Community Acquired Infection

REVIEW

The emergence of nanocarriers in the management of diseases and disorders

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Abstract

Drugs can be delivered using oral nanocarriers in controlled, site-specific releases. Target receptors are physically, chemically, and biologically conjugated while administering a specific medicine. Since micro carriers have a 200 nm width, nanomedicine typically refers to objects with that size. Drugs can be delivered by nanocarriers to parts of the body that are inaccessible. Nanocarriers cannot deliver large pharmaceutical dosages due to their small size. Emulsion-based nanocarriers often have poor drug loading and encapsulation, which restricts their potential for therapeutic use. Various therapeutic nanocarriers exist. Ultrabright nanocarriers, polymeric nanocarriers, smart nanocarriers, nanocomposites, protein nanocarriers, nucleic acid-based nanocarriers, carbon nanotubes, and nanobubbles are examples of novel nanocarriers. All of them have successfully treated cancer. This review looks at targeted drug delivery methods and nanocarriers.

Key words: ultrabright; polymeric; nanocomposites; carbon nanotubes; nanobubbles

INTRODUCTION

Application of nanotechnology in medicine or nanomedicine is revolutionising the medical practice both in the areas of diagnostics and therapy. Over the last several decades, numerous nanocarriers have been developed that include liposomes, polymeric particles, drug conjugates, dendrimers, solid lipid nanoparticle, protein and carbohydrate as well as inorganic system like iron, carbon, silica and so on.[1] The biocompatible and biodegradable carriers hold great potential to be used in drug delivery applications. Nanocarriers has found its interest in biomedical application due to its nano size nature, its increased surface area for higher functionalization with target specific molecules, thus leading to lower dosage and minimal side effects and an improved *in vivo* biodistribution.[2] Various nano-formulation techniques have been developed and employed for improving drug delivery, *e.g.,* nano-micelles, liposomes, solid lipid nanoparticles, nanoparticles/crystals, polymeric nanoparticles, dendrimers, nano-hydrogels, self-assembly techniques *etc.* Each has their limitations and advantages based on drug encapsulation efficiencies, biodegradability, biodistribution, colloidally stable minimum particle size, and surface functionalization capabilities. Most of the administration of such formulations is through systemic circulation and few through pulmonary or sub-dermal route. On the other hand, advancements in enhanced imaging technologies in biomedical field have been made using various nanomaterials, *e.g.,* fluorophores, quantum dots, gold nanoparticles and iron oxide nanoparticles.[2]

Recent advances in many fields like biotechnology also allow the selection and the preparation of novel macromolecular compounds such as peptides, proteins and DNA analogs to be used as drugs (*e.g.*, hormones, monoclonal antibodies, vaccines) for therapeutic purposes. Such compounds show powerful and selective therapeutic activity, but unfortunately they must often be dropped at some development stage, because of their high enzymatic susceptibility, short shelf life or unsuitable efficacy after the administration to the patient, owing to

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Received: 03 August 2022; Revised: 12 October 2022; Accepted: 09 January 2023; Published: 19 April 2023
https://doi.org/10.54844/cai.2022.0139

immunogenic reactions or poor bioavailability.[3] In some cases, from a physicochemical point of view, they cannot reach or enter target cells. Moreover, the drug must cross several biological barriers to reach the site of action, and along its path it can be inactivated or produce undesired side effects. Several approaches have been evaluated to overcome these issues. The drug targeting is a promising tool to solve most of the aforementioned problems. This approach consists of designing a system able to selectively deliver the drug to the area of interest.[3] Transport systems can be designed to control the dispatch of the loaded drug to target areas, increasing its local concentration and bioavailability, while prolonging its retention, half-life and effectiveness. This strategy can avoid diffusion of the drug into normal organs, thus avoiding negative side effects.[4]

