



Nanocarriers Used Most in Drug Delivery and Drug Release: Nanohydrogel, Chitosan, Graphene, and Solid Lipid

İlaç Dağıtım ve İlaç Salımında En Çok Kullanılan Nanotaşıyıcılar: Nanohidrojel, Kitosan, Grafen ve Katı Lipit

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ABSTRACT

Over the past few years, nanocarriers have become an ideal solution for safe and efficient drug delivery and release. This is mainly due to the extraordinary characteristics that nanomaterials exhibit when compared with their larger scaled forms. A variety of these carriers are more popular due to their high biocompatibility, ensuring greater efficacy especially in cancer treatments. Nanocrystal, liposomal, and micelle designs of these materials as nanocarriers for drug delivery and release have been extensively researched throughout the past 50 years. Successful applications have not only ensured a greater focus on therapeutic development but also created a new solution available in the pharmaceutical market. Herein, a brief review of research studies focused on nanocarrier materials and designs to achieve superior benefits of drugs for disease treatments is presented. Nanohydrogels, chitosan, graphene oxide, and solid lipid nanoparticle nanocarrier designs and applications are selectively given due to the great attention they have gained from being highly biocompatible and easy-to-manipulate nanocarrier options from organic and inorganic nanocarrier materials. Each summary exhibits the progress that has been achieved to date. With greater understanding of the current state in the development process of these nanomaterials, there is a rising chance to provide better treatment to patients, which is a desperate need in pharmaceutical technologies.

Key words: Nanocarrier, drug delivery, nanomaterials, controlled drug release, targeting

ÖZ

Geçtiğimiz yıllarda, nanotaşıyıcılar güvenli ve verimli ilaç dağıtım ve salımı için ideal bir çözüm haline geldi. Bu, temel olarak nanomalzemelerin daha büyük ölçekli formlarıyla karşılaştırıldığında sergiledikleri olağanüstü özelliklerden kaynaklanmaktadır. Bu taşıyıcıların çeşitliliği yüksek biyoyumluluk nedeniyle daha popüler olup, özellikle kanser tedavilerinde daha fazla etkinlik sağlar. Son 50 yıl boyunca, nanokristal, lipozomal ve misel tasarımları bu malzemelerin ilaç dağıtım ve salınımı için çok araştırılmıştır. Başarılı uygulamalar sadece terapötik gelişimde daha fazla odaklanma sağlamakla kalmadı, aynı zamanda farmasötik pazarda da mevcut yeni bir çözüm yarattı. Bu çalışmada, nanotaşıyıcılar araştırmaların kısa bir derlemesi ve ilaç tedavisi için ilaçların üstün yararlarını elde etmek için nanohidrojel, kitosan, grafen/grafen oksit ve katı lipid nanoparçacık tasarımları sunulmuştur. Bu malzemeler biyoyumluluğu yüksek ve manipülasyonu kolay olmaları sebebi ile son yıllarda en çok tercih edilen nanotaşıyıcı malzemeleri olmuştur. İlaç dağıtım ve salınımında en fazla ilgi çeken bu nanotaşıyıcı malzemeleri, bugüne kadar olan gelişimleri özetlenmiştir. İlaç dağıtım için nanotaşıyıcı ihtiyacının ve bu nano malzemelerin gelişim sürecinde mevcut durumun daha iyi anlaşılmasıyla, farmasötik teknolojilerinde hastalara daha iyi tedavi sağlama şansı artmaktadır.

Anahtar kelimeler: Nanotaşıyıcı, ilaç dağıtım, nanomalzemeler, kontrollü ilaç salımı, hedefleme

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INTRODUCTION

Materials that have one or more dimensions lower than 100 nm are considered nanomaterials.¹ To be more specific, in 2011 the European Commission defined a nanomaterial as follows:

“A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm.”²

Nanomaterials have great research and development/product development potential in medical applications. Some of these applications include DNA/RNA nanotechnology, diagnosis by molecular imaging, biosensing, nanomedicine, and nanocarriers for drug delivery.³ A considerable number of nanomaterials have been developed, produced, and utilized for these application fields, such as nanohydrogels, chitosan/starch/cellulose nanoparticles, graphene (GR)/GR oxide (GO) nanosheets, iron oxide nanoparticles, gold nanoparticles, cerium oxide nanoparticles, and carbon nanotubes/nanoparticles.

