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An Introduction to Nanotechnology and Drug Delivery

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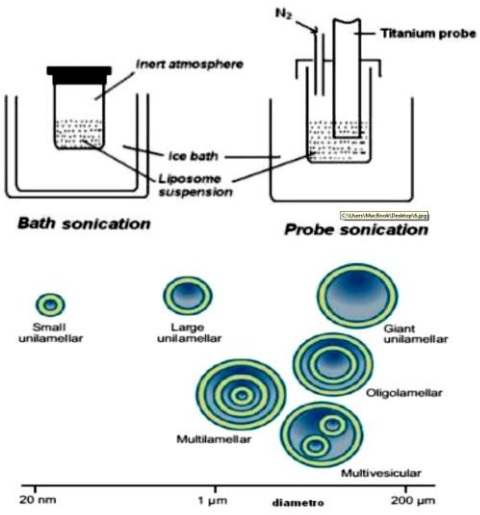
ABSTRACT

One of the most common causes of death in today's society is cancer. The treatments used in the treatment of cancers have their own side effects that have created many problems in the complete treatment of cancer. In classical and conventional drug delivery systems, the drug is distributed aimlessly and generally throughout the body, and the cells take part in the drug from the blood based on their position relative to the drug. As a result, a significant amount of the drug is wasted and eliminated without being used by the body. The most important disadvantages of the old methods of drug delivery are drug wastage, high cost of raw materials, the occurrence of side effects related to the dose, physical and chemical incompatibilities, as well as clinical drug interactions. Nano-liposomes are nanometer-scale liposomes that are one of the most useful drug delivery systems in the field of drug release and retention, which both provides a higher level than liposomes and increases solubility and access to bioavailability as well as improved drug release. Important reasons for the use of nano-liposomes in the pharmaceutical industry are their similarity to cell membranes and trapping of hydrophobic and hydrophilic substances, drug delivery to the target tissue, control of drug flow in the bloodstream and good biocompatibility. Another important feature of nano-liposomes is the coating of water-soluble drugs in the central aqueous portion and fat-soluble drugs within its bilayer membrane. Nano liposomes can be effective in reducing drug toxicity and increasing drug efficacy.

GRAPHICAL ABSTRACT



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Introduction

Cancer is one of the most common causes of death today. According to the National Cancer Institute, the prostate, breast, lung and intestine are the most common sites of cancer, respectively. The results of the largest and most recent studies on 32 types of cancer in 195 countries show that the number of cancer deaths in Iran almost doubled from 1990 to 2016, but according to available documents, the cancer tsunami has not yet occurred in Iran. On the other hand, cancer mortality rates vary depending on when we diagnose cancer and also people's access to diagnostic and treatment services. In general, three treatments are used to treat cancers, including surgery, radiation therapy, and chemotherapy, each with its own advantages and disadvantages. Different treatments used in the treatment of cancers are associated with their own side effects because in these types of methods, in addition to cancerous tissue in some areas, healthy tissue is also damaged. The type and extent of side effects vary depending on the treatment method, duration of use and its amount [1, 2].

The use of current methods of chemotherapy and the use of radiation in the treatment of cancer has problems, so an innovative technological practice to solve this problem using nanoparticles as intracellular agents is being researched. In recent years, the strategy of using nanoparticles as a carrier system for special purposes and drug delivery and active agents has made significant progress. The use of nanocomposites is increasingly pervasive as it permeates all aspects of life. Meanwhile, the use of nanocomposites in medical processes has become increasingly used. One of the practical aspects of nanotechnology that is considered today is the use of nanocomposites as a drug delivery system in the treatment of cancer [3, 4]. The purpose of developing these systems, which generally consist of drug, carrier or coating, and targeting factors, is the controlled release of the drug, maintaining the drug concentration within the therapeutic range for an appropriate duration, and specific drug delivery to the target tissue. The effect of EPR should be considered in the case of nanoparticle drug delivery. In other words, the development of targeted nanoparticles that can deliver drugs directly to cancer cells at a constant rate may have a better effect and less toxicity for the treatment of primary and advanced metastatic tumors [5].

Based on the what stated above, it can be said that nanocarriers can have many benefits compared with free drugs, including preventing premature destruction of the drug and its early reaction with the biological environment, as well as Increase the absorption of drugs into target tissues (e.g. solid tumors). In general, the goal of any optimization in nanoparticles is to increase their targeting to increase the likelihood of drug delivery to tumor cells and reduce drug-induced side effects. Despite the success of nanoparticles in treating cancer cells in in vitro studies, they have unfortunately not been effective in in vitro studies. Among the physically stimulating agents of pharmaceutical nanoparticles are temperature, light, magnetic and electric fields, and chemical and biological factors include pH, ions, antibodies and enzymes.

