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Innovative drug carrier systems containing graphene

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ABSTRACT: Research on graphene and graphene oxide have increased in recent years due to their properties, which give advantages for drug delivery systems. They have hexagonal and two dimensional-2D structures with one atom thick. Drug delivery systems which include these molecules are able to go into cells and reach tissues and organs. Additionally, a high amount of drugs can be loaded due to their large surface area. Graphene oxide has functional groups that gain more ability to adsorption than graphene. Both of them are used for both therapeutic and diagnostic purposes including medical imaging. They also both have antibacterial activity and graphene oxide has stronger activity than graphene. Due to its structural properties graphene oxide is more preferred in drug delivery studies. In this review studies of graphene and graphene oxide containing drug delivery systems have been overviewed.

KEYWORDS: Graphene, graphene oxide, drug carrier systems, nanotechnology.

1. INTRODUCTION

Graphene and graphene oxide can be used for various purposes in health products due to their structural properties. Due to their large-surface area, single-atom-thick and 2-dimensional-(2D) structure, high amounts of active substance/drugs can be loaded (1)(2). They can increase the stability of active substances and due to their fine structures, they can easily penetrate into cells or tissues. In addition, both molecules have specific antibacterial activities. With the developments in technology, research on drug delivery systems (DDS) have been increased which aimed to develop DDS systems that are more efficient, less toxic, more biocompatible, low in production costs and better patient compliance. Graphene and graphene oxide, designed for use in innovative drug delivery systems, are cheaper to manufacture than most of the materials used in other delivery systems. Due to these structural benefits and low production costs, studies on drug delivery systems related to graphene and graphene oxide are increasing day by day (3)(4).

DDS can be used either in transporting radiocontrast agents or drugs that provide the substances for treatment or diagnostic imaging via carrying them to the target tissue or organ. They ensure this transfer in a controlled, safe and effective manner (5). The proper transport of the drug to the area where it will act is one of the main problems in the pharmaceutical and biotechnological fields (6). By using advanced drug delivery systems, it is aimed to obtain desired effects of drugs within the expected time, reach the target tissue by efficiently passing the barriers and have no or minimal effect on other tissues other than the target tissue or organ (7). In this direction, the duration of the medication can be shortened, and the side/adverse effects can be reduced fewer amounts of active substances and carriers can be used that has resulted as low cost of the dosage forms.

Nanotechnological drug carrier systems are being developed for some purposes such as passing through the biological barriers easily, increasing the solubility of insoluble or poorly soluble drug substances, increasing the stability, reducing the toxicity, increasing the biocompatibility, targetting the drug

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to the desired tissue, providing efficacy with less amount of drug and achieve an efficient drug release. However, they are not suitable for the release of active substances with low potency. In addition, the manufacture and storage of nanocarrier systems are more difficult than the other carrier system (8). Nanocarrier drug delivery systems can pass through the cell nuclear membrane in cells, causing genetic damage or mutation. This problem can be a problem for healthy cells, and this is of great importance in the design of nanocarrier systems, and extensive studies are being carried out to ensure that the drug reaches the targeted tissue or organ to prevent this problem. This strategy is based on the basic principle of killing cancer cells preferentially without any significant toxic effects on normal cells. (9).

The combination of nanocarriers and drugs is called "nanopharmaceuticals" (8) and nanopharmaceuticals are able to use in diagnosis (PET, SPECT, Computerized Tomography, photoacoustics, Cherenkov Radiation, etc.) and treatment. Their size is in the range of 10-1000 nm. While the nanopharmaceuticals used for diagnosis does not need to be degrading in the body in which excretion from the body after imaging is sufficient, in case their use in treatment active substance need to be transformed under physiological conditions. Nanopharmaceuticals are able to provide long shelf-life and long-term stability. One or more active substances can be loaded into a nanocarrier system that can target more than one location. Nanocapsules, nanosponges, nanoemulsions, nanosuspensions, nanofibers and nanogels are widely used examples of nanocarrier systems. Due to the advantages that gain to the nanocarrier systems, graphene and graphene oxide systems have been studied extensively in nanocarrier systems. Expected properties of these systems can be briefly listed as (10)(11): no interaction with the active substances, compatible with the body, non-toxic either for use in diagnosis or treatment, must be degradable in the body, not to be disintegrated under physiological conditions in case of use in the diagnosis, need to carry the active substance to the desired location and release it, need to be pharmaceutically stable under physiological conditions, in case of use in a sterile product they can be sterilized by proper method.

2. STRUCTURE AND PROPERTIES OF GRAPHENE AND GRAPHENE OXIDE

Graphene has a honeycomb (hexagonal) structure and there is sp2 hybridization between carbon atoms. Graphene is one atom thick and has a 2-dimensional sheet structure. Each carbon atom is attached to three other carbon atoms (12). The angle between the C-C bonds is 120°. The bond lengths between C-C atoms are on average 1.42 Å. Graphene has 0.42 nanometers thickness and is good in terms of electrochemical, thermal, optical and mechanical properties (13), which let it use in many different areas. The graphene molecule makes π-π bonds with aromatic structures and ensures the retention of drug molecules with aromatic structures (14). Graphite-derived materials also have antibacterial properties. The antibacterial activity of graphene is lower than oher graphite derivatives (15). Graphene is one of the strongest materials in the world. The specific strength of graphene material is 48,000 kN m kg^{-1}. The specific strength of graphene is about 300 times that of steel, with a specific strength of 154 kN m kg^{-1})Despite being so sturdy, it is quite light. The thermal conductivity of graphene is on average 3000 W mK-1. Compared to copper, which has an average thermal conductivity of 400 W mK-1, the thermal conductivity of graphene is high and its electrical conductivity is one million times higher than copper. Graphene is very elastic and can be chemically functionalized quickly (16). Graphene has a high drug carrying capacity. Since graphene is hydrophobic, its solubility is good in organic solvents (17).

Figure 1. Graphene structure (18)

The basic structure of graphene oxide is also similar to graphene. Although it has a similar structure to graphene, its properties are different from graphene in some cases. The electrical conductivity of graphene

oxide is very low compared to graphene (19). Since the sp2 bonds of graphene oxide are broken, their electrical conductivity is low (17). On the other hand, its chemical activity feature is much higher than graphene (19). The graphene oxide molecule also has a honeycomb structure and the graphene oxide molecule also has a 2-dimensional structure with a thickness of one atom as graphen. The average thickness of the graphene oxide layers is 1.1 ± 0.2 nm (20). In graphene oxide, some of the carbon atoms hybridize to sp3 and some to sp2. In addition to graphene, the graphene oxide molecule contains carboxyl groups, 5- or 6-membered lactol rings (O-C-O), ketone and hydroxyl groups (19). Graphene shows greater dispersion in organic solvents. On the other hand, graphene oxide shows better dispersion in aqueous solutions because it is hydrophilic. It contains many functional groups such as epoxy groups, hydroxyl groups and carboxyl groups. These carboxyl groups increase the drug adsorption ability of graphene oxide (21).

The presence of oxygenated groups at the edges of graphene oxide enables biochemical and bioconjugation reactions, that functionalize the surface of the graphene oxide-based carrier system with antibodies, proteins and DNA fragments. Graphene oxide is biocompatible and semiconductor. It has very high mechanical resistance and a high specific area (21)(16). It has been proven by the studies that graphite-based materials show antibacterial properties and antibacterial activity by reducing graphene oxide, graphite and graphite oxide, respectively. Graphene oxide contains a high concentration of functional groups, which increases their interaction with bacteria and resulted in its intracellular accumulation in bacteria. In case of contact with the cell membrane, graphene oxide nanolayers are able to damage the cell which resulted in cell death. In addition, in some bacterial cells, graphene oxide adheres to the cell membrane and prevents the cell from accessing nutrients from the microenvironment. In this way, it causes growth inhibition in the cell. Graphene oxide can also have a toxic effect on the cell by inducing oxidative stress in the cell (15).