The targeting method should ensure that the pharmacological impact only occurs in the target area. Today's systems are built of three major blocks: the pharmacologically active chemical, a carrier to enhance the amount of active molecules per system (often a nanosized carrier), and a targeting moiety to bring the whole system to the desired location of action. Ehrlich recognised antibodies as the best targeting moieties due to their affinity and specificity for antigen. Since then, numerous different targeting strategies and carriers have been created based on novel facts on toxicity, tolerance, biocompatibility, and acceptability by living creatures.[5] Nanotheranostic techniques combine medication delivery and imaging enhancement in a single nanocapsules/system. Most nanoparticles can be coupled with polyethylene glycol (PEG) tails to promote colloidal stability and circulation with minimal blood protein adsorption in systemic circulation. Targeted distribution of nano-carrier to certain cell types can be done by conjugating specific antibodies, aptamers, or other peptides.[6]

TYPE OF NANOCARRIERS IN THE MANAGEMENT OF DISEASES AND DISORDERS

Ultrabright nanocarriers

Bioimaging contrast agents are fluorescent nanoparticles. Today, researchers are investigating ultrabright nanocarriers. Molecular-based Fluorescent nanoparticles (NPs) with brightness similar to semiconductor quantum dots are an example. These ultra-bright NPs incorporate emitting dyes as individual moieties or aggregates in a silica or polymeric matrix and are more biocompatible than semiconductor quantum dots. Ultrabright materials created by heavily doping the structural matrix, requiring tight dye contact. Interactions between molecular emitters' ground and excited states produce proximity- and aggregation-caused quenching (ACQ). PCQ and ACQ combined with FRET amplify nanoprobe quenching. The Table 1 shows some of the reported researches and reviews on ultrabright nanocarriers.[5–10]

Polymeric carriers

Polymeric nanocarriers offer clinical potential. The polymeric nanocarrier is expected to have diagnostic and therapeutic uses. Biocompatibility, biodistribution, side effects, and biological obstacles are all issues for carrier systems in living beings. Nanocarriers have multifunctional properties to address this difficulty. Polymeric nanocarriers are useful for active or passive breast cancer targeting. Micelles are nanoscopic amphiphilic colloidal aggregates

Table 1: Reported researches and reviews on ultrabright nanocarriers

No.	Author	Year	Encapsulated Material	Formulation	Description/Applications
1	Peng *et al.*[5]	2018	Cellulose acetate	Ultrabright fluorescent nanoparticles	For imaging tumors through systemic and topical applications
2	Melnychuk *et al.*[6]	2018	Dyes in a polymer matrix	Ultrabright fluorescent nanoparticles	Amplified detection of nucleic acids
3	Goetz *et al.*[7]	2016	Lanthanide	Ultrabright nanoparticles	Photosensitizing behaviour was used of targeting delivery
4	Shulov *et al.*[8]	2015	Rhodamine	Ultrabright nanoparticles	For bioimaging and light-harvesting delivery
5	Sun *et al.*[9]	2013	Polyethyleneimine	Ultrabright/Multicolorful Fluorescence	Combined imaging and therapy applied
6	Bok *et al.*[10]	2012	Organosilicate	Ultrabright suprananoparticles	Fluorescence imaging for the theranostic application

Table 2: Reported researches and reviews on polymeric nanocarriers

No.	Author	Year	Encapsulated Material	Formulation	Description/Applications
1	Pieper *et al.*[11]	2019	Doxorubicin	Polymeric nanoparticle	Assessed of anticancer efficiency
2	Shelake *et al.*[12]	2018	Fenofibrate	Polymeric nanoparticle	Bioavailability enhancement of the poorly soluble drugs
3	Patel *et al.*[13]	2017	Hydrophobic or hydrophilic drug	Polymeric nanoparticle	Tumor targeting for the bioavailability enhancement
4	Bohrey *et al.*[14]	2016	Diazepam	Polymeric nanoparticle	biocompatibility and controlled drug release
5	Solar *et al.*[15]	2015	Superparamagnetic iron oxide	Polymeric nanoparticle	Multifunctional platform for the diagnosis and treatment of cancer