By intravenous administration, macrophages rapidly remove lipophilic nanoparticles from the bloodstream and transport them to the liver or spleen. This is an advantage if the goal is to treat the liver, but if the goal is to deliver drugs to other areas, the effect of macrophages must be overcome.

In addition, one of the problems with drug delivery is the binding of drugs to proteins in the blood, which reduces the amount of free drug in the blood and thus reduces the amount of drug available to cancer tissue. To solve these problems, a group of optimized carriers called secret carriers have been created.

Familiarity with cancer and common treatments

Cancer is a major public health problem worldwide. Global demographic characteristics predict that the incidence of cancer will increase in the coming decades, with an increase of 420

million new cases by 2025. Breast, colorectal, prostate, lung and gynecological cancers are the most common cancers diagnosed in Europe. Severe lung problems continue to be a major cause of cancer and mortality in the world. Cancer is one of the oldest and most destructive diseases known in the world that kills many people every year. In cancer, cell proliferation is uncontrollable and cell death does not occur. With the exception of blood cancers, other cancers cause abnormal tumors or cell masses.

This primary tumor grows due to new angiogenesis and over time acquires the ability to metastasize and spread to other parts of the body, which eventually leads to death [6]. Cancer can be the leading cause of death in developed and underdeveloped countries, but it is more prevalent in middle-income countries, and this is probably due to the prevailing economic conditions. Geographical differences in cancer prevalence can be explained by many factors such as early diagnosis, age factor, risk factors, screening test and access to treatment quality. According to the International Agency for Research on Cancer (IARC), 14.1 million cases of cancer were reported worldwide in 2012, of which 8 million were underdeveloped, representing about 82% of the world's population.

In its 2015 study, the International Institute of Cancer at Dana Farber ranked Denmark and five Western countries at the top of the list of cancer patients. In its latest survey in May 2017, the International Atomic Energy Agency ranked countries by type of cancer. However, developed European countries have the highest rates of cancer and are at the top of the table overall.

In Iran, the most common cancers include breast, prostate, stomach, leukemia, colon, bladder and larynx. The deadliest cancers in Iran in 2016 included cancers of the stomach, lung, leukemia, esophagus, colon, brain and nervous system, breast, prostate, liver and pancreas. In 2016, there were 385,000 deaths in Iran, of which 12.8%, about 49,000 deaths in both men and women, were due to total cancer. Of the total number of cancer deaths, 18,000 were in women and the rest were 31,000 in men. The number of deaths from total cancers in both sexes in Iran during 1990 was equal to 24,000, in other words, the number of deaths due to cancer in Iran from 1990 to 2016 almost doubled. The causes of cancer in our country are different in different geographical areas and the distribution of cancer in different regions of our country is very variable and vary depending on geographical conditions, ethnicities, lifestyle and risk factors. Cancer is an abnormal condition in which a group of cells disregard the physiological laws of cell division and grow uncontrollably. Cancer cells do not respond to signals that activate the normal cell cycle because they have a degree of self-sufficiency that does not lead to controlled growth. It can be fatal if cancer cells continue to multiply. In fact, 90% of cancer deaths are due to the spread of cancer cells to other tissues, which is called metastasis.

Tumor Biology

Cell division, when independent of growth factors, forms tumors that involve a series of stages. In the first stage, a large mass of cells known as hyperplasia is formed due to uncontrolled cell division. Other changes occur in the next stage, when these abnormal cells spread to a limited area of the tissue and lose their original function, in which the tumor is not invasive and is considered benign. In the advanced stage, tumor cells acquire the ability to metastasize. They begin to attack the surrounding tissues. This stage is considered malignant and is very difficult to treat. However, not all tumors will go to this level if they are identified sooner. Although tumor cells are able to grow independently of normal factors, they still need nutrients and oxygen to grow. All-natural tissues are adequately supplied with capillaries to supply the required materials to each cell. Similarly, as tumors grow, they form new blood vessels to deliver nutrients to cells in the center of the tumor mass that have access to normal blood vessels.

Liposomes

Liposomes are small, artificially designed vesicles that consist of two layers of phospholipids that surround one or more water chambers. The load on liposomes varies as well as the composition and size of lipids (from 20 to 10,000 nm), and these changes strongly affect their behavior in vivo. Many liposomes formulations are rapidly absorbed by macrophages and can be used to deliver specific macrophage drugs or to target inactive drugs, ultimately allowing the drug to circulate slowly from these cells to the general public be transferred.