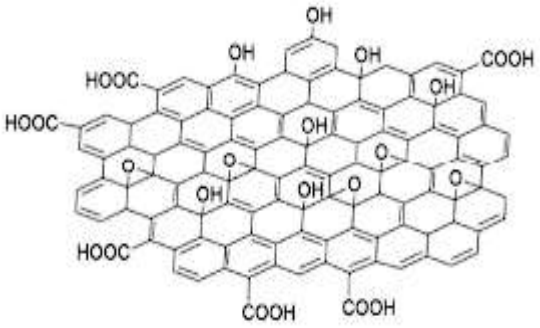

Figure 2. Graphene oxide structure (22)

3. GRAPHENE AND GRAPHENE OXIDE CONTAINING DRUG CARRIER SYSTEMS

Graphene has water-dispersible, biocompatible, and non-toxic properties, suggesting it can be used in biomedical applications such as anticancer therapy, biomedical imaging, and drug delivery. GO's physicochemical properties such as water dispersibility and colloidal stability make it a viable material for drug delivery and therapeutic applications (22). Due to its 2D small structure enable to carry of the active substance to target tissues and organs, high stability, antibacterial property and low cost make it to study in drug delivery. Graphene oxide can also be used in dressings containing self-medicated hydrogels. These dressings are very tight and adhere very strongly to the skin. It helps to mechanically close the wounds by pulling the skin on both sides of the open wound forcefully towards each other. In these dressings, besides the drug carrier benefits of graphene oxide, its antibacterial properties were also utilized. In addition, active ingredient-loaded graphene oxide-based hydrogels for the destruction of drug-resistant bacteria on the skin have been proven to help treatment, regarding their antibacterial properties on infected skin. (21). In the light of the results of the studies and data graphene and graphene oxide have started to be used in a wide variety of drug delivery systems including nanoparticles, carbon nanotubes, nanofibers, nanoemulsions, nanocapsules, liposomes, erythrocytes, microspheres, dendrimers and hydrogels (23). The studies carried out with above mentioned DDS, are briefly summarized below.

Nanoparticles

Nanoparticles used in drug delivery systems are colloidal particle systems smaller than a micron (< 1 µm) size. Nanoparticle systems can adsorb drugs throughout the tissue matrix and dissolve or disperse in the targetted tissue and thus, resulting in the release of the active substance in the targetted region. Nanoparticles can be produced from natural materials such as gelatin, albumin or synthetic materials such as polylactides, poly(alkylcyanoacrylates) and also produce by solid lipid polymers. In this direction biocompatible nanoparticles that can degrade and dissolve in the target tissue can be synthesize. The release mechanism of the drug generally occurs as diffusion, swelling, erosion and degradation of nanoparticles in the body. Both hydrophilic and hydrophobic drug active ingredients can be loaded with high capacity and stability. It can be used in various drug administration ways for controlled drug delivery (24).

Since graphene oxide has more advantages than graphene, graphene oxide is mostly preferred in nanoparticle synthesis. Wang et al. (25) investigated the effectiveness of graphene oxide-based nanocarriers in the therapeutic treatment of cancer. A nanoparticle system containing galactosylated chitosan/graphene oxide/doxorubicin (GC-GO-DOX) was designed and evaluated. The results showed that the drug loading capacity was high at 1.08 mg/mg (drug per polymer) and revealed that the prepared nanoparticles remained stable under physiological conditions. Doxorubicin released from nanoparticles in pH 5.5 PBS medium is two times higher than the release in pH 7.4 PBS medium. In addition, in cell proliferation tests performed in this study, CS-DO-DOX nanoparticles were found to have high cytotoxicity in cancer cells. The obtained data showed that graphene oxide-based nanoparticle drug delivery systems could be promising candidates for chemotherapy. In addition to this study, graphene oxide-based nanocarrier systems using different chemotherapeutic agents in different cancers have been supported by other studies. Zhao et al. (26) created a drug delivery system (DDS) based on graphene oxide nanoparticles (GON) of appropriate size and shape to effectively deliver the drug by combining biocompatible PEGylated alginate (ALG-PEG) brushes onto the GON with a disulfide bridge bond. Studies showed that graphene oxide-based nanoparticles can be loaded with doxorubicin at high capacity with good stability and biocompatibility under physiological conditions. It was observed that the nanoparticles prevented the leakage of DOX until they reached the target tissue.In another study carried out by Gonzales et al. (27), the effectiveness of graphene oxide/iron oxide nanoparticles in the diagnosis of cancer in magnetic resonance and fluorescence imaging was investigated. It was observed that iron oxide increased the functionality of graphene oxide and showed less cytotoxicity compared to nanoparticles containing only graphene oxide. Magnetic resonance imaging with these created nanoparticles enabled the imaging of cancerous environments and was found to be successful. In another study conducted by Deb et al. (28), graphene oxide-polyethylene glycol-folic acid(GO-PEG-FA) nanoparticles were synthesized and their effectiveness in breast cancer treatment was examined. These nanoparticles were loaded with camptothecin. Camptothecin is an alkaloid with antitumor activity. The release of camptothecin is higher at acidic pH due to increased hydrophilicity and water solubility at acidic pH. The conjugation of GO with PEG and FA has led to a controlled drug release. The effectiveness of nanoparticles loaded with camptothecin and functionalized with polyethylene glycol and folic acid was investigated on MCF-7 breast cancer cells and found as a good candidate for therapy. In the study that was conducted by Kooti et al. (29), the performance of nanoparticles consisting of graphene oxide, cobalt ferrite and silver in drug delivery systems with antibacterial activity was investigated. These nanoparticles were loaded with ciprofloxacin and they showed low cytotoxicity, high stability and strong antimicrobial activity. In the examination by electron microscopy, it was observed that nanoparticles cause irreversible cell wall damage to the bacterial cell wall. In addition, a synergistic effect was observed between the drug ciprofloxacin and GO-$CoFe_2O_4$-Ag. It is thought that the conjugation of ciprofloxacin with the GO-$CoFe_2O_4$-Ag nanocomposite as it is prepared can prevent the development of resistance of microbes and increase the antimicrobial activity of the antibiotic.

Carbon Nanotubes

Carbon nanotubes (CNT) are unique structures with high thermal conductivity, high electrical conductivity, high stability, very strong and extremely high aspect ratio bonding patterns presented between atoms (30). CNTs are hollow carbon graphitic nanomaterials with diverse properties and a good molecular array. They are hollow monolithic in the form of nanoneedles and desired functional groups can be added to the outer layers of CNTs. With this special nano-needle-shaped structure of CNTs, they can enter the cell by passive diffusion transport through the lipid bilayer. In addition, it can enter the cell with this special form by other methods such as endocytosis. This special hollow monolithic structure of CNTs, the ability to bind

the desired functional groups to the outer surface and gain different properties, make CNTs promising drug carrier systems. Compared with other nanomaterials, CNTs appear to be more effective in biological applications. For example, the main application of quantum dots alone is cancer cell imaging, while CNTs also have the potential to be used in imaging, drug delivery and thermal ablation. Therefore, the application of CNTs to deliver drugs to their domains has become one of the main interests of different research groups.(31).