Nanomaterials exhibit extraordinary optical, electronic, and/or mechanical properties when compared with their greater scaled forms. They can differ in color, conductivity, reactivity, surface area to volume ratio, and surface tension from macro forms. Due to this, nanomaterials have attracted the attention of scientists for their potential utilization in vaccines, drug development, and drug delivery.⁴ Over many years, many nanomaterials have been adopted as nanocarriers, i.e. nanohydrogels, oil-in-water (O/W) emulsions, liposomes, and nanoparticles based on synthetic polymers or natural macromolecules.⁵ The very first studies were conducted by Couvreur et al.⁶ and Kreuter and Speiser.⁷ in the late 70s, where the team exploited polymeric nanocapsules as lysosomotropic carriers and adjuvants.

Drug nanocarriers usually serve two main purposes: targeted drug delivery to specific tissue, organ, or cells and controlled drug release. The foundation of drug delivery is based on biocompatible nanoparticles or nanocapsules and targeting molecules. Biocompatible materials are selected and incorporated to enhance the hydrophilicity of hydrophobic carrier systems or drugs. Targeting molecules are generally antibodies or avidin/biotins that directly target tissue, organs, or cells. Drug release features of nanocarrier systems are provided by the environmentally sensitive structure of the carrier. Controlling drug release ensures paramount therapeutic effect by releasing the delivered drug with high efficiency in the targeted area and preventing any healthy tissue damage that could be caused by some drugs such as chemotherapy agents.⁸ Nanocarriers that have been designed from polymer-based nanoparticles are solid colloidal particles that are approximately 10-500 nm in size.⁴ Drug incorporation into nanocarriers is based on 5 methods: dissolution, entrapment, adsorption, attachment, or encapsulation.⁹ Herein a brief review of nanocarrier systems is given. A summary of the literature including easily manipulated popular nanomaterials that have been adopted as nanocarriers (nanohydrogels, chitosan (CS) nanoparticles, GR/GO nanocarriers, and solid lipid

nanoparticles) is given. Nanohydrogels and CS nanoparticle derivatives are the most heavily rotated amphiphilic nanocarrier materials. GR/GO nanomaterials are favored nanocarriers since they are present in a wide range of carrier designs. Finally, solid lipid nanocarriers (SLNs) are currently the most promising and novel lipophilic drug carriers.¹⁰

NANOHYDROGEL CARRIERS

Nanohydrogels can be defined starting with the descriptions of macro-scaled hydrogels. Hydrogels are three-dimensional hydrophilic polymer chain networks that are crosslinked. These networks can consist of natural or synthetic polymers and display swelling behavior when introduced to water or physiological fluids. Moreover, they are able to revert to their initial state when removed from the presence of water/biological fluids.¹¹⁻¹³ Due to this unique behavior, hydrogels have gained attention and been adopted in biomedical applications such as drug delivery, drug release, and vaccine design.¹⁴

Drug delivery and drug release system designs that utilize hydrogels have been and are still considered appealing in medicine due to their crosslink-controlled pore structures. Moreover, physiochemically, hydrogels are very similar to the extracellular matrix of the human body. With also a very high content of water, hydrogels are known to have very high biocompatibility. A main disadvantage is their viscosity, which created an alternative solution: nanohydrogels. These submicron particles made excellent drug carriers that could easily be extruded through an injector needle. In addition, decreasing size ensures an increase in surface area that provides further bioconjugation.^{11,15}

Nanogels, in the range of 10-100 nm size, are small enough to be used as systemic drug carriers. For designs that include clearance of nanogel carriers by kidney filtration the diameter is lower than 10 nm. Drug release to tissue, organs, or cells is through the meshes of nanohydrogels, which are typically between 5 and 100 nm in size.¹⁶ Mesh sizes in environmentally dependent designs such as temperature- and pH-sensitive ones change with the stimuli according to the crosslink bond concentration that forms or breaks.¹⁵ Regulating the breakages of crosslinking bonds that form the initial mesh size of the carriers will provide control of drug release acceleration. Other designs include utilization of the swelling capacity of nanohydrogels.¹⁷ As swelling continues, mesh sizes increase and gradually release the encapsulated drug.¹⁵

Nanohydrogel carriers that are environmentally dependent include designs sensitive to pH, temperature, electric field, light, enzyme, calcium, glucose, redox, etc.¹⁸ In this paper, some of these designs are summarized according to their sensitivity features as below. From this summary, it can be stated that as nanohydrogel carriers there are several popular materials that are prominent when compared with others. In Table 1, materials that receive the greatest attention from scientists are listed.