In other words, liposomes are small artificial spherical vesicles made from natural non-toxic cholesterol and phospholipids. Due to their size and hydrophilicity and hydrophobicity, in addition to biocompatibility, liposomes are suitable systems for drug release. The properties of liposomes are very different from the composition of lipids, surface loading, size and method of preparation. In addition, the choice of two-layer components determines the "strength" or "smoothness" and charge of the two layers. For example, unsaturated phosphatidylcholine species from natural sources, egg or phosphatidylcholine or egg or soy, are multilayered and less stable, while long-chain acyl-saturated phospholipids. Choline have a hard and impermeable layer.

Drugs with different levels of lipophilicity can be trapped in liposomes. Hydrophobic drugs are completely trapped in the lipid layer, highly hydrophilic drugs are completely in the aqueous humor, and other drugs are easily divided between the lipid and aqueous phases in two layers and in the aqueous nucleus [7].

Most phospholipid liposomes are permeable and not sufficiently resistant, so the drug loaded usually leaks during storage. To prevent this problem, cholesterol is usually added to the lipid membrane to increase the stiffness of the liposomes. Cholesterol also acts as an antioxidant. It is found that cholesterol improves the loading of hydrophilic drugs by reducing the permeability of the bilayers and since it is placed in a lipid free space. Therefore, it reduces the loading of hydrophobic drugs and only increases the loading when the primary drug from liposomal formulations tends to oxidize spontaneously, except for those with fully saturated phospholipids, usually by temperature, light, metal ions and a number of soluble substances.

Advantages and disadvantages of liposomes

According to what has been described, the advantages of liposomes can be listed as follows:

a) Liposomes increase the effectiveness and therapeutic index of the drug (actinomycin-D),

b) They increase drug stability through encapsulation,

c) Liposomes are non-toxic, flexible, biocompatible, fully degradable,

d) Liposomes help reduce exposure of sensitive tissues to toxic drugs,

e) They reduce side effects. The disadvantages include low solubility, leakage and fusion of enclosed drug/molecule, relatively high production costs, and low stability.

Nano liposomes

Nanoliposomes are the nanometer version of liposomes that are one of the most widely used encapsulation and release systems. In a broad sense, liposomes and nanoliposomes have the same chemical, structural and thermodynamic properties. However, compared with liposomes, they have a higher specific surface area and the potential to increase solubility and access to higher bioavailability, improve controlled release, and enable accurate targeting of encapsulated material.

The constituent structures of nanoliposomes

The main chemicals in nanoliposomes are lipid or phospholipid molecules. As mentioned, phospholipids are amphiphilic and have both hydrophilic (water-soluble) and hydrophobic (fat-soluble) properties. The phospholipid head group is hydrophilic and its fatty acid tail is hydrophobic. Along with lipid and/or

phospholipid molecules, nanoliposomes may contain other molecules such as sterols in their structure. The combination of sterols in nano liposomal layers can cause major changes in the properties of these vesicles. Cholesterol is the most widely used sterol in the production of lipid vesicles.

Cholesterol does not form bilayer structures on its own but can enter phospholipid membranes in very high concentrations. Cholesterol is used in nanoliposome structures to enhance the stability of vesicles by modulating the fluidity of the lipid layer. In general, cholesterol modulates the fluidity of phospholipid membranes. This helps stabilize the nanoliposomes and reduces the permeability of the lipid membrane to solutes. The amount of cholesterol used in nano liposomal formulations depends more on the proposed application. The main structural components of liposomes/nanoliposomes are similar [8].

Classification of liposomes by structure

Liposome size can vary from very small vesicles (0.025 μm) to large (2.5 μm). Vesicle size has a serious effect on determining the circulating half-life of liposomes, and the size and number of bilayer phospholipid layers affect the amount of drug capsules in liposomes. Based on their size and number of two layers, liposomes can also be classified into one of two categories: a multilayer vesicle (MLV) and a bilayer vesicle.

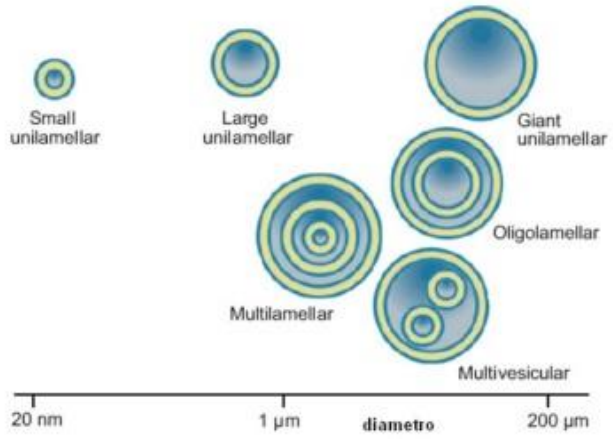

Figure 1: Classification of liposomes based on structural parameters

In bilayer liposomes, the vesicle has a single phospholipid bilayer that encloses the aqueous solution. In multilayered liposomes, the vesicles have an onion-like structure.