Despite these unique properties, if no surface modification is performed on CNTs, they can show cytotoxic effects mostly on some mammalian cells. CNTs become non-immunogenic and biocompatible with surface modifications. In addition, the hydrophilic properties of CNTs can be increased by functionalization. For this process, CNTs can be reacted with strong acids, and with this process, the formation of carboxylic acid groups on the surface of CNTs increases their dispersibility in aqueous media. Apart from this process, hydrophilic molecules can be attached to CNT surfaces by covalent or non-covalent methods to increase the hydrophilic property. An example of this surface coating is poly(ethylene glycol) (PEG). The hydrophilicity, biocompatibility and immunogenicity of CNTs can be increased after coating with PEG. CNTs have a cage-like structure, which enables the loaded active ingredients/drugs isolated from their solvent environments (30).

Carbon nanotubes are divided into two groups a single-walled (SWCNT) and multi-walled (MWCNT) nanotubes. Single-walled ones have a diameter in the range of 0.4-2 nm and consist of a single carbon layer, that diameter varies depending on the temperature at which they are synthesized, and they can be produced in larger radius at higher synthesis temperatures. In contrast, multiwall NCTs are mostly structures with 1-3 nm inner tubes and multiple carbon layers with diameters between 2-100 nm for outer tubes. The basic carbon arrangement of SWCNT and MWCNT carbon nanotube types is different from each other. The production of CNTs can be accomplished by heating in a controlled flame environment using carbon black and graphite. In scientific studies, it has been understood that molecular interactions responsible for the adsorption of proteins and peptides occur on the surfaces of SWCNTs (31). In addition to individual amino acids, adsorption of secondary and tertiary protein structures and conformations can be achieved. In this way, they can be used in drug, gene transfer, *in vivo* imaging, targeting and cancer treatment by providing the adsorption of peptide and protein structures. In studies examining capped/encapsulated/coated SWCNTs, it has been observed that these drug-loaded capsules can effectively inhibit the growth of tumor cells *in vivo* in experiments on mice. In addition, they showed antibacterial properties in tests against *B. cereus* and *E. coli*. In the study that PEG and Tween coated SWCNTs given intravenously to mice caused an increase in the expression of proteins with antioxidant activity in the liver tissue and detoxification properties with no toxic effects were observed. The effectiveness of functionalized SWCNTs in cancer treatment has been proven in studies. In addition, magnetic nanotubes were sent to lung cancer cells in studies with magnetic SWCNTs, which are single-walled nanotubes, and it was observed that doxorubicin release from the nanotube started after pH/NIR irradiation. This study suggested that magnetic SWCNTs could be an effective treatment method by combining photodynamic therapy and chemotherapy (30). MWCNTs were found to be more effective than SWCNTs in the thermal treatment of cancer, due to MWCNTs release by high dimensional vibrational energy when exposed to near infrared light. With the release of this vibrational energy within tumor tissue, a localized heat is generated that can kill cancer cells. The reason why MWCNTs show more vibrational motion is because they have more available electrons per particle, and because they contain more metallic tubes than SWCNTs, they can absorb infrared radiation faster and more. Because of the advantages of graphene and graphene oxide, they are mostly preferred in the production of CNTs. Although graphene or graphene oxide-based CNTs included a product that has not yet been released in the pharmaceutical market, much researches have been carried out either on diagnosis or therapy to reach this goal (30)(31).

In a study carried out by Fan et al. (32), the efficiency of graphene-iron oxide carbon nanotubes for delivery of fluorouracil, an anticancer drug, investigated. In *in vitro* cytotoxicity tests, it was observed that non-drug loaded nanocapsules were not toxic in liver cells even at high concentrations. The prepared nanohybrids have high drug loading capacity. This may be due to hydrogen bonding and π-π interaction between 5-FU and graphene sheets. It has been observed that drug-loaded nanotubes are effective in cancer treatment. In the study of Rezayan et al. (33) graphene oxide-based carbon nanotubes in combination with N-isopropylacrylamide (PIN)loaded with doxorubicin and paclitaxel were produced and it was obtained that nanotubes were able to successfully reach the target tissue and achieve controlled release without leaking the drug before they reached the target tissue. Because carbon nanostructures are insoluble in water, they tend to aggregate in aqueous media through Van der Waals interactions. It is not preferred in drug

delivery systems because the aggregation that occurs increases the particle size and therefore is not suitable for cell penetration, prevents its circulation in the blood and increases the toxicity of the carrier. If carbon structures are functionalized with a hydrophilic polymer such as PIN, it can prevent aggregation and increase the biocompatibility of carriers. While PIN can form many hydrogen bonds with water and prevents agglomeration, it is thought that the prepared formulation makes it more stable in the bloodstream and creates a suitable combination for the delivery of DOX and PAX. In the study of Asghar et al. (34) the effects of graphene oxide-based nanotubes on human sperm were investigated and single-walled carbon nanotubes based on graphene oxide were designed. The results showed that graphene oxide carbon nanotubes at 25 µg/mL concentration did not affect sperm viability. Also in this study, it has been shown that reduced graphene oxide does not initiate reactive species in human sperm, exposure to these nanomaterials does not inhibit the sperm segregation process, and microfluidic separation systems can select sperm with low oxidative stress after exposure. In the study of Liqiang et al. (35) the toxicity of graphene oxide-based multi-walled carbon nanotubes on human cells was investigated. Human bone-marrow neuroblastoma line, human epithelial carcinoma cell line and zebrafish were used in the study. It shows that GO has moderate toxicity to organisms, as it induces cell growth inhibition and slight hatching delay of approximately 20% of zebrafish embryos at a dose of 50 mg/L, but did not cause a significant increase in embryo apoptosis. This study is thought to cause real toxicity to organisms that pose potential environmental risks and brings a new perspective to the geometric structure-related toxicity of graphitic nanomaterials.

Nanofibers

Nanofibers are nano-sized systems with a fiber diameter range of 1-1000 nm and can be applied to various administration routes such as topical, oral, transdermal and transmucosal. Due to the special structure of nanofibers, degradation in physiological environments is prevented until they reach the targetted tissue and drug release is actualized in the targetted tissue (36).

The most common method used in the production of nanofibers is the electrospinning method, in which nano-sized fibers are produced by applying a high electrical voltage to a polymer solution or melted polymer liquid. There are two methods of loading active ingredients into nanofibers. The first one is the dissolution or dispersion of the active substance in the polymer solution before electrospinning. The second method is the physical or chemical bonding of drug active ingredients on the produced nanofibers (37). One of the biggest features of nanofibers is that the properties of the produced nanofibers can be changed by a wide variety of parameters. The parameters that can be changed during production are the parameters of the polymer solution (solvent, excipient, polymer ratio), environmental conditions (temperature and relative humidity of the production part) and production process parameters (the distance between the Taylor cone and the collector, the applied voltage size and the flow rate of the polymer solution from the syringe) (38)(39).