Temperature-sensitive nanohydrogel carriers

Temperature-sensitive nanohydrogel carriers are systems that exhibit swelling behavior that is dependent on temperature changes and are a widely studied field.¹⁹ A temperature-sensitive drug-release design was reported by Ichikawa and Fukumori²⁰ in 1999. The design consists of a water-soluble hemostatic drug core inside a thermosensitive poly[N-isopropylacrylamide (NIPAAm)] nanohydrogel containing an ethyl cellulose shell. Ichikawa and Fukumori²⁰ stated that the mentioned shell could change and revert to its initial size with temperature changes between 30°C and 50°C in water and that nanohydrogels exhibit positive thermosensitive swelling. The drug release rate is reported to be not only temperature dependent but also nanohydrogel concentration dependent.²⁰ A very recent study introduced thermosensitive 5-fluorouracil (5-FU; a chemotherapeutic drug employed for solid tumor treatments) containing methyl cellulose (MC) nanohydrogels for decreased side effects of chemotherapy. In this 2018 study Dalwadi and Patel²¹ produced MC nanohydrogels by a tip probe-sonicator method from MC hydrogels. 5-FU release depends on both temperature and its biodegradability. Within 48 h the drug is released in the injected area, preventing a cytotoxic drug burst in a very large area as in conventional chemotherapy.²¹

pH- and/or ionic-strength-sensitive nanohydrogel carriers

pH and/or ionic strength sensitivity allows nanocarriers' mesh size to be manipulated according to the environmental pH. Elsaeed et al.²² synthesized poly(NIPA-co-AAC) nanohydrogels by inverse microemulsion polymerization method in 2010. On average, the diameter of these nanohydrogels is reported to range between 60 and 80 nm. The team delivers a possible drug release methodology that is pH dependent through poly(NIPA-co-AAC) nanohydrogel by characterizing its swelling behavior between the pH values of 4.00 and 8.00 (ionic strength=0.4). That study shows that the nanohydrogels' swelling capacity increased with environmental pH.²² In an earlier study, in 2004, Dufresne et al.²³ reported pH-sensitive poly(N-isopropylacrylamide) derivative copolymers or poly(alkyl(meth)acrylate) diblock copolymers were produced as indomethacin (a nonsteroidal anti-inflammatory drug), fenofibrate (a drug for treating abnormal blood lipid levels), and doxorubicin (DOX) and aluminum chloride phthalocyanine carriers. PNIPAM copolymers were stated to be synthesized by free radical polymerization while the poly[alkyl(meth)acrylate] diblock copolymers were synthesized by atom transfer radical polymerization. The team carried out both *in vitro* and *in vivo* assays. Dufresne et al.²³ refer to the PNIPAM derivatives as a potential safe alternative to Cremophor®EL, a common carrier for various poorly water-soluble drugs. Furthermore, poly[alkyl(meth)acrylate] derivative [poly(ethylene glycol) (PEG)-b-(EA-co-MAA)] nanoparticles were stated to be excellent carriers for hydrophobic drugs that could be used orally. The carrier system is reported to exhibit dissociation behavior with increasing pH.²³

CHITOSAN NANOCARRIERS

Chitin is a long-chain polymer derivative [poly(b-(1-4)-N-acetyl-D-glucosamine)] of glucose with significance as the raw material of CS nanocarriers (CSNs). When chitin is deacetylated up to about 50%, it transforms into CS, which has a linear backbone linked through glycosidic bonds.^{24,25} CS's efficient bio-adhesiveness and permeabilization capacity make it one of the most popular nanocarrier materials amongst other hydrophilic polymers.²⁶ Moreover, CS is a nanocarrier that has a high loading efficiency of drugs. Based on the protonation of -NH₂ at the C-2 position of the D-glucosamine repeat, one of the most important characteristics of CS is its solubility in aqueous acidic media as given in Figure 1.²⁴ Thus, CS nanocapsules provide an effective solution for the delivery of hydrophobic drugs.²⁷ All the mentioned features of CS nanoparticles make it an excellent nanocarrier material.