polymer dispersed in aqueous medium. Their inner cores are formed of hydrophobic polymer blocks that hold drug reservoirs. The hydrophilic polymer shells give micelles water solubility and lengthy blood circulation time *in vivo*. Physical or chemical crosslinking of polymers creates polymeric nanogels, which are 3D nanosized hydrogels. Nanogels' customizable chemical and physical structures and *in vivo* stability govern medication delivery. Polymeric nanofibers have fibrous diameters less than 1 m. Polymeric nanofibres distribute drugs *in situ*. Many studies demonstrate nanofibers can boost anticancer medication effects. Antibacterial, intelligent textiles, smart clothes, electromagnetic shielding, and flexible sensors are some applications of conductive fabrics. The Table 2 displays polymeric nanocarrier research and reviews.[11–15]

Ultrasound mediated nanocarriers

With ultrasound, nanoparticles transport liquid emulsions and solid genes *in vitro* and *in vivo*. Small packaging lets nanoparticles enter tumours. Ultrasonic medication and gene delivery utilising nanocarriers has good potential because many pharmaceuticals and genes can be delivered to specified areas noninvasively.[16–18] Due to their tiny size and lengthy circulation period, polymeric nanocarriers are valuable in diagnostic and therapeutic applications. These nanocarriers transport medications across capillary and cell membrane barriers. It's also employed as gene/drug-loaded nanocarriers. Polymeric nanocarriers can improve intracellular medication uptake and should be tiny enough to circulate freely in blood circulation. On the other hand, it should be large enough to avoid renal excretion yet stable enough to prevent biodegradation until ultrasonic triggered.[19–20]

Ultrasound and DNA-bound bubbles improve *in vitro* and *in vivo* DNA transfection compared to bare DNA alone. Coating nanoparticles with polymer chains prevents blood protein adsorption and RES cell recognition. Ultrasound-mediated drug/gene delivery uses nanocarriers. Nanobubbles operate as medication carriers in ultrasonography. By utilising this carrier, time and space-controlled medication delivery may be achieved.[21,22] Techniques for loading bubbles with drugs include associating them with the superficial shell and encapsulating drugs in the bubble's oil reservoir. In addition, drugs can be encapsulated in a nanoparticle and linked to the microbubble surface. Unknown medication delivery mechanisms. Low- and high-intensity ultrasound cause bubbles to behave differently. Low-intensity ultrasound stabilises cavitation. Another proposed method for ultrasound-mediated drug/gene delivery is localised tissue temperature rise, which increases phospholipid bilayer fluidity and membrane permeability. Endocytosis and active membrane transport also create effects. Contact aided distribution mixes nanodroplet phospholipid membranes into target cell membranes, releasing their payload directly into the cytoplasm.[23–26] The Table 3 shows some of the reported researches and reviews on ultrasound mediated nanocarriers.[16–20]

Smart nanocarriers

In smart nanocarriers, the 8 most important nanocarriers are reported: liposomes, micelles, dendrimers, meso-porous silica nanoparticles (MSNs), gold nanoparticles (GNPs), super paramagnetic iron oxide nanoparticles (SPIONs), carbon nanotubes (CNTs), and quantum dots (QDs). Smart drug delivery systems (SDDS) assist identify physiochemical distinctions between cancer and healthy cells. Passive and active targeting are used to identify cancer cell sites. Passive targeting indirectly increases tumour permeability. Overexpressed cancer cell surface receptors are used for active targeting. Nanocarriers release dugs by external or internal stimuli, depending on their nature and smartness.[27–29] Nanoparticles are 1–100 nm smart nanocarriers. Nanoparticles are classified as VSSA. Nanocarriers transport modules on nanoparticles. Conventional nanocarriers can't carry and release medications at the proper concentration at the targeted spot. Smart nanocarriers have these properties.[30,31] Co-deliver genetic materials, imaging agents, and chemotherapeutics. The RES removes the nanocarrier from circulation and it assembles in the liver, spleen, or bone marrow. PEGylation solution is used to avoid this cleaning. PEGylation decreases cell drug absorption.[32–35]

