes containing Mit did not achieve the same threshold of toxicity

as free Mit. According to the scientists, the release of encapsulated Mit from endocytosed liposomes and subsequent escape from endosomes or lysosomes was less than that of free Mit, which is consistent with earlier research. Liposomes have a lengthy history of use as a drug delivery vehicle for APIs with poor pharmacokinetics, bioavailability, or solubility (Schurmann et al. 1994; Gasco 1993, 1997).

Nanostructured lipid carriers (NLCs) are a new class of lipid nanoparticles that combine the benefits of several nanocarriers, such as liposomes, multifunctional NLC DDS for pulmonary co-delivery of an anticancer medication and siRNA via inhalation. This NLC has an analogue of LHRH on the surface, an encapsulated anticancer drug (doxorubicin or paclitaxel), and electrostatically bound siRNAs targeted to MRP1 mRNA as a suppressor of drug efflux pumps (pump drug resistance), as well as siRNA targeted to BCL2 mRNA as a suppressor of antiapoptotic defence (nonpump drug resistance). The suggested NLC efficiently delivered its payload to lung cancer cells after inhalation in mouse orthotopic models of human lung cancer, although healthy lung tissues and organs were much less exposed when compared to intravenous injection. The results showed effective tumour growth reduction and no harmful effects on healthy organs, confirming the great efficacy of NLC DDS for tumor-targeted delivery of anticancer medicines and siRNA mixes directly to lung cancer cells by inhalation (Schroit et al. 1986; Wang et al. 2004; Terada et al. 2006) (Table 16.2). Advantages of liposomes nano carrier are wide range of drug delivery system with disadvantage of cationic lipids causing toxicity (Table 16.1). The impact of liposomes loaded nanocarrier on cancer cell results good as shown in Fig. 16.2.

16.3.4 Polymers Nano Carrier in Drug Delivery

Polymeric nanoparticles are colloidal materials of nanoscale dimensions that can encapsulate, adsorb, or covalently bind pharmaceuticals. Minko and colleagues attached an LRHR homolog to one end of PEG and an anticancer medication called camptothecin (CPT) to the other (LHRH-PEG-CPT) (Vauthier and Bouchemal 2009; Qiu and Bae 2006). When compared to free CPT and PEG-CPT conjugates, the conjugation considerably increased cytotoxicity in human ovarian cancer cells. On mice with xenografts of human ovarian cancer, the LHRH-PEG-CPT compound was also tested. When compared to CPT alone and PEG-CPT, LHRH-PEG-CPT dramatically reduced tumour size. The targeting polymer (LHRH-PEG) accumulated primarily in the ovaries (endogenous LHRH-R) of mice without tumours and in the cancer tissues (specific targeting) of mice bearing human ovarian carcinoma xenografts, whereas the non-targeting conjugate (PEG) accumulated in the liver and in the tumour tissues (enhanced permeability retention effect of nanocarriers) (Lestrell et al. 2019). The tumor-targeted polymer accumulated at about twice the rate of PEG alone, suggesting the anticancer drug's precise targeting effect and improved efficacy in this LRHR-targeting DDS. As a result, several molecules of the targeting peptide and anticancer medicines were covalently coupled with bis

(2-carboxyethyl)-PEG using citric acid as a multivalent spacer (Prakash et al. 2021). In vitro cytotoxicity and in vivo antitumor activity of conjugates containing up to three copies of the LHRH targeting moiety and the anticancer drug, and found that conjugates containing multiple copies of the targeting molecule and drug had amplified in vitro and in vivo activity. In addition to the anticancer medication CPT and the LHRH targeting moiety, one or more copies of the BCL2 Homology 3 domain (BH3) peptide were linked to PEG via a citric acid spacer to reduce cellular anti-apoptotic defence, which is principally responsible for ovarian cancer cell treatment resistance. This multifunctional DDS elicited a robust apoptotic response in human ovarian cancer cell lines, and numerous treatments with DDS led to nearly full regression of the primary tumour and prevented the formation of malignant ascites in nude mice with the human ovarian cancer xenograft.

PEG polymer, dendrimers, and liposomes have typical sizes of 30 nm, 5 nm, and 100 nm, respectively. The LHRH analogue, paclitaxel (TAX) anticancer medication, and near-infrared cyanine Cy5.5 imaging agent were all used as targeted DDSs in this work. Adding the LHRH peptide to DDS increased their anticancer activity to a level that was comparable across all three types of nanocarriers. As a result, tumour targeting reduces the disparities in anticancer efficacy and unfavourable side effects on healthy tissues between DDS of diverse architecture, size, molecular mass, and composition. The in vivo bio distribution of these three nanocarriers differed significantly, despite the fact that the major accumulation site in each case was a tumour. Furthermore, the size variation between these nanocarriers was caused by their composition, which should be taken into account. Overall, this study contributed to the field of targeted drug delivery by establishing that the most important component in DDS design for high therapeutic yield is tumor-specific receptor targeting Table 16.2). Advantages of polymer nano carriers are biocompatibility, biodegradability on-toxicity hydrophilicity with disadvantage toxic degradation, toxic monomers aggregation (Table 16.1). The impact of polymer loaded nanocarrier on cancer cell results good as shown in Fig. 16.2.

16.3.5 Carbon Nanotubes (CNTs) Nano Carrier in Drug Delivery

Carbon nanotubes (CNTs) have been used in the delivery of medicinal agents such as peptides, proteins, nucleic acids, genes, and vaccines, as well as in the regeneration of bone and neural tissue. LHRH-R expression is much higher in several malignancies than in normal tissues, including tissues of the reproductive organs. a CNTs can be loaded with bioactive peptides, proteins, nucleic acids, and medicines before being delivered to cells and organs (Prodana et al. 2011; Shaffer and Koziol 2002). The multiple rolled layer carbon nanotubes (MWCNTs) are basically used in the transporters for a medication dependent on platinum metal for the best treatment of breast cancer. This technique for functionalization includes the carboxyl functionalization of CNTs and exemplification of cisplatin loaded (CDDP) into MWCNTs includes for the cancer as ovarian, cervical, oesophageal, and types of

cancer. Advantages of carbon nano carriers are better flow, improved hydrophilic properties with disadvantage potential material toxicity, and lack of solubility in aqueous media (Table 16.1). The impact of carbon loaded nanocarrier on cancer cell results good as shown in Fig. 16.2.

16.4 Conclusion and Future Perspectives

LHRH-targeted DDS (LHRH-PEG-Camptothecin) do not have effect on the plasma concentration of luteinizing hormone (LH) following systemic administration. It improves drug efficacy and decreases side effects; LHRH receptors have been discovered in many types of cancer like lung, breast, and ovarian, etc. LHRH-targeted drug delivery system has been shown to be effective carriers in treatment of different types of cancer. LHRH-targeted-DDS for anticancer improves drug efficacy and decreases side effects. Different types of nanoparticles have proven useful in imaging and delivery of therapeutics; it includes increasing tumor penetration, increasing circulation time, enabling non-invasive tracking of nanoparticles over time, and optimizing selective release and targeting of contents within desired regions.

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