After the changes in the parameters changed in these three main sources after production, the fiber diameter, thickness and pores of the nanofibers produced can be checked and examined with microscopes. This provides more possibilities for use in drug delivery systems, as a wide variety of nanofiber models can be created with so many parameter changes. The polymer materials chosen for the production of nanofibers and the internal structure of the nanofibers are the main factors affecting the drug release properties. Nanofibers designed for immediate drug release are mostly simple and homogeneously designed structures prepared in the form of a drug-polymer or drug-polymer mixture (36). Nanofibers designed for long-term drug release may contain a core-shell structure that allows loading of more than one type of active drug substance and/or an outer polymer layer that acts as a barrier to controlling drug release rate. Sandwich type nanofibers are nanofibers produced by sequentially passing different polymer solutions through an electrospinning device (40)(41). The drug release time can be extended by adjusting the radii of the beads in the structure of these produced nanofibers. It is possible to produce nanofibrils (fibril emphasizes a thin fiber) that are stimulated by temperature, pH or electroresponsively to release drugs. Stimulus-activated nanofibrils can be in a simple matrix type nanofiber structure or their outer layer can be covered with a core shell. One or more types of stimulus sensitive polymers can be used in the manufacture of such nanofibrils. Such nanofibrils can also be used for biphasic drug release. The sandwich model can also be used to ensure biphasic drug release. Studies on graphene and graphene oxide-based nanofibers have been increased and studies are mostly carried out on drug release and tissue engineering (42)(43).

In the study of Heidari et al. (43) PCL/gelatin/GO based electrospun nanofibers were prepared and used for nerve tissue engineering. Their effectiveness was examined, and the antibacterial property of

graphene oxide was proved in the form of a nanofiber system by succeeding an antibacterial effect on *S. aureus* and *E. Coli*. PCL/gelatin scaffolds containing graphene had higher hydrophilicity and showed higher biodegradation compared to PCL/gelatin nanofibers due to the presence of hydroxyl groups in the graphene structure. This is because with the addition of graphene to the nanofibers, the nanofibers became more hydrophilic, but the scaffold integrity was preserved. Cell culture studies have shown that PCL/gelatin/graphene nanofibrous mats provide a favorable microenvironment for cell migration, adhesion, and proliferation. Also, no cytotoxicity was detected in the presence of graphene. Liu et al. (44) examined polyvinyl alcohol/chitosan/graphene oxide-based nanofibers in their study and it was found that these nanofibrils showed good mechanical properties and high antibacterial activity. FESEM images showed that the dispersed single GO layer embedded in the nanofibers, the GO layer and PVA/CS chains formed by self-assembly. The mean diameters of the biocomposite nanofibers decreased with increasing GO content. Raman spectra showed the presence of GO in biocomposite nanofibrous mats. As a result of this study, PVA/chitosan/graphene oxide nanofibers were accepted as a promising candidate in wound healing and drug delivery applications.

In the study of Abdoli et al. (45), tetracycline hydrochloride loaded polyvinyl alcohol/gum tragacanth/graphene oxide nanofibrils were prepared and their effectiveness in transdermal drug delivery was examined. The results showed these nanofibers inhibited bacterial growth in the antibacterial test results. Graphene oxide doped PVA/GT nanofibers have higher mechanical strength compared to PVA/GT nanofibers and the diameter of nanofibers decreased when GO was added. Drug release is slower in the presence of graphene oxide. In addition, nanofibers prepared by MTT test were found to be biocompatible and have low cytotoxic effect. In the study of Ardeshirzadeh et al. (46), nanofibrils based on polyethylene oxide/chitosan/graphene oxide were produced via electrospinning process. These fibrils were loaded with doxorubicin. The drug release study showed that higher drug release occurred at pH 5.3 due to the reduced interaction between DOX and PEO/CS/GO nanofibers compared to drug release at pH 7.4. Cell viability results showed that DOX-loaded PEO/CS/GO/DOX nanofibrous scaffold can be used as an alternative DOX source compared to plain DOX to avoid the adverse effects of free DOX. It is thought that it can be used as a promising system in the future as a drug delivery system in the treatment of lung cancer, since it can perform controlled release for a long time. Ciprofloxacin was loaded on chitosan/polyvinyl alcohol/graphene oxide nanofibers for wound dressing application by Yang et al. (47) and their effectiveness was investigated. The release of the absorbed drug in the GO nanolayers regulated the drug release profile, preventing the "burst" release of the drug in the initial phase of release, and the drug release was improved when GO was added. The results showed that nanofibrous membranes with antibiotig drugswere found to be effective on *E. coli*, *S. aureus* and *B. subtilis*. The viability of all human cell samples was over 110% and it was understood that this developed system was perfectly cytocompatible with Melanoma cells. Although nanofibers show great promise for drug release, many more scientific studies are needed to prove that they can be used in treatment today.

Liposomes

Liposomes are spherical, bi-lipid layered structures that can be produced in the diameter range of 50-1000 nm (48). Liposomes are divided into two groups unlayered and multilayered according to the number of layers. The diameter of monolayer liposomes is between 50-250 nm. Monolayer liposomes are aqueous and have a large center and are therefore preferred for loading highly water-soluble active substances. The diameter of multilayered liposomes is between 1-5 micrometers. Multilayered liposomes consist of many lipid layers, which are arranged concentrically within each other. Multilayer liposomes, unlike monolayers, are preferred for loading more fat-soluble active ingredients (49).

The main reasons for preferring the use of liposomes in drug delivery systems are the content of the liposome, its size, its drug loading capacity, its stability until the active substance is transported to the target tissue and its interactions with cells. Their interaction with the cells is mostly by adsorption or after adsorption the cell takes the liposome in through endocytosis. Apart from these two interaction methods, liposomes can interact with cell membranes and fusion can occur (50).

Liposomes can be produced in suspension, cream, gel, dry powder or aerosol form depending on the purpose of use. The surfaces of liposomes are designed to carry different molecules that can be bound to penetrate into different tissues and cells. However, the problem that affects the use of liposomes during treatment is the digestion of liposomes by phagocytic cells in the human body, which is restricted the liposomes to reach the target tissue. In order to eliminate this problem, the surfaces of liposomes have been coated with molecules that do not activate the immune system in scientific studies. This method has been

tried for tumor treatment but has not been successful. The reason for its failure was attributed not to the digestion of liposomes by phagocytic cells, but to insufficient blood flow in the tumor tissues. Poly(ethylene glycol) coated liposomes were prepared to overcome this problem andthey succeeded to prevent the interaction between the liposome surface and serum proteins (51). In addition, it has been understood that cholesterol-rich, small, rigid liposomes developed cannot be cleaned by Mononuclear Phagocytic System (MFS) and that liposomes maintain their stability in plasma. Studies on temperature-sensitive liposomes have also been conducted. The reason for these studies is that the temperature in cancerous tissues can rise above 40°C. Thus, it is aimed to develop liposomes targeting cancer tissue. Great success has been achieved in some of the studies of liposomes for cancer treatment, and therefore there are formulations that have been approved for use in cancer treatment with some studies. There are studies in which liposomes are also successful in the treatment of some infectious diseases. Besides being used for treatment, liposomes can also be used for diagnosis and imaging. MRI, tomography, scintigraphy and sonography can be given as examples of imaging techniques used for diagnosis (52). Although there are not many studies on graphene-based liposomes, there are studies on graphene oxide-based liposomes. Studies on graphene oxide-based liposomes have been mainly focused on cancer therapy. In these studies, it has been observed that graphene oxide-supported liposomes increase the stability of drugs and prevent the early release of the loaded anticancer drug from the liposomal space until it reaches the target tissue. In general, positive results were obtained in the treatment of tumors and it was thought that it could be a promising method in the future (48).