Nanocarriers can be help to identify the cancer cells exactly out of healthy ones. Physiochemical differences between cancer cells and healthy ones are only the

Table 3: Reported researches and reviews on ultrasound mediated nanocarriers

No.	Author	Year	Encapsulated Material	Formulation	Description/Applications
1	Tharkar *et al.*[16]	2019	Cancer treatment	Ultrasound mediated nanocarriers	Nano-enhanced drug delivery system for the cancer treatment
2	Baghirov *et al.*[16]	2018	Antitumor drug	Ultrasound mediated nanocarriers	Delivery in brain parenchyma targeted
3	Paris *et al.*[17]	2018	Mesoporous silica	Ultrasound-mediated cavitation	Controlled-release drug delivery using silica nanocarriers
4	McClure *et al.*[18]	2016	Antitumor drug	High-intensity focused ultrasound	Targeted drug delivery for the tumor targeting
5	Zhou *et al.*[20]	2014	Gene and other curative drug	Ultrasound mediated nanocarriers	Ultrasound molecular imaging for the gene based delivery

identification marks to separate the two types of cells. The modification of nanocarriers are done with the help of ligands matching the overexpressed proteins. These ligands help to identify the cells with the receptor proteins. Third, the drug conveying to the target site is not the termination of the process. In smart carrier the releasing of the drug under stimulation is the next big challenge. Fourth, changes are also done for the anti-cancer drugs codelivery together with other substances, including genetic materials, imaging agents or even additional anti-cancer drugs. The potential codelivery observed by Liposomes, micelles, dendrimers, GNPs, quantum dots and MSNs.[36–38] The Table 4 shows some of the reported researches and reviews on smart nanocarriers.[21–25]

Nanocomposites

It's nanoparticles that mix components to improve specific qualities (composite). Nanoparticles (clay, metal, carbon nanotubes) dilute a matrix, usually polymer, in nanocomposites. Nanocomposite mechanical, electrical, thermal, optical, electrochemical, catalytic characteristics will differ from component materials.[39] Inorganic components include zeolites, two-dimensional layered materials like clays, metal oxides, metal phosphates, chalcogenides, *etc.* Experiments have shown that almost all nanocomposite materials have better characteristics than their macro composite counterparts. Nanocomposites promise novel applications in mechanically reinforced lightweight components, non-linear optics, battery cathodes and ionics, nano-wires, sensors, and other systems.[40] *In situ* growth and polymerization of biopolymer and inorganic matrix are ideal for bioceramics and biomineralization. Lamellar nanocomposites increase interphase interactions. Intercalated and exfoliated nano-composites are two types. In the first, polymer chains alternate with inorganic layers in a set compositional ratio and number of polymer layers in intralamellar space. In exfoliated nano-composites, the number of polymer chains between layers is almost continually changeable. Intercalated nano-composites have good charge and electronic transfer. Mechanically, exfoliated nanocomposites are better. Polyamides, polypropylene, polyethylene, styrenics, vinyls, polycarbonates, epoxies, acrylics, polybutylene terephthalate, and polyurethanes are prominent nanocomposites polymers.[41] The most popular filler is montmorillonite clay, which has a platy structure and a 1000 : 1 aspect ratio. Property improvement requires modest loading. Nanocomposites improve modulus, flexural strength, thermal distortion temperature, barrier characteristics, and other benefits, unlike standard mineral-reinforced systems, which sacrifice impact and clarity.[42,43] The application of Nanocomposites commercially increasing at higher rate. Less than two years it observed that, the worldwide production is estimated to exceed 600,000 tonnes and is set to cover the following key areas in the next five to ten years.[44]