Moreover, CS exhibits pH-sensitive behavior due to the percentage of its acetylated monomers and their distribution in the chains.²⁸ This behavior is utilized for controlled drug release by scientists. A common example for this is drug delivery to tumor cells and controlling release since the pH of tumor cells is significantly lower than that of healthy cells.²⁹ A summary of the literature that features CSNs as drug delivery systems is provided in Table 2 in chronological order. Production methods for CS carriers differ however, the most common method used being ionotropic gelation, which is based on the capability of polyelectrolytes to crosslink in the presence of counter ions.³⁰

As can be seen in Table 2, Fernández-Urrusuno et al.³¹ proposed the use of CS nanoparticles as potential drug carriers for transmucosal delivery in 1999. In their design the team loads insulin into CS nanoparticles to be given nasally to conscious normoglycemic rabbits. It is reported that there was a 40% reduction in the serum glucose levels.³¹ Aktaş et al.³⁴ reported the use of PEG-grafted CS nanoparticles as peptide drug carriers. They observed nanoparticle formation through intermolecular hydrogen bonding in an aqueous solution. The incorporation and release of insulin were dependent on the degree of introduction of the PEG chain on CS and observed sustained release phenomenon over time.^{52,53} Pérez-Álvarez et al.⁵¹ reported one of the most recent studies in this field revealing the state of art in 2019. Their work exploits the designed CSN as a great candidate for polyoxometalate delivery into tumoral

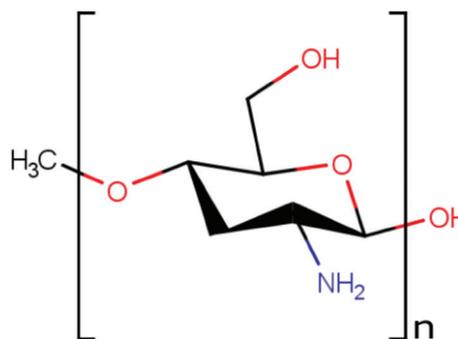


Figure 1. Chitosan monomer

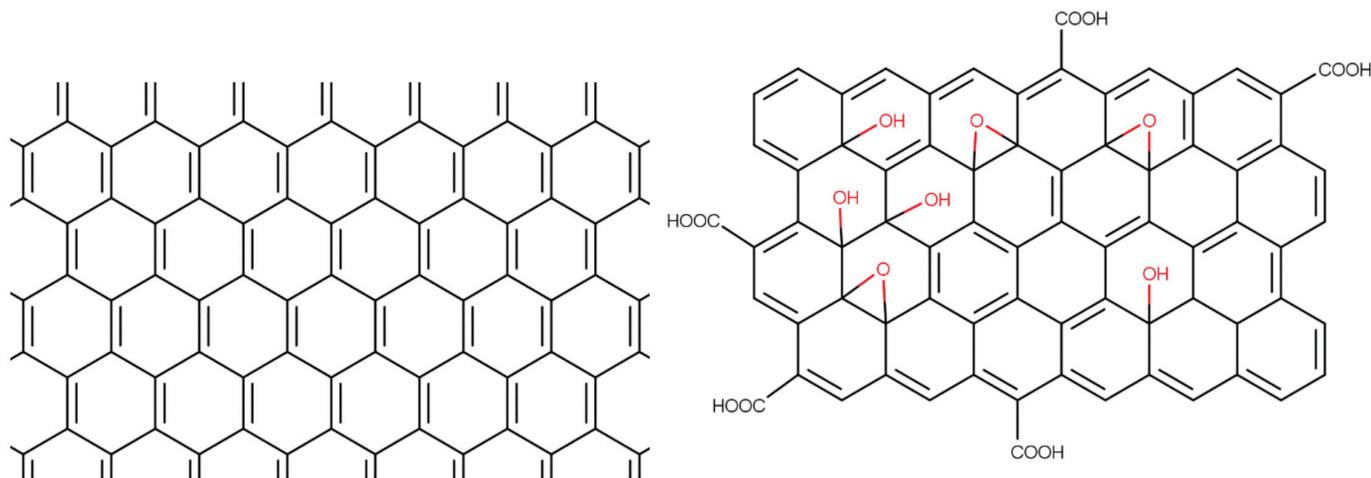


Figure 2. Molecular structure of graphene and graphene oxide

cells. CSN production is achieved by dissolving low molecular weight CS in 1% (v/v) acetic acid solutions for crosslinking in inverse microemulsion medium, which results in the attainment of nanometric CS gel particles. Utilizing the pH-sensitive characteristics the team managed to inhibit cytotoxic drug release.⁵¹