Hashemi et al. (53) studied the efficacy of graphene oxide layered liposomes for photo-chemotherapy. Doxorubicin was loaded into the prepared liposomes have been developed for chemo-photothermal destruction of breast cancer cells. This system was named layer Lipo-graph (LBL Lipo-graph) and consists of layers of graphene oxide (GO) and graphene oxide conjugated poly (L-lysine) (GO-PLL) deposited on cationic liposomes encapsulating doxorubicin. The photothermal response was examined with IR camera imaging. The drug release profile shows that LBL Lipo-graph releases much faster in an acidic environment than a liposome control. The drug release profile of LBL Lipo-graph demonstrated the thermosensitivity and pH sensitivity of the nanoparticles. Toxicity analysis showed that LBL Lipo-graph could effectively destroy MD-MB-231 cells upon NIR irradiation. The presence of GO-PLL in the outer layer of the LBL Lipo-graph can increase cellular uptake and drug accumulation within cells. Moreover, the presence of multiple functional groups on the GO-PLL provides an efficient binding facility for active targeting of LBL Lipo-graph. At the end of the study, these liposomes were found to be successful in photo-chemotherapy. Zheng et al. (54) investigated the effect of chitosan/oxidized hydroxyethyl hydroxy/graphene oxide/asiaticoside liposome-based hydrogels and the effect of these liposome-based hydrogels on peripheral nerve regeneration and scar prevention effect. The application of electrical stimulation with the addition of GO to the formulation can accelerate nerve regeneration by enabling the differentiation and proliferation of nerve cells. The asiaticoside released from the hydrogel had inhibitory effect on the growth of fibroblasts and secretion of collagen and eliminated scars for regenerative nerves. shows that the hydrogel will be a promising candidate for peripheral nerve regeneration. Hydrogels were found to be successful as promising candidates for peripheral nerve regeneration. In the study of Prasad et al. (48) the efficiency of graphene oxide supported liposomes in photo triggering tissue visualization and tumor treatment was investigated. Folic acid functionalized graphene oxide-based liposomes were investigated in the experiment. The GOF-supported liposomal nanohybrid exhibited better water dispersibility, fast photothermal response, approximately 90% cell viability, and hemocompatibility. In addition, in vivo studies demonstrate specific biodistribution and localized breast tumor diagnosis, longer-term tumor accumulation and major tumor regression using a single dose diffuser nanohybrid. Graphene oxide supplementation increased the stability of drug-loaded liposomes in the extracellular environment and prevented the premature release of drugs from the liposomal space. According to the results it was found to be effective in both imaging and breast cancer treatment.

Nanoemulsions

Nanoemulsions are called colloidal dispersions of two thermodynamically unstable types of immiscible liquids. Nanoemulsions consist of droplets ranging in diameter from 10 to 200 nm (55). These droplets are covered with a protective emulsifier molecule. The surfaces of these droplets are amorphous and have a negatively charged lipophilic character. Oils, lipids, surfactants, water and hydrophilic co-solvents can be found as components in nanoemulsions. For the oil phase in its components, glycerols,

vegetable oils, free fatty acids and triglycerides can be used. The oil type to be selected for the oil phase is mostly chosen due to the solubility of the active drug substance to be used (56).

Nanoemulsions are one of the promising DDS to increase the bioavailability of hydrophobic active ingredients and bioactive food ingredients. They also reduce the toxic effects of the drugs. Most drugs are lipophilic (hydrophobic) and thus cause problems of low solubility and low bioavailability in the body. Nanoemulsions are nanocarrier systems with high surface area and high stability. However, they are thermodynamically unstable. Nanoemulsions can be used in the administration of drug active substances by transdermal and transmucosal routes (57). The main application areas of nanoemulsions in medicine are the treatment of reticuloendothelial system (RES) infections, cancer treatment, liver enzyme replacement therapy and vaccination. There are three types of nanoemulsions and they are oil-in-water nanoemulsions, water-in-oil emulsion, and bi-continuous nanoemulsions. Despite their small size, nanoemulsions have large surface areas that allow greater absorption. Nanoemulsions can be formulated as spray, liquid, foam or cream. In cell culture studies, they increase the penetration of fat-soluble drug substances and food supplements into cells. They increase the solubility of hydrophobic drug active ingredients in tissues. They can also be used for taste masking. The production of nanoemulsions requires less energy than most other drug delivery systems. Nanoemulsions are structures that are resistant to droplet aggregation and coalescence. With scientific studies, it has been found successful in the transport of food components and drugs with hydrophobic character as a drug delivery system, in the transport of drugs in parenteral, ocular, topical and oral routes (57)(55).

Oil/water phase nanoemulsions increase the bioavailability of fat-soluble vitamins and bioactive foodstuffs by facilitating their dissolution in the gastrointestinal tract. In addition, they increase the diffusion of bioactive substances into the intradermal layers. Thus, they are preferred in cosmetics due to their nano size, transparency and low viscosity. Nanoemulsions are also used in the transport of antibiotics, chemotherapeutic agents and other active pharmaceutical ingredients. Its effectiveness has also been proven in the transport of disinfectants, antiseptics and cosmetic agents in addition to the transport of drugs (57). There are few studies either on graphene or graphene oxide-based nanoemulsions. In one of these studies, nanoemulsions containing graphene oxide were tested for the treatment of liver cancer in the study by Ran et al. (58). Folic acid (FA) Bound Chitosan (CS) and Graphene oxide (GO) nanocomposites (NCs): FA-CS-GO-NCs were obtained by ionic crosslinking of positively charged FA-CSGO solution conjugates and negatively charged nanoemulsionand loaded with the active ingredient of *Ginkgo biloba* leaves, polyprenol, which is accepted to be effective in the treatment of the hepatocellular carcinoma. This formulation has high encapsulation efficiency (over 90%) and storage stability (until 30 days). The prepared nanoemulsions were applied to MHCC97H liver cancer cell culture, and it was observed that a greater effect in inhibiting malignant tumors in the liver due to the presence of graphene oxide in the formulation was achieved. Thus, nanoemulsions have been accepted as a potential in the treatment of hepatocellular carcinoma.

Nanocapsules

Nanocapsules consist of a liquid, solid or empty core and a solid shell. They are similar to vesicular systems in terms of structure and are also called nano-vesicular systems due to this similarity. The inner liquid core is surrounded by a membrane and active ingredients are loaded into this core in a solid, liquid or molecular distribution. Moreover, in some designed nanocapsules, the drug substance can be carried on the nanocapsules surfaces (59)(60)(61). Due to their solid shells, nanocapsules can protect the active ingredients until they reach the targetted tissue. This solid shell is also able to protect the active substance from pH, temperature, enzymes and other biological factors. In addition, the polymer shell can be functionalized by smart molecules and targeting the nanocapsule to the tissue can be achieved. The polymeric shell of the nanocapsule plays an important role in loading the drug substance, protecting the active substance, providing the drug release and sometimes targeting (59). Although it is desired to be completely biodegradable, non-biodegradable but biocompatible polyethylene glycol (PEG) and polyvinyl alcohol (PVA) can be used in the production of nanocapsules. Natural or synthetic polymers are preferred in the production of nanocapsule shells. The most preferred natural polymeric substances are polysaccharides. This is due to its high biocompatibility, mucoadhesive properties and good gelation properties. The polymers to be selected in the synthesis of the shells vary according to the active drug substance to be loaded and the target organ. The core part of the nanocapsules is mostly designed with lipophilic character. The reason for this is that lipophilic drugs increase the solubility capacity and the oil phase is more convenient to transport reliably. Therefore, the core is often designed to be in the oleic phase. The components to be used for the oleic phase also vary according to the structure of the active ingredients. In addition, the oils to be

selected for core synthesis can not only encapsulate the active ingredient, but also help the treatment itself. An example of this is acai oil. In the studies, it was indicated that in addition to the drug active substance in nanocapsules designed with acai oil seeds, acai oil showed anti-inflammatory and anti-proliferative effect (62).