Superior strength fibres and Improvements of films in mechanical property have resulted in major interest in nanocomposite materials in numerous automotive and general/industrial applications. These include potential for utilization as mirror housings on various vehicle types, door handles, engine covers and intake manifolds and timing belt covers.[45]

In general more applications currently being considered include usage as impellers and blades for vacuum cleaners, power tool housings, mower hoods and covers for portable electronic equipment such as mobile phones, pagers *etc.* Nowadays nanocomposite research is conducted and is widespread by companies and universities across the globe.[46] The production of Nanocomposites is modified by incorporating the clay into polymers this method also more cost-effective. It shows a marked increase in oxygen, carbon dioxide, moisture and odour barrier properties, increased stiffness, strength and heat resistance, and maintains clarity to film and impact strength. Nanocomposites also show more important applications in numerous industrial fields, a number of key technical and economic barriers exist to widespread commercialization. This technique includes improve performance, the complex formulation relationships and routes to achieving and measuring nanofiller dispersion and exfoliation in the polymer matrix.[47–50] The Table 5 shows some of the reported researches and reviews on nanocomposites.[26–29]

Protein nanocarriers

Proteins are natural molecules with specific biological and manufacturing features. Nanomaterials from protein, albumin, and gelatin. These nanoparticles are biodegradable, nonantigenic, metabolizable, surface modifiable, stable during *in vivo* release and storage, and

Table 4: Reported researches and reviews on smart nanocarriers

No.	Author	Year	Encapsulated Material	Formulation	Description/Applications
1	Li *et al.*[21]	2019	Mesoporous silica	Smart nanocarriers	Targeted fluorescence-photoacoustic bimodal imaging
2	Moradi *et al.*[22]	2019	Dopamine	Smart nanocarriers	Brain targeting approach by the nanocarriers
3	Hossen *et al.*[23]	2018	Drug material	Smart nanocarrier	Smart drug delivery systems
4	Cui *et al.*[24]	2015	Anticancer drugs	Smart nanocarrier	Self-assembled smart nanocarriers
5	Choi *et al.*[25]	2011	Doxorubicin and camptothecin	Smart nanocarrier	Controlled release drug delivery

easy to create and monitor. Covalently attaching drugs and ligands to these particles. Protein nanoparticles reduce toxicity, increase medication release, improve bioavailability, and improve formulation. Protein nanoparticles work at lower doses and reduce medication resistance.[51–53] The nanoparticles boost medication solubility and surface area. Oral, vascular, and inhalation delivery can identify nanoparticles. The Table 6 shows some of the reported researches and reviews on protein nanocarriers.[31–35]

Nucleic acid based nanocarriers

Cancer therapy uses nucleic acid nanocarriers. Due to its endless cell growth, infiltration of healthy tissues, and metastasis, cancer is a leading cause of death worldwide. Radiation and chemotherapy have more adverse effects and damage cancer and healthy cells. Targeted drug delivery reduces conventional drug delivery's negative effects. Nucleic acid-based nanoparticles are a cancer-fighting medication delivery method. Fast-advancing nucleic acid-based nanomedicine will result in excellent tumor-targeted medication delivery. Nucleic acids may be an excellent nanocarrier and cancer treatment tool due to their focused medication delivery, biocompatibility, and self-programmability.[54–56] The Table 7 shows some of the reported researches and reviews on nucleic acid based nanocarriers.[36–40]

Carbon nanotubes

CNTs are cylinder-shaped molecules with single-layer carbon atom sheets. Single-walled CNTs have a diameter of less than 1 nm, while multi-walled CNTs have sizes more than 100 nm. Micrometers or millimetres measure their length. CNTs have particular electrical, thermal, and mechanical properties inherited from graphene, making them attractive for novel material creation.[57] Mainly there are 2 types of carbon nanotubes one is single walled and another one is multi walled carbon nanotubes the difference of types is only their purity, length and functionality.[58–60] The Table 8 shows some of the reported researches and reviews on carbon nanotubes.[41–45]