Typically, several unilateral vesicles are formed inside with a smaller size and a multifaceted structure separates the concentrated phospholipid spheres by layers of water (Figure 1).

Material and methods

General methods of preparing nanoliposomes

Some common methods for preparing nanoliposomes are described below, which include four general steps:

- **Drying fats from organic solvents:** First, fat molecules or phospholipids are dissolved in an organic solvent and then this organic solution is replaced with an aqueous solution. The organic solvent in which the fat or phospholipid molecules are dissolved is then evaporated from the solution.
- **Dispersion of lipids in aqueous media:** At this stage, lipid molecules are dispersed in this aqueous medium to form liposomes with various dimensions and layers.
- **Purification of the resulting liposome:** Liposomes of the desired size and type are purified from various prepared products.
- **Final product analysis:** In the last step, the properties and characteristics of purified liposomes should be identified using different tools and methods.

Two general methods of passive and active loading are used to make nano liposomes. In the former method, drugs are trapped before or during the fabrication of nano liposomes, which are divided into three different categories: mechanical dispersion, solvent dispersion, and detergent disposal (removal of non-encapsulated materials). On the latter, it is related to a specific type of compound with ionizing groups or compounds that are soluble in both water and fat and can penetrate into nano siposomes after their formation stage.

Classification of nano liposomes based on micro particle and production methods

Ultrasound method

The basis of this method is the use of sound energy to create cavities and stir particles. The cavities created by the sound effect cause the gas bubbles in the liquid to expand and contract. As the waves produced increase, the bubbles begin to oscillate, bursting, resulting in the formation of small vesicles. This method is used in the preparation of monolayer nano liposomes. This method is divided into three types of probation, water bath and extravagance. Ultrasound is a simple way to reduce the size of liposomes and the process of making nano liposomes.

The ultrasound method is based on resizing and transmits MLVs to a bath sonicator or a probe audio device (Figure 2). For the ultrasound probe, place the tip of the sonicator in a flask containing MLV and turn the sample off and on at various intervals.

At this stage, nano liposomes are formed, which are mostly in the form of small one-sided vesicles (SUVs). Otherwise nano liposomes can be produced using a bath sonicator (Figure 2).

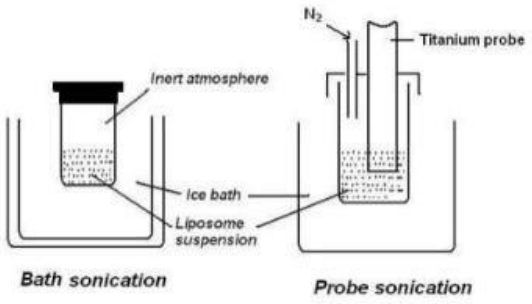

Figure 2: Different types of sonicators

Ultrasound probe

The tip of the sonicator probe is immersed directly in the dispersion of liposomes. The input energy to the dispersion of lipids in this method is very high. The connection of energy at the tip leads to local heat.

As a result, the container should be deep in water/ ice. One of the most important problems of this method is the heating of the solution due to direct contact with the probe and also the possibility of contamination of the sample by particles separated from the probe surface. In order to prevent the solution from heating up, the sample container can be placed in ice [8].

Ultrasound bath

The dispersion of liposomes in a cylinder is placed in a sonicator bath. In this method, it is usually easier to control the temperature of lipid dispersion compared to direct dispersion ultrasound using a probe.

Ultrasonic material can be stored in a sterile container under an inert space. That is why today this method is preferable to rehab with a probe. Using this method, small single-layer nano liposomes between 15 and 150 nm can be produced.

Result and Dissection

In a comprehensive study, Hummels et al. (2006) [9] examined carboplatin nano capsules and their highly toxic and phospholipid formulations of carboplatin. As mentioned earlier, platinum-based drugs are widely used in cancer chemotherapy.

However, their clinical use is limited due to their inherent toxicity and resistance. Their research was conducted with the aim of increasing the therapeutic indices of these drugs by encapsulation in lipid formulation. Previously, they proposed a method for efficient encapsulation of cisplatin in a lipid formulation by providing cisplatin nano capsules. In this study, they showed that carboplatin, a cisplatin-induced anticancer drug with different chemical properties, could be effectively encapsulated in lipid formulation using a similar method.