GRAPHENE AND GRAPHENE OXIDE NANOCARRIERS

Professor Andre Geim and Professor Kostya Novoselov made a groundbreaking disclosure by finally discovering a production method for GR in 2004. The research was outstanding since it had not been possible previously to produce a single layer of graphite (carbon atoms with sp² bonds in the shape of honeycomb). Later, GR became known as the basic building block of graphitic materials such as spherical nanoparticles that are also known as 0D fullerenes, 1D carbon nanotubes, and 3D graphite.⁵⁴⁻⁵⁸

Following the discovery, scientists began to reveal GR's unique characteristics provided by its submicron dimension and the π -conjugation in its structure. GR is revealed to exhibit extraordinary thermal, mechanical, and electrical properties.⁵⁷ Further research provided a better understanding of the physical and chemical structure of GR's surface, which has created interest in medical and pharmaceutical technologies as well as other fields of science. GR is researched and utilized for nanoscaffolds, chemical/biosensing, imaging, drug delivery and controlled drug release.⁵⁹ In the area of nanomedicine and nanocarriers, GR and its composites are important due to its large surface area where every single atom is exposed on the surface (2600 m² g⁻¹), layer number, lateral dimension, surface chemistry, and purity.⁶⁰⁻⁶² Hereby, GR could be considered a superior candidate as an ideal nanocarrier with the mentioned characteristics that allows a high drug load capacity.⁵⁸

One of the most popular derivatives of GR is GO, GR with oxygen-containing functionalities (epoxide, carbonyl, carboxyl, and hydroxyl groups). GR and GO have a major difference

that affects their drug delivery performance when used as nanocarriers: GO is highly hydrophilic, whereas GR is hydrophobic so that it requires surface modifications for use in biological fluids. Thus, any nanocarrier design that uses GR should take into consideration the possible impurities and negative effects such as cytotoxicity.^{61,63} This leads researchers to gravitate towards GO-containing designs rather than GR nanocarrier designs.

In Table 3, a summary of GR/GO nanocarrier designs is given. As can be seen, Hummer's method for production is the most popular choice, where graphite oxidative exfoliation is applied with NaNO₃. Although Hummer's production method is usually opted for rather than other complicated methods, over the years it can be seen that nanocarrier designs have evolved into more complex systems that apply chemotherapy and photothermal therapy for treating cancer.

In 2008, Liu et al.⁸⁷ published a study that demonstrates PEG-functionalized GO nanocarriers used as a noncovalent physisorption chemotherapy drug delivery system. The team reveals that the nanocarriers have an adequate *in vitro* cellular uptake capacity.⁸⁷ A very recent study by Bullo et al.⁸⁸ examined the state of the art in GO nanocarriers. GO is reported to be synthesized by Hummer's method. GO is modified with PEG for higher biocompatibility and loaded with two chemotherapeutic drugs: protocatechuic acid and chlorogenic acid. The carrier is then coated with folic acid to target cancer cells since tumor surface membranes have a greater number of folate receptors. The final size of the nanocarrier system is stated to be 9-40 nm with a median of 8 nm. The team reveals that drug release of this design took more than 100 h, which ensures a steady therapeutic effect.⁸⁸

SOLID LIPID NANOPARTICLES

Nanocarriers designed with a polymer foundation have a certain advantage in terms of the wealth of possible chemical modifications, including the synthesis of block and comb polymers.⁸⁹ Designs that use SLNs exploit this advantage by combining the advantages and avoiding the disadvantages of