In addition to açai oil, antioxidant, antifungal, antibacterial and antimutagenic effects have been observed in studies with essential oils such as lemongrass oil and turmeric oil in the core of nanocapsules. While nanocapsule cores can be produced with lipophilic character, they can also be designed with hydrophilic character. For example, gemcitabine hydrochloride and doxorubicinshow hydrophilic character, these active ingredients were loaded into nanocapsules with hydrophilic cores... Nanocapsules can also be designed to be hollow. The cores of nanocapsules can also be in solid form to support the loading capability for different charges. In addition, by using nanocapsules the bioavailability of drug/active ingredients can be increased, their side/toxic/adverse effects can be reduced, and targeting can be achieved (59).

Graphene-based nanocapsules have been mostly studied for electricity, battery and industry. But there are few studies of graphene oxide based nanocapsules in drug delivery systems. In the study of Cui et al. (61) the effectiveness of graphene oxide-based nanocapsules functionalized with folic acid was investigated and nanocapsule shells were prepared with chitosan. Also, oleic acid-modified Fe_3O_4 NPs (OA-Fe_3O_4 NPs) were encapsulated into FA-MRMGONCs and equipped with magnetic guide functionality suitable for FA-MRMGONCs.The produced nanocapsules were able to carry hydrophobic drugs to the target tissue without leaking, and they were able to release into the target tissue in a controlled manner. In the study of Li et al. (63), graphene oxide-chitosan nanocapsules were produced and their effectiveness as a drug delivery system was investigated. The produced graphene oxide-chitosan-based nanocapsules were examined under transmission electron microscopy (TEM) and hollow structures with a diameter of 570 nm were observed. These nanocapsules were loaded with ibuprofen active ingredient, and their effectiveness was examined. Since chitosan chains can tighten the nanocapsule wall, reduce swelling and slow down the degradation rate, genipin was added to the formulation to cross-link the nanocapsules, and the morphologies of the formulations were examined by TEM. It was observed that the cross-linked nanocapsules had a strong structure and could maintain their structure. Genipin (GO/Cs)x increased the stability of nanocapsules and prevented the collapse of the capsules in aqueous solution. As a result of the study, it was understood that this type of based nanocapsules could achieve a higher drug carrying capacity and a longer controlled drug release.

Erythrocytes

Erythrocytes are biconcave, disc-shaped cells without nuclei, the surface-volume ratio is high and allows them to change shape without tearing the cell membrane while passing through the capillaries. The average lifespan of erythrocytes is 120 days (64). Erythrocytes are one of the most effective natural carriers due to remain in circulation for a long time. In addition, their abundance in circulation and their ability to be easily sent to the target tissue create great advantages in their use as a carrier system. Despite these properties, the production, storage and licensing processes of erythrocytes are difficult (64)(65).

Drug loading to erythrocytes can be achieved in two ways. The loading patterns are the encapsulation of the erythrocytes into the internal volume and binding the active substances to the erythrocyte surfaces. The main reasons for the use of erythrocytes in drug delivery systems are to prolong the circulation of the active substance and increase the bioavailability of the drug. In addition to increasing the pharmacokinetic optimization of drugs, erythrocytes can also change their functionality and protect active ingredients from plasma inhibitors during transport. This is mostly achieved by masking with the glycocalyx. It has also been proven that erythrocytes can transfer drugs up to endothelial cells in some cases, which could be useful for developing vascular drug delivery (65).

Studies have been carried out for imaging and treatment of erythrocyte drug delivery systems. In the drug encapsulation process, erythrocytes are usually placed in a hypotonic environment and temporary membrane openings of 20-50 nm are formed in the membrane during hemolysis. Extracellular drugs, including therapeutic enzymes, peptides and nucleic acids, can be loaded through these temporally formed membrane gaps. After drug loading, these gaps can be closed again and drugs are encapsulated in erythrocytes. The main problem is the rapid leakage of drugs from some drug-encapsulated erythrocytes under physiological conditions and to overcome this problem, membrane stabilizing agents such as glutaraldehyde can be added to erythrocyte drug delivery systems. However, the deformability of erythrocytes can also be reduced with the membrane stabilizing agents and decreased deformability may result in increased recognition of erythrocytes by the reticuloendothelial system (RES) organs, especially

liver and spleen, and macrophages trying to digest erythrocytes. In addition, changes in the structure of erythrocytes may occur during drug loading, and as a result of these changes, macrophages can target erythrocytes (66).

Drugs loaded with erythrocyte drug carriers can be passively targeted to tissues with intravascular lesions and abundant blood. Due to this function, it may also be effective for the treatment of some hypervascular malignant tumors, the transport of anticoagulant drugs such as leukemia drugs, low molecular weight heparin and plasminogen activators (64). There are not many studies on the erythrocyte transport system containing graphene molecules. One of them was carried out by Li et al. (67) was investigated the efficacy of graphene oxide associated erythrocyte drug delivery systems for photothermal cancer treatment. Doxorubicin was wrapped in nanoparticles and the red blood cells (RBC) membrane (RM) was used as a shell. RM provided the formulation with biocompatibility and the ability to avoid clearance by the reticuloendothelial system (RES). In addition, folic acid was added to the formulation for selective recognition of tumor cells. Also, erythrocytes were functionalized with folic acid to target them to the folate receptor. During the experiment, a high amount of erythrocyte accumulation was observed in the tumor tissues and cells and the drug remained for a long time, besides that, the formulation showed good stability, photothermal response and fluorescence. The cloak of the RBC membrane on the formulation effectively camouflaged the molecules, reducing interference by the liver or kidney. According to thestudy, it has been accepted that graphene oxide associated erythrocyte drug delivery systems can be effective in real-time imaging and photothermal chemotherapy.

Dendrimers

Dendrimers are three-dimensional spherical, nanometric-sized monodisperse structures with many and long branching structures (68). The entire branched structure depends on the inner core. After the main branches emerge from the core, branching may continue over the branches (69). There is more than one dendrimer synthesis method available. Basically, there are two methods for dendrimer synthesis. These are the convergent method and the divergent method. In the convergent method, dendrons, which are the branched parts of the dendrimers, are synthesized individually and then connected to the focal points. In divergent method synthesis, dendrimers consist of dendrons that spread radially from a central focal point. In the divergent method, dendrons are grown away from the nucleus and this method is more preferred for production (70). The reasons for their acceptance as an ideal drug carrier are the high hydrophilic character and biocompatibility of dendrimers (69).

New generation dendrimers with larger internal volume voids can be loaded with greater amounts of active pharmaceutical ingredients. Advanced large-size dendrimers have a more densely packed surface than smaller-sized dendrimers. Due to this dense packaging ability, they can gain high encapsulation efficiency and long-term drug retention capabilities (70).

Dendrimers have also been found successful in transdermal formulations. Oral applications of dendrimers have also been examined in scientific studies In addition to these, ocular administration and studies on gene release have resulted in positive results. Topical gels using dendrimers are commercially available (68). In addition, targeting the drug to the desired site can be accomplished by surface modification of dendrimers using various targeting moieties. In this way, it will be possible to reduce the side effects by moving away from the traditional therapy where the drug accumulates at toxic levels in healthy tissues such as the liver, spleen, kidneys and bone marrow. In recent years, the use of dendrimers in biological systems has been increasing. The well-defined structure, polyvalent character and monodispersity make dendrimers effective for drug delivery applications. Dendrimers are used for drug delivery and targeting of drug molecules. However, their use is limited due to their high production costs, and they are also not subject to GRAS status due to the inherent toxicity problems associated with them. Besides drug delivery, dendrimers have been found to be of great importance in gene delivery, boron neutron capture therapy, photodynamic therapy, and as magnetic resonance imaging contrast agents (70).