Carboplatin nano capsules showed very high cell death in vivo. The IC50 value of carboplatin nano capsules per plate of carcinoma cell lines was reported to be up to 1000-fold lower than that of free carboplatin. Cellular Pt content analysis and confocal fluorescence imaging showed that the improved cell killing was due to increased Pt accumulation in cells, which is due to the uptake of the formulation by endocytosis [10]. Lee and

colleagues (2006) also found that lipid levels were a determining factor in the loading of lipophilic drugs. In this study, a reduction in drug loading from 42 to 15% was reported when the lipid component was reduced to 0.1.

Likewise, Liu et al. (2008) analyzed the combined parameters of solubility and diffusion coefficient to screen for the best lipids and polymers in order to achieve maximum load of Verapamil. The encapsulation efficiency was more than 90% and the loading rate was between 1.36 and 5%.

In their study, Mishangfan et al. (2008) successfully prepared solid-nano support nano cliposomes using ethanol injection method, and discussed the important parameters affecting the encapsulation efficiency of solid-acid nano cliposomes. The results showed that the average particle size of nano-liposomes was less than 100 nm and the zeta potential was in the range of -10 and -20 mV. A study published in vitro showed that the system of nano-liposomes prepared from salidroside is stable compared with free salidroside's [11]. Alcasses et al. (2010) studied nanoparticle technologies for cancer treatment and the unique approaches of nanoparticles in cancer delivery systems as well as the use of organic and inorganic materials. They also performed experiments on the use of drug conjugates and polymer-liposomes and achieved positive results.

Flig et al. (2010) investigated the effects of high doses of oral silybinin and phytosomes administered to patients with prostate cancer during the 2 weeks prior to prosthesis. Although silybinin phytosomes were able to obtain high plasma concentrations, low silybinin concentrations were observed in prostate tissue. The weak effects of silybinin on prostate cancer may be due to limited research time.

Phytosome size can also play an important role as long as they are at the nanoscale. In 2011, Prasad Raw et al. Conducted studies the preparation methods and size control parameters of polymer nanoparticles in South Korea. Two general methods have been used to prepare nanoparticles that have become more common in the last two decades: Dispersion of fabricated polymers and polymerization of monomers. In this study, other methods were used to produce polymer nanoparticles such as solvent evaporation, supercritical fluid technology, micro emulsion, mini-emulsion, emulsion without surfactant, etc. Of course, the choice of each of these methods depends on the number of factors such as size, the size distribution and area of application of nanoparticles.

Mendal et al. (2013) stated that the parameters affecting the load and encapsulation efficiency of the drug in the drug delivery system using lipid-polymer hybrid nanoparticles are the solubility of the drug in the aqueous phase, the miscibility of the drug in the lipid phases and polymer, lipid intake, drug-lipid interaction, aqueous phase pH and nanoparticle preparation methods.

Rip et al. (2014) investigated drug synthetics as well as the ability to cross the nutrient blood barrier in pegylated glutathione nano liposomes in rats using fluorescence. Carboxyfluorescein was used as a processing tracer that was extinguished in the nucleus of nano liposomes. In this efficient method, he measured the fluorescence of intact liposomes in the liver, spleen, kidneys, lungs, brain and spinal cord, as well as endothelial cells and the brain. This study finally showed that GSH-PEG-coated nano liposomes can significantly increase brain drug delivery compared to non-pegylated nano liposomes [106]. Hu et al. (2013) developed a drug delivery system of mitomycin c loaded in phytosomes with an average particle size of 210 nm. A laboratory study showed a stable release of mitomycin C after the first burst release.

These results indicate that the phytosome can protect mitomycin C from rapid uptake into the systemic circulation by intensifying in the hydrophobic portion of the carrier.

Cook et al. (2014) conducted a study on smart nanoparticles for drug delivery in the United States and used different drug particles in the development of various drug delivery systems. In this study, due to the very suitable surface area

of nano rates and the consequent creation of unique properties, nanoparticle formulations were used to improve the behavior of various drugs, especially drugs that have less solubility.

Ghanbarzadeh et al. (2014) investigated the use of factorial design and response level to prepare naproxen liposomes with the desired properties. They stated that RSM is a rapid technique for establishing a functional relationship between the experimental response and a set of input variables. The preparation of liposomes using RSM seemed to be appropriate and to predict the range of variables and favorable conditions, provides a predictive model for achieving the highest efficiency. The desired goals can be achieved by systematic formulation in the shortest possible time.