Table 1. Popular nanohydrogel materials utilized as nanocarriers

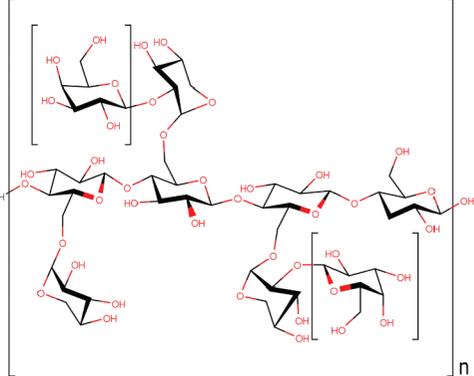
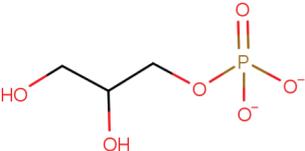
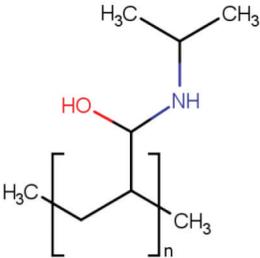
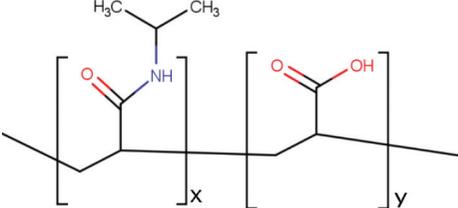
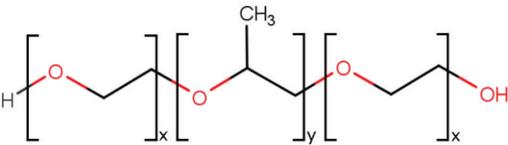
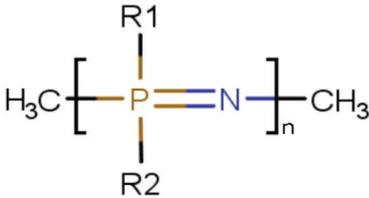
Nanohydrogel carrier material	Structure
Xyloglucan	
Glycerophosphate	
Poly (N-isopropylacrylamide)	
Poly (N-isopropylacrylamide-co-acrylic acid)	
Ploxamer (Pluronic)	
Poly (Organo phosphazene)	

Table 2. A literature summary of CSNs

Date	Drug	Nanocarrier design & advantages	CS nanoparticle production	Reference
1999	Insulin	Blood glucose control nasal absorption pH selective release	Ionotropic gelation with Penta-sodium tri-polyphosphate	31
2005	Epirubicin	Chemotherapy chitosan-bound magnetic nanocarrier	Carboxymethylated Chitosan covalently bound onto Fe ₃ O ₄ nanoparticles	32
2005	BSA	Carboxymethyl konjac glucomannan-chitosan nanoparticles	Dropping method	33
2005	Z-DEVD-FMK	Cerebral Ischemia Therapy CS-PEG-BIO-SA/OX26	Chitosan acetylation 13.7%	34
2005	Insulin	Oral/Nasal Drug Carrier CS nanoparticles, CS nanocapsules and CS-coated lipid nanoparticles	Ionotropic gelation	35
2006	Triclosan Furoscimide	Higher solubility in water hydroxypropyl cyclodextrin containing chitosan nanocarrier	Ionotropic gelation	36
2006	Protein complex P1	Transmucosal drug carrier glucomannan-coated chitosan nanoparticles	Ionotropic gelation	37
2006	Salmon calcitonin	Oral drug carrier carrier for peptide drugs through the intestinal epithelium	Ionotropic gelation	38
2007	-	Transmucosal drug carrier hydrophilic cyclodextrin-chitosan core and chitosan coating	Ionotropic gelation	39
2008	Indomethacin	Ophthalmic Drug Delivery	Ionotropic gelation by addition of TPP anions	40
2009	HP-b-CD complex simvastatin	Oral delivery of drugs that are insoluble in water	Ionotropic gelation with Penta-sodium tri-polyphosphate	41
2010	Bleomycin	Chemotherapy Fe ₃ O ₄ containing chitosan nanoparticles	Ionotropic gelation with Penta-sodium tri-polyphosphate	42
2010	siRNA	PEGylated Chitosan Nanocarriers Imidazole-modified chitosan-IAA nanoparticles	Complex coacervation of nonmodified chitosan or chitosan-IAA with siRNA	43
2010	Glutathione	Oral Drug Carrier Chitosan and Chitosan/cyclodextrin NPs	Ionotropic gelation	44
2010	Mesalazine	Colon Specific Drug Delivery Superparamagnetic chitosan-dextran sulfate NPs	Ionotropic gelation	45
2011	Silver NPs	Colon Cancer Apoptosis Chitosan-based nanocarrier of silver NPs	Ionotropic gelation with Penta-sodium tri-polyphosphate	46
2011	Curcumin	Hydrophobic drug delivery for cancer treatment Carboxymethyl chitosan nanocarriers	Ionic cross linking between carboxyl group	47
2014	100% iron saturated-bovine lactoferrin	Osteoarthritis treatment	-	48
2014	Rosmarinic acid	Antioxidant delivery	Ionotropic gelation with Penta-sodium tri-polyphosphate	49
2015	Paclitaxel	Chitosan based glycolipid-like nanocarrier		50
2019	Polyoxometalates	Breast cancer therapy pH selective release	Crosslinked in inverse microemulsion medium	51