Self-Nanoemulsifying drug delivery dystem (SNEDDS)

Nanoemulsion or nanoemulsions are SNEDDS. When put into aqueous phase under mild agitation, anhydrous isotropic mixes of oil, surfactant(s), and medicine create O/W nanoemulsions (typically with globule size less than 200 nm). GI motility provides agitation for nanoemulsion production. This system can additionally comprise co-emulsifiers, co-surfactants, and/or solubilizers to increase drug integration or enable nanoemulsification in SNEDDS.[61,62] The Table 9 shows some of the reported researches and reviews on

Table 5: Reported researches and reviews on Nanocomposites

No.	Author	Year	Encapsulated material	Formulation	Description/Applications
1	Shabatina *et al.*[26]	2020	Antibacterial substances dioxidine or gentamicin sulphate	Nanocomposites	Cu/dioxidine nanocomposites
2	Sharma *et al.*[27]	2018	Ondansetron	Nanocomposites	Controlled drug delivery
3	Ghaderi-Ghahfarrokhi *et al.*[28]	2018	Diphenhydramine hydrochloride and diclofenac sodium	Nanocomposites	Modified halloysite nanotubes of targeted delivery
4	Jafarbeglou *et al.*[29]	2016	Clay	Nanocomposites	Combination in composites and hybrids

Table 6: Reported researches and reviews on protein nanocarriers

No.	Author	Year	Encapsulated material	Formulation	Description/Applications
1	Wu *et al.*[31]	2014	Poly (lactic-co-glycolic acid)	Protein nanocarrier	Encapsulation and delivery of proteins and peptides
2	Mattu *et al.*[32]	2013	Tripolyphosphate-crosslinked chitoson nanoparticles	Protein nanocarrier	Encapsulation and delivery of biomacromolecule
3	Lee *et al.*[33]	2009	Polyionic complex micelles	Protein nanocarriers	Protein delivery into cytoplasm
4	Hanafy *et al.*[34]	2017	Folic Acid	Hybride Polymeric Protein nanocarriers	Targeted delivery of TGFβ inhibitors to hepatocellular carcinoma cells
5	Kang *et al.*[35]	2015	Biological fluid like blood, carbohydrates and protein	Protein nanocarriers	Exhibiting specific cell targeting

Table 7: Reported researches and reviews on nucleic acid based nanocarriers

No.	Author	Year	Encapsulated Material	Formulation	Description/Applications
1	Chen *et al.*[36]	2017	Polyacrylamide	Nucleic acid-based hydrogel nanoparticles	Controlled drug release of the formulation
2	Almalik *et al.*[37]	2013	Hyaluronic acid coated chitosan triphosphate	Nucleic acid nanoparticles	CD44-mediated nucleic acid delivery
3	Gill *et al.*[38]	2006	Nucleic Acid	Nucleic acid nanoparticle	Catalytic labels for the chemiluminescent Detection of DNA and proteins
4	Li *et al.*[39]	2007	Lipid and Nucleic acid	Lipid based nanoparticles	Nucleic acid and gene delivery carrier
5	Lee et al.[40]	2012	Peptides and Folate	Nucleic acid nanoparticles	For targeted *in vivo* siRNA delivery

Self-nanoemulsifying drug delivery system.[46–50]