There are not many studies on drug delivery systems of graphene-based dendrimers. Haşimi et al. (71) investigated the efficacy of citric acid dendrimers functionalized with graphene oxide including doxorubicin in cancer treatment. The results showed that the encapsulation ability of graphene oxide-citric acid dendrimers was high and the combination of graphene oxide-citric acid and its fluorescent properties provided traceability in *in vivo* studies. It has been observed that these dendrimers release drugs at a high rate at low pH. In vitro cellular uptake of GO-G3/DOX against DU 145 cells was examined by the confocal laser microscopy technique. It was found that free DOX molecules reached the nucleus after 2 hours, but most of the DOX bound to the hybrid remained outside the cell nucleus after 2 hours of incubation. This is

thought to be due to insufficient drug discharge. As the number of discharged DOX molecules increased over time, more DOX molecules were transported to the cell nucleus after 8 hours of incubation, keeping GO-G3 out of the cell. In the study, graphene oxide-citric acid dendrimers including doxorubucin were found to be slightly more toxic than graphene oxide itself.

Siriviriyanun et al. (72) examined the phototherapeutic functionality of dendrimers containing graphene oxide in their study. Folic acid and graphene oxide were chemically bonded on a hydroxyl-terminated fourth generation poly (amidoamine) dendrimer and these dendrimers were tested on Hela cells. Death of Hela cells was observed when incubated with a 780 nm laser for 15 minutes. The photosytotoxicity study revealed that under two-photon excitation at 780 nm, the hybrids can absorb near-infrared light and generate reactive oxygen species that can oxidize HeLa cells and cause their death, suggesting phototherapeutic behavior. Hybrids were found to be highly biocompatible against HeLa cells by cytotoxicity study. It concluded as it can be used in photodynamic therapy for cancer treatment. Karimi et al. (73) investigated the efficiency of ironoxide-graphene oxide-PEG-based dendrimers as a pH-sensitive drug delivery system. Doxorubicin was loaded into the dendrimer as the active ingredient and it was found that the DOX active agent for dendrimers had a loading efficiency of 92.6%. MCF-7 cancer cells were used to investigate the efficiency and the efficiency of the dendrimer-DOX structure was higher than the activity of free DOX. The encapsulation efficiency and drug loading efficiency of the formulation were ~92.6% and ~9.26%, respectively. It showed that the apoptotic effects of the formulation were higher compared to free DOX. In addition, intracellular uptake of the drug in the formulation occurred within 4 hours and showed a higher uptake percentage compared to the free drug. It was concluded that this designed carrier system has the advantages of good biocompatibility, low cost, excellent colloidal stability, high specific surface area, low cytotoxicity and high adsorption capacity, which is able to be an effective candidate in anticancer drug delivery systems. In the study(74), dendrimer was synthesized by esterification reaction between phloroglucinol and terephthalic acid. 3,4-dihydroxybenzoic acid was used to increase the biocompatibility of the formulation. Dendrimer-functionalized graphene oxide (GO) was prepared to enable the delivery of venlafaxine hydrochloride (VH) as an antidepressant drug. It was observed that the highest percentage of adsorption was obtained at pH=7 and contact time at 30°C for 20 minutes. The release of drug from the nanocarrier in simulated intestinal fluid (SIF) and simulated gastric fluid (SGF) was studied. While the total amount of drug released in gastric juice was 99% (pH = 1.2), only 40% of VH was released after 6 hours in an almost neutral environment at pH = 7.4. Drug release occurred via Higuchi and first order kinetic mechanism. The cytotoxicity of the formulation was investigated by apoptosis methods using 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) and PC-12 cell lines. The obtained data showed that the prepared formulation was biocompatible.Pourjavadi et al. (75) investigated the pH-sensitive doxorubicin release of dendrimers containing iron oxide and graphene oxide in their study. Two types of drug carriers based on mesoporous silica coated magnetic graphene oxide were synthesized and investigated whether they are pH sensitive for doxorubicin release. One of the carrier was multiethylene amine impregnated onto the formulation and the other was supramolecular polypseudorotaxane. The drug was stored in mesoporous silica pores or adsorbed on GO by hydrophobic interaction and then cyclodextrin was added onto the surface of nanoparticles at pH 7.4. In the formulation, cyclodextrin was added to prevent the drug from leaking out at neutral pH. The drug release profile showed that the supramolecular nanocarrier was more sensitive to pH changes. The drug release content was approximately 100% at pH 5.5 and zero at pH 7.4 for 48 hours. Moreover, the dendrimer structure facilitated the release of doxorubicin. The prepared formulation is suitable for cell uptake. At pH 5.5 (endosomal pH), the drug was released from the pores of the mesoporous silica and the GO surface by opening of cyclodextrin from dendrimer-like multi-amine chains. Formulation of effectiveness in pH sensitive drug release was also proven in this study.

Microspheres

Microspheres have high specific surface areas and the average size of the microspheres is 1 µm. Among the variety of microspheres, the most common are solid, mesoporous, porous, and core-shell microspheres (76). Microspheres can be produced from synthetic and natural polymers. The most preferred synthetic polymers are polylactic acid and polylactic-co-glycolic acid, and the natural polymers are albumin, casein and gelatin. Despite natural polymers have high absorbability and low toxicity, their high water solubility creates a disadvantage for their use in long-release systems. Therefore, they are used in rapid drug release systems. Although release times of the natural polymer based microspheres can be extended with cross-linking agents; they can cause toxic effects. Microspheres are also effective in drug targeting. They are particularly effective in targeting macrophages. The size and charge of microspheres are also important in

targeting macrophages. Microsphere drug delivery systems can be administered intravenously and orally (77).