Table 3. A literature summary of GR/GO nanocarriers

Date	Drug	Nanocarrier	Nanocarrier design & advantages	GR or go synthesis	Nanocarrier size on average	Reference
2010	Camptothecin (CPT) Doxorubicin (DOX)	FA-GONS-p-amino benzenesulfonic acid	Sulfonic acid groups render stability in physiological solutions Target: human breast cancer cells	Hummer's method	GONS (thickness) < 150 nm	64
2011	Ellagic acid (EA)	GONS-Pluronic F38(F38), GONS - Tween 80(T80), GONS-Maltodextrin (MD)	High drug loading (For GO-T80, 1.22 g per 1 g)	Hummer's method	GONS-F38 (thickness)=6-7 nm GONS-T80 (thickness)=7-8 nm GONS-MD (thickness) =5-6 nm	65
2011	Doxorubicin (DOX)	PEG-GONS	Both chemotherapy and near infrared (NIR) photothermal therapy Lower systematic toxicity	Hummer's method	-	66
2011	Tamoxifen Citrate (TmC)	Pyridinium bromide (PY+-Chol)-Graphene (GR)	Enhanced the apoptosis of cancer cells	-	PY+-Chol-GR (hydrodynamic diameter)=150-200 nm	67
2013	Doxorubicin (DOX)	Polyethylene Glycol-Branched Polyethyleneimine-Reduced GO (PEG-BPEI-rGO)	Photothermally controlled anti-cancer drug delivery Higher cancer cell death	Reduction by hydrazine monohydrate	100-200 nm	68
2013	5-fluorouracil (5-FU)	Fe ₃ O ₄ -GONS	pH dependent chemotherapy High drug loading capacity of up to 0.35 mg mg ⁻¹	Hummer's method	-	69
2013	Doxorubicin (DOX)	PVP-GONS-FA	pH sensitive nanocarrier Both chemotherapy and near infrared (NIR) photothermal therapy	Hummer's method	GONS=100 nm	70
2013	Doxorubicin (DOX)	FA-GONS-Chitosan (CHI)	High drug loading efficiency (0.98 mg/mg) & prolonged drug release rate pH sensitive drug release	Hummer's method	-	71
2014	Doxorubicin (DOX)	GO/integrin αvβ3 mono-antibody (Abs)/ polyethyleneimine (PEI)/citraconic anhydride functionalized poly(allylamine) (PAH-Cit)	Charge-reversal, target specific nanocarrier Drug release in acidic intracellular organelles	Hummer's method	GO/PEI/PAH-Cit/ DOX=20-200 nm	72
2014	Doxorubicin (DOX)	Hyaluronic acid (HA)-GONS	Targeted and pH sensitive drug delivery High loading efficiency of drug (42.9%)	Hummer's method	GONS (lateral)=10-200 nm	73