Bean et al. (2015) conducted research on the loading of ifosfamide into PLGA-Dextran polymer nanoparticles for the treatment of osteosarcoma, the most common bone cancer.

Among other things, the drug nanosystem showed significant effects on the MG63 cell line compared with the free drug. The size distribution of nanoparticles produced was also reported to be 45.3 to 124 nm. In another study, Ebrahimifar et al. (2016) investigated the potentiating effects of curcumin on the cell killing of paclitaxel, methotrexate, and vincrostine in gastric cancer cells.

The aim of this study was to evaluate the effect of curcumin on the effectiveness of some anticancer drugs in gastric cancer cells. The results showed that cell viability was significantly reduced after incubation of AGS cells with curcumin. The combined use of curcumin with free chemotherapy to treat gastric cancer has been suggested as a way to better manage this deadly cancer [12].

Shirzad et al. (2016) investigated the cell viability of nano poliposomal cisplatin coated with the synthesis of ethylene glycol metabolite. In this study, pegylated nano liposomal cisplatin was successfully synthesized using the reverse phase evaporation method.

The present nano-formulation showed higher cell death than free drug in human ovarian cancer cell line (A2780 CP) after 48 hours of incubation. These findings provide a new approach to the use of liposomal drug carriers in cancer chemotherapy.

Also, in another study in 2016, Mehrabi et al. examined the effect of pegylated liposomal nanoparticles containing autoposide on breast cancer cell line. In this study, the reverse evaporation method was used to prepare nanoparticles. The results of this study showed that auto poside loaded on the pegylated liposomal nano carrier has more antitumor activity on cancer cells than free drug.

In another study by Ochi et al. (2016), two plant anticancer compounds, glycyrrhizinic acid and silybinin, were encapsulated in nano phytosomes to improve their poor bioavailability, and their effects on liver carcinoma cell lines were evaluated.

Examination of cell viability in HEP G2 cell lines showed that common nano-phytosomes encapsulated with silybinin and glycyrrhizic acid were three times stronger than those of silybinin (25% by weight) and glycyrrhizic acid (75% by weight) uniquely were present.

The results showed that the ability of phytosome technology in the preparation of encapsulated systems increased the therapeutic effects of silybinin by the synergistic effects of glycyrrhizic acid [13].

Ebrahimifar et al. (2017) prepared and studied the properties and cell lethal effects of carboplatin containing pegylated nanoliposomes on ovarian cancer cell lines. The aim of their study was to evaluate the therapeutic efficacy of carboplatin using pegylated liposomal nanoparticles.

Nanoparticles were synthesized using thin film hydration method. The results showed that the drug nano system improved the efficacy of carboplatin against both A2780S and A2780CP cell lines compared to the free drug.

Hardy Sayyah et al. (2017) used a magnetic pegylated liposome to load a hydrophobic drug

and study-controlled drug release in a study. In this study, it was predicted that magnetic pegylated liposomes would have a promising induction magnet in the presence of heat and would be used to combine chemotherapy and thermotherapy in the treatment of cancer. Also, Al-Masari (2017) used scorpion venom as a therapeutic agent in a study on the efficacy of liposomal nanoparticles in the treatment of colon cancer. This in vitro study reported the positive effect of using nanoparticles in improving the lethal function on intestinal cancer cell line.

Peri Tarab et al. (2018) investigated the synthesis of phytosomes with chitosan for ginger transmission in the treatment of respiratory infections both in vitro and in vivo. They successfully prepared ginger phytosomes by anti-fouling method and effectively loaded on chitosan to prepare a phytosomal drug delivery system.

The characteristics of the drug composition in vitro showed a stable release of gingerol from the phytosome complex. In vitro studies also showed a dose-dependent concentration that confirmed the anti-cancer activity of the phytosome system in ginger.

Finally, it was shown that the combination of chitosan and phytosomes can be a good option for the treatment of respiratory infections through oral administration [14]. Niknejad et al. (2018) investigated the ratio of lecithin to cholesterol, the time of formation and the ratio of aqueous and organic phases, which are of great importance for the efficiency of nano liposomes. They obtained the optimal conditions obtained from the preparation process by thin film hydration method, the ratio of cholesterol to lecithin was 7: 1, the formation time was 140 minutes and the ratio of aqueous phase to organic phase was 1: 4. The average size of metformin hydrochloride-based nano liposomes based on lecithin and phosphatidylethanolamine were 52 and 83 nm, respectively. High stability was demonstrated during storage.