Many studies have been carried out for microspheres containing graphene oxide. These studies are mainly on antibiotic therapy. In the study of Pooresmaeil et al, (78) the effectiveness of chitosan/graphene oxide microspheres for pH-controlled delivery of amoxicillin was investigated. Due to the structure of chitosan biopolymer, pH-sensitive microspheres that can perform sustained release were developed and the effectiveness of these amoxicillin-loaded microspheres on *S. aureus* and *E. coli* was investigated. The obtained results showed that the drug loading value increased as a result of the increase in the GO nanosheet content. An increase in hydrogen bonding and electrostatic interactions between amoxicillin, a caionic drug, and anionic GO nanosheet was observed. In addition, amoxicillin drug molecules were able to charge higher for microspheres with high GO content via π–π interactions. In addition, in all prepared microspheres, amoxicillin interacts with the polar functional group of chitosan, increasing drug loading or drug trapping in the pores. The results showed these pH-sensitive systems could be effective against gastric bacterial infections. In addition, it has been found to be safe in terms of toxicity. According to Yashaswini et al. (79) synthesized calcium ion cross-linked alginate (Alg), alginate-graphene oxide (Alg-GO) and alginate-graphene oxide-dexamethasone (Alg-GO-Dex) composite microspheres for bone tissue engineering and studied their activity. An in vitro biomineralization study was performed using a simulated body fluid (SBF) solution. The biocompatibility of the prepared formulation was examined with osteoblast-like cells (MG-63) and it was found to be biocompatible. The formulation has more than 80% porosity and the distribution of GO in the alginate matrix is uniform. The drug provided sustained release from the microspheres. Excellent apatite formation was observed after immersing the Alg-GO microsphere in SBF solution for a period of 30 days, and the addition of dexamethasone to the microspheres was found to increase cell proliferation with apatite formation. Moreover, the addition of dexamethasone to Alg-GO microspheres significantly increased the mineralization in the SBF solution compared to Alg-GO. However, the addition of graphene oxide to the alginate matrix provided more binding of MG-63 cells and increased the encapsulation efficiency of the drugIn the study of Wu et al. (80), chitosan/graphene oxide airgel microspheres were produced and their effectiveness was examined. The efficacy of these prepared microspheres in the treatment of hyperbilirubin was studied. It was understood that the prepared microspheres were in a nanoporous structure (ranging from 20 nm to 40 nm) with ahigh surface area (174.69m^2/g) and special size distribution. In the treatment, these microspheres showed an adsorption capacity of 178.25 mg/g for bilirubin within 2 hours and this value was high. The dynamic adsorption experiment showed that the aerogel microspheres adsorbed much more bilirubin with a short time of about 30 min. The adsorption isotherm showed that the adsorption of bilirubin in microspheres was fitted with the Freundlich isotherm, which indicates multilayer adsorption. In addition, it was understood that they showed good blood compatibility in hemolysis rate and coagulation time tests in blood tests. Zhang et al. (81) investigated the efficacy of fluorescent chitosan/graphene oxide hybrid microspheres designed for *in vitro* expansion of stem cells. The produced microspheres were found as biocompatible. They support the growth and reproduction of cells. In cell cultures studies, cells placed in microspheres increased approximately four times after 5 days.

Hydrogels

Hydrogels are polymeric networks with a three-dimensional structure that can absorb very large amounts of water, drug substance and biological fluids (82). They have the ability to absorb more than 1000 times their own dry weight. Hydrogels can be applied in drug delivery systems by topical, oral and parenteral routes. In addition to these, they are widely used in biomaterials and contact lenses. Most hydrogels are composed of hydrophilic polymers held together by crosslinking. Chemical crosslinks in hydrogels are provided by permanent covalent bonds between polymer chains. There are also physical crosslinks in hydrogels. In these, reversible interactions take place in contrast to chemical cross-links. The reasons for conducting studies in drug delivery systems are that hydrogels can encapsulate active substances and proteins thanks to their highly hydrated and porous structure and are suitable for controlled release (83). In addition to these, its hydrophilicity, high water absorbency, biocompatibility, ability to stay in circulation for a long time and targetability makes it stand out in drug delivery systems (82). Hydrogels can also be used in tissue generation with its compatible structure and hydration supporting features. In tissue generation, they can be used as cell supporting structures that resemble the structure of natural tissue and facilitate the transport of nutrients and waste materials. Hydrogels can be loaded into more than one type of active pharmaceutical ingredient due to their unique structures. The fact that most hydrogels are composed

of water, their structures are similar to natural tissues, and their mechanical structure that can be adjusted to soft and hard tissues are promising properties for drug delivery systems (83).

Various studies are carried out on graphene-based hydrogel drug delivery systems. Mauri et al. (84) synthesized graphene-based nanogels that thermally release drugs and examined their effectiveness. The nanogels prepared in the study met the biocompatibility criteria and were able to release the drug in the physiologically adjusted temperature range (25°C, 37°C and 44°C). As a result of this study, it was understood that graphene-based hydrogels could be used as thermally triggered drug delivery systems. Graphene oxide hydrogel drug delivery system studies are carried out. In the study by Ghawanmeh et al. (22), the effectiveness of graphene oxide-based hydrogels in anticancer drug delivery was investigated. The drug loading capacity of graphene oxide hydrogels was found as high and hydrophobic drugs could be loaded easily. In another study, Doxorubucin, a hydrophobic and small molecule drug, was loaded into hyaluronic acid/GO composite hydrogels with hydrophobic interactions and non-covalent interactions. Hyaluronic acid/GO composite hydrogels exhibited an approximately 90% increase in drug loading efficiency and prolonged release over a 10-day period.The synthesized hydrogel was found to have low toxicity (85). Chitosan/tripolyphosphate/graphene oxide hydrogels were produced by Jafari et al. (86) to enable sumatriptan succinate drug delivery and their effectiveness was investigated. In this study, two types of hydrogels were produced. One contains graphene oxide, the other does not. When these two models were compared, it was observed that there was an increase of 100-200% in the degree of swelling of those with GO. On the other hand, a decrease of 20-45% was observed in drug release rates. According to the results as the GO ratio increased in the hydrogel beads, the drug release occurred more slowly and in a controlled manner. The produced hydrogels were also evaluated in terms of cytotoxicity and antibacterial, and their biocompatibility and antibacterial activity were proven. In the study by Rasoulzadeh et al. (87), the efficiency of carboxymethyl cellulose/graphene oxide hydrogel beads in anticancer drug delivery was investigated. It was observed that the addition of graphene oxide to hydrogels increased the swelling rate of hydrogels, and also it was found as the amount of graphene oxide in the hydrogels increased, the drug release decreased, which was due to the carboxylic acid groups of graphene oxide interact strongly with the amine groups of DOX. Besides, the amount of DOX release from the nanocomposite hydrogel beads at pH 6.8 under acidic conditions was greater than at pH 7.4 due to stronger H-bond interaction under the basic condition than under the acidic condition. The presence of nanoparticles has a significant effect on the slow release of the drug from nanocomposite hydrogels. Swelling of the carrier is minimal at pH 1.2 and release studies have not been conducted at this pH. Wang et al. (88) investigated the transport of anticancer drugs in hydrogels by binding graphene oxide to konjac glucomannan/sodium alginate hydrogels. 5-fluorouracil anticancer drug was loaded into the prepared hydrogels and drug release rates at different pHs were investigated. After 12 hours, the amount of release was found as follows: at pH 1.2 it was about 38.02% and at pH 6.8 it was 84.19%. Due to these results, it has been accepted that a pH-dependent controlled drug release can be prepared by using konjac glucomannan-sodium alginate hydrogels functionalized using graphene oxide as a carrier system. GO is a good drug binder to control the release rate of drugs, and the prepared formulation may be a suitable polymer carrier for site-specific drug targeting in the intestine.

4. CONCLUSION

Graphene and graphene oxide have a wide variety of advantages, especially for use in drug delivery systems, they both show great promise in terms of their large surface areas, single-atom-thick 2-dimensional structures, low toxicity, and their effectiveness. In today's drug delivery system studies, we encounter studies with graphene oxide rather than graphene. The reason for this is the hydrophilic structure of graphene oxide and the different molecular groups connected to the honeycomb molecular structure. In terms of these properties, its drug adsorption ability is higher than graphene. In addition, the antibacterial activity of graphene oxide is higher than graphene. Both substances are inexpensive to manufacture compared to most sources used in drug delivery systems. Graphene and graphene oxide-based nanoparticle, carbon nanotube, nanofiber, liposome, nanoemulsion, nanocapsule, erythrocyte, dendrimer, microsphere, hydrogel drug delivery system studies have yielded promising results. In line with the results of studies conducted in recent years, it is indicated that the continuation of drug release system studies containing graphene oxide will be very beneficial. It is thought that these studies will be promising in light of developments in pharmaceutical technology, especially for the development of new dosage forms in cancer treatment.

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