2014	Doxorubicin (DOX)	PEG-Poly (allylamine hydrochloride) (PAH)-2,3-dimethylmaleic anhydride (DA)-GONS	pH sensitive drug release Both chemotherapy and photothermal therapy	Hummer's method	PEG-PAH-DA-GONS=70 nm	74
2015	Paclitaxel (PTX)	PEG-GO	Nontoxic chemotherapy carrier Increased biocompatibility and physiological stability	Hummer's method	PEG-GO-PTX (lateral)=50-200 nm	75
2015	Irinotecan (IRI) Doxorubicin (DI)	Poloxamer 188-GONS	Photothermal therapy with dual chemotherapies in one system	Hummer's method	GONS=200 nm	76
2015	Indomethacin (IMC) Doxorubicin (DOX)	poly(N-isopropylacrylamide) (PNIPAM)-GO	Enhanced thermal stability Improved dispersibility in aqueous and cell medium	Hummer's method	GONS=0.85 nm NIPAM-GONS=3.2 nm	77
2016	Doxorubicin (DOX)	Gold Nanoparticle (AuNP) - Folic Acid - GONS	Targeted chemotherapy and photothermal ablation	-	AuNP-FA-GONS (Hydrodynamic size)=188.2±7.2 nm AuNP-GO (diagonal)=135 nm	78
2018	Doxorubicin (DOX) Camptothecin (CPT)	Folic acid (FA)-Graphene Oxide Nanosheet (GONS)	FA linked GONS for high affinity to folate receptor	Hummer's method	2.7 nm	79
2018	Tetracycline (TC)	Carboxymethylcellulose (CMC)-Zn-Based Metal-Organic Framework (MOF-5)-GO	Efficient oral drug delivery Effective protection against stomach pH	Hummer's method	CMC/MOF-5/GO (diameter)=344 nm	80
2018	Doxorubicin (DOX)	Carboxymethylcellulose (CMC)-Zn-Based Metal-Organic Framework (MOF-5)-GONS	Targeted delivery and controlled release of chemotherapy human blood cancer cell lines	Hummer's method	GONS (Thickness)=30 nm CMC/MOF-5/GONS=80 nm	81
2019	Quercetin (QSR) Gefitinib (GEF)	Polyvinylpyrrolidone (PVP)-GO	High biocompatibility Enhanced anticancer activity within a dosage range	Hummer's method	GO=166.5 nm PVP-GO=300-400 nm	82
2019	Cis-diamminedichloroplatinum (II) (CisPt)	Maghemitey-Fe ₂ O ₃ -GO	Efficient Malignant glioma chemotherapy GONP accumulates in U87 human glioblastoma subcutaneous tumor xenografts	Hummer's method	GO (width)=80-100 nm GO (thickness)=6.3 nm	83
2019	Methotrexate (MTX)	Polyethylene Glycol bis Amin (PEGA)- GO Magnetic NS (GOMNS)	Magnetic Iron NPs Increased efficacy in chemotherapy with pH dependent drug release and biocompatibility	Hummer's method	-	84
2019	5-Fluorouracil (5-FU) Curcumin (CUR)	Chitosan-rGO	Increased efficiency of chemotherapy against colon cancer	-	-	85
2019	Doxorubicin (DOX)	κ-Carrageenan (κ-Car)-GONS-biotin	Targeted therapy for cervical cancer pH-sensitive drug release	Hummer's method	κ-Car-GONS-biotin (thickness)=219 nm	86

other colloidal carriers.

Lipids are defined as molecules that are hydrophobic or consisting of both hydrophilic and hydrophobic parts that are insoluble in water and soluble in organic solvents.⁹⁰ IUPAC gave the following further detailed definition in 1995:

*"A loosely defined term for substances of biological origin that are soluble in nonpolar solvents. They consist of saponifiable lipids, such as glycerides (fats and oils) and phospholipids, as well as nonsaponifiable lipids, principally steroids."*⁹¹

SLNs are developed by researchers as a substitute colloidal carrier with a spherical morphology for drug delivery and drug release.⁵ SLNs have an average size of between 150 and 300 nm but could reach up to 1000 nm according to the surfactant used during production and are composed of roughly 0.1-30 (% w/w) solid fat.⁹² Size and solid to liquid fat ratio affect the long-term stability, drug-loading capacity, and drug-release behavior of SLNs.⁹³ As mentioned, SLNs have several favored assets such as low to no toxic effect on healthy tissue and ease of production in greater units of production, ability to load both lipophilic and hydrophilic therapeutic agents, and high drug load capacity.⁵ The most common use of SLNs as nanocarriers is for oral drug delivery. Other than this example, several drugs have been loaded using SLNs for drug delivery, such as doxorubicin and idarubicin,⁹⁴ thymopentin,⁹⁵ and camptothecin.⁹⁶

DISCUSSION AND CONCLUSION

Nanocarriers provide researchers with a highly applicable alternative method for targeted drug delivery and controlled drug release. The first and foremost reason that nanocarriers have become such a great focus in pharmaceutical technologies is that nanomaterials demonstrate extraordinary characteristics when compared with their larger scaled forms. These characteristics are summarized in this review as color, visible light, reactivity, surface area to volume ratio, conductivity, and surface tension. A variety of these carriers are more popular due to their high biocompatibility, ensuring greater efficacy especially in cancer treatments. Successful applications have not only ensured a greater focus on therapeutic development but also created a new solution available in the pharmaceutical market. In this paper, nanocarrier materials that have gained the most attention in drug delivery and release are summarized under the titles of nanohydrogels carriers, CSNs, GR and GO nanocarriers, and SLNs. Besides these nanomaterials there are also a great number of different nanocarrier designs that are not included in this review, such as gold nanocarriers,⁹⁷ starch and/or cellulose nanocarriers,⁹⁸ cerium oxide nanocarriers,⁹⁹ and carbon nanotube incorporated nanocarriers.¹⁰⁰ It is clear that, with further information gathered on nanocarriers for drug delivery and the current state in the development process of these nanomaterials, there is a high possibility to deliver better treatment to patients desperate in need of efficient treatment strategies.

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