Dave et al. (2019) investigated, synthesized, and described Celecoxib-loaded Peggy liposomal nanoparticles for biomedical applications. These nano-liposomes were prepared by thin film hydration method using different molar ratios of the drug to lipids. Celecoxib causes problems for the stomach when administered orally, but liposomes were able to provide a continuous combination of drugs and, after overcoming drug-induced problems, were easily administered by injection.

Hassanzadegan et al. (2019) performed an in vitro study of the anticancer effect of pegylated nano liposome particles with carboplatin on brain cancer cell lines. The aim of this study was to evaluate the efficacy of liposomal nanocarriers containing the anticancer drug carboplatin. The effect of a platinum-based chemotherapeutic agent (carboplatin) is limited due to intracellular resistance. New therapeutic strategies are needed to improve the therapeutic effects of carboplatin. In this study, the reverse phase evaporation method was shown to be an effective method for the preparation of liposomes loaded with carboplatin. In addition, the physicochemical properties of carboplatin-containing nanoparticles were investigated. The effect of nano-drug on A172 and C6 brain cancer cell lines showed increased cell death compared to free drug. The results showed that carboplatin cell killing was correlated with drug concentration and significantly increased for pegylated nanoparticles containing the drug.

Zare et al. (2020) investigated pegylated liposomal nanoparticles containing autopsied using reverse phase evaporation method. The nanoparticles prepared by this technique were examined for size, size distribution, zeta potential, encapsulation efficiency and cell lethality. The results showed that the synthesized nanoparticles had high encapsulation efficiency and the effects of cell lethality and nanoparticle efficiency on lung cancer cell lines were improved.

Chengchi et al. (2020) investigated the synthesis of nano phytosomes for the synthesis of silymarin phospholipids with increased bioavailability and protective effect on the liver.

They found that the homogenization process could significantly improve the rate of dissolution and absorption in the gastrointestinal tract without causing molecular interaction.

By combining phytosome and nanosuppression technologies, a drug delivery system called silymarin phospholipid nanoparticles was developed using advanced bioavailability of silymarin in both in vitro and in vivo conditions and has been shown to improve performance Protects the hepato [15].

Table 1: Examples of the use of nano phytosomes in the treatment of cancer

Research results	type of study		Active pharmaceutical raw materials
Improving the oral bioavailability of silibinin	Hep G2 cell line	External	Silibinin or Silybin
	Skin Cancer	Within body	
	Prostate Cancer	External	
		Clinical trials (first stage)	
Improves oral bioavailability but not success in prostate tissue accumulation		Clinical trials (first stage)	
Improving oral bioavailability and its accumulation in cancerous tissue	Breast Cancer	Clinical trials (first stage)	
Improving the oral bioavailability of curcumin and significantly reducing liver accumulation in plasma	Colon cancer and plasma level measurements	External	Curcumin
Improves anticancer activity and wound healing potential	Skin Cancer	External	Sinigrin
Improving oral bioavailability and its accumulation in cancerous tissue	Solid tumor mice 22H	External	Mitomycin
Improving oral bioavailability	Cell line MDA-MB 231	Within body	Luteolin
Improved anticancer activity	MCF-7	Within body	Quercetin

Use of cisplatin in the treatment of various cancers

Harrington et al. (2000) investigated the effect of increasing doxorubicin and cisplatin encapsulated with Piglet liposome in radiotherapy in a xenograft tumor model. In this study, they evaluated concomitant chemotherapy and radiotherapy using doxorubicin encapsulated liposome (PLED) and encapsulated cisplatin liposome (PLEC) against head and neck cancer xenograft tumors in mice [16].

Bagherpour et al. (2014) in an in vitro study on the effect of cisplatin loaded on poly cyanocrylate nanoparticles on ovarian cancer cell line (A2780CP). Nanoparticles were synthesized by mini-emulsion polymerization method and their size; nanoparticle size distribution and zeta potential were determined. Loading and retention efficiencies were also measured. Finally, it was found that the toxicity of the free drug cisplatin was more than three times in the nanoparticle state and in addition, the stability of the nanoparticles was confirmed after about two months.

Marzban et al. (2015) investigated in vitro and in vivo optimization of the therapeutic efficacy of pegylated cisplatin liposomes by combining different ratios of anionic lipids. They stated that poor segregation of drug from cisplatin liposomes is a major limiting factor in its use as a drug delivery system. One way to circumvent this

problem was to introduce anionic lipids into the inhibitory layers to enhance their interaction with the cell membrane. Their results showed that the inclusion of anionic lipid in 10% mol could improve the therapeutic effectiveness of liposomal platinum.

In another study in India, Patil and colleagues (2017) investigated the biocompatibility properties of a platinum drug subtype loaded into a chitosan nanoparticle. Cell killing studies have shown that the use of this nanoparticle as a carrier of ogralaplatin improves the drug inside the tumor [17].

Keats et al. (2017) evaluated the synthesis of polyols and aspartic sodium (PAA) nanoparticles synthesized with cisplatin and its effectiveness in the treatment of bladder cancer (BC) in vivo. The results showed that mice with bladder cancer treated with cisplatin-coated nanoparticles had no symptoms of T1-grade tumors, whereas 20% of mice treated with free cisplatin had tumors of this insert in the bladder, indicating that the role of nanoparticles in increasing the therapeutic effects of cisplatin in the treatment of bladder cancer [18].

Soods et al. (2017) evaluated nano diaminotrans (NDAT) particles synthesized with cisplatin (187 nm) and their effectiveness in treating bladder cancer in an in vivo environment. The results showed that nanoparticles caused a significant reduction in tumor volume compared to the time of free cisplatin use. Akbarzadeh et al. (2018) examined the transfer of cisplatin by liposomal folic acid nanoparticles in the liver cancer cell line and its effect. The nanoparticles were prepared using the reverse phase evaporation method. The results showed that the superior strength of the nanoparticles by targeting cisplatin had 23% more cell killing compared with the non-target counterpart. The findings of this study confirmed the strength of targeted pegylated liposomal nanoparticles.

Also, Alavi et al. (2019) investigated polybutyl cyanoacrylate nanoparticles with cisplatin as an anti-cancer agent. Their study was performed with the aim of improving cell mortality and accumulation of nanoparticle concentrations for the treatment of lung cancer by modulating temperature and the presence of polyethylene glycol (PEG) as effective factors on the properties of nanoparticles. Nanoparticles were synthesized using anionic polymerization method. The results showed that the nanoparticles significantly increased cisplatin cell viability in vitro by almost twice and increased the therapeutic effects of the in vivo environment by increasing the lifespan of mice with lung cancer by 20% compared to the free drug.

Shirzad et al. (2019) investigated the role of polyethylene glycol size in cell killing and release of pegylated nanoparticles containing cisplatin. In similar studies, high molecular weight (Mw) polyethylene glycol is commonly used to coat liposomes. Experimental results showed that PEGs with higher molecular weight usually better activity in vitro.

Also, the percentage of cisplatin released from Pegyle nano liposomal cisplatin and free cisplatin after 35 hours were 46% and 97%, respectively. 64% more was reported [19].

Cisplatin is one of the most commonly used drugs in chemotherapy. It has a strong anti-tumor effect. However, its clinical use is limited due to dangerous side effects, including damage to the DNA of normal cells. Ghaffari et al. (2020) examined the development of a new cisplatin liposomal nanoparticle formulation for the treatment of breast cancer. The aim of this study was to prepare and describe cisplatin-containing nano liposomes. They optimized liposome formulas by modifying the ratio of SPC80 (soy phospholipids with 75% phosphatidylcholine) and cholesterol. Then, new pegylated liposomal formulations containing SPC80, cholesterol and DSPE - MPEG (5:10:85 ratio) were designed and fabricated to be used as a therapeutic agent to achieve better drug efficacy. The results showed that the pegylated nano liposomes had an average diameter of 119.7 nm and also the cell lethal effect of the liposomal drug was higher than the free drug, which confirmed the efficiency of cell adsorption. This study showed

that cisplatin plays an important role in improving drug efficacy and dose reduction by loading nano liposomes [20-23].

Conclusion

The origin and progression of cancer depends on many factors in the cell, i.e. mutations, immune conditions and hormones, as well as external environmental factors, i.e. smoking, chemicals, infectious organisms, and radiation therapy. These elements work together to cause abnormal cell behavior and uncontrolled proliferation. The resulting abnormal cell mass grows in the body and affects the natural tissues around it, and sometimes spreads to other parts of the body, metastasis.

According to the most plausible model for cancer, there are some mutations in a key gene that control cell division that can also cause normal cells to proliferate abnormally, leading to proliferation, or delete all parts of the chromosome. Ever since the recognition of malignancy, the goal of further research has been to discover new and quality methods for treating cancer. Currently, more than 60% of ongoing trials to assess the health and quality of medicine worldwide are focused on cancer.

The choice of treatment and its progression depends on the type of cancer, its location and stage of progression. As mentioned earlier, surgery, knife-based radiation therapy, chemotherapy, and radiotherapy are some of the traditional and widely used therapies. Of course, some modern methods also include hormone therapy-based therapies, anti-angiogenic therapies, and stem cell therapies.

Conflict of Interest

We have no conflicts of interest to disclose.

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