Nanobubbles

Nanoscaled ultrasonic contrast agent (UCA) can be utilised as a theranostic agent due to its imaging capacity. Poly (lactic-co-glycolic acid) (PLGA) nanobubbles are stable, have high-efficiency coating, stable loading, tiny size, and controlled release. At 10 microL/mL, UCA had a 450 nm diameter and delivered 25.5 dB *in vitro* improvements. The UCA provided great *in vivo* power doppler and pulse inversion harmonic pictures at low sound power levels. Nanobubbles were small enough to pass through tumour cell membranes. Differential centrifugation separates particles by size. Perfluoropropane gas protects bubbles for more than two weeks.[63] The acoustic behaviour of the nanosized contrast agent was examined using Power Doppler imaging in a normal rabbit model. Experiments showed that a 3 minutes, 20 g sample was the best for tumour imaging and US-mediated targeted therapy. EPR helps nanobubbles accumulate in malignant tissues. Experiments showed that coumarin put into nanobubbles can transport drugs to cells. The 1% Tween 80, 3 mg/mL lipid nanobubbles demonstrated the best *in vivo* liver imaging. Other experiments produced small, positively charged chitosan nanobubbles. Nanobubbles can protect DNA. Ultrasound stimulated DNA transfection *in vitro*. No DNA-loaded nanobubble concentrations transfected without ultrasound. After 30 seconds of ultrasound, transfection was moderate. Shorter sonication times did not transfect DNA cargo into cells, while longer sonication times impacted cell viability. None of the transfection dosages exhibited formulation-induced cytotoxicity. This chitosan nanobubble could be used in ultrasound-responsive DNA delivery formulations.[64,65] The Table 10 shows some of the reported researches and reviews on nanobubbles.[51–55]

TOXICITY AND BIOCOMPATIBILITY OF NANOCARRIERS

It is vital to investigate the biocompatibility of nanoparticles because they will be entering the body for

Table 8: Reported researches and reviews on carbon nanotubes

No.	Author	Year	Encapsulated Material	Formulation	Description/Applications
1	Mohseni-Dargah *et al.*[41]	2019	Pyridine multi-walled carbon nanotubes	Carbon nanotubes	Delivery of *iC9* suicide gene for killing breast cancer cells
2	Pardo *et al.*[42]	2018	Doxorubicin and gemcitabine	Carbon-based quantum dots and nanotubes	Cancer targeting and drug delivery of the prepared formulation
3	Abbaspour *et al.*[43]	2007	Piroxicam	Carbon nanotubes	Electrochemical monitoring of piroxicam
4	Dumortier *et al.*[44]	2006	1,3-dipolar cycloaddition reaction and the oxidation/amidation treatment	Carbon nanotubes	Non-cytotoxic and preserve the functionality of primary immune cells
5	Guo *et al.*[45]	2007	Radioactive ^{99m}Tc atoms	Carbon nanotubes	Biodistribution of functionalized multiwall carbon nanotubes in mice

Table 9: Reported researches and reviews on self-nanoemulsifying drug delivery system

No.	Author	Year	Encapsulated Material	Formulation	Description
1	Shanmugam *et al.*[46]	2011	Phosphatidylcholine	Solid self-nanoemulsifying drug delivery system	Enhanced bioavailability of highly lipophilic bioactive carotenoid lutein
2	Friedl *et al.*[47]	2013	Cremophor RH 40 and triacetin	Solid self-nanoemulsifying drug delivery system	Develop a novel mucus diffusion model
3	Fahmy *et al.*[48]	2015	Avanafil	Solid self-nanoemulsifying drug delivery system	Improve aqueous solubility and Enhanced Bioavailability
4	Shakeel *et al.*[49]	2016	Ibrutinib	Solid self-nanoemulsifying drug delivery system	Enhance dissolution and bioavailability/ pharmacokinetic profile of anticancer drug Ibrutinib
5	Shakeel *et al.*[50]	2014	Glibenclamide	Polymeric solid self-nanoemulsifying drug delivery system	Delivery of glibenclamide using coffee husk

Table 10: Reported researches and reviews on nanobubbles

No.	Author	Year	Encapsulated Material	Formulation	Description
1	Wang *et al.*[51]	2009	Coumarin-6	Nanobubbles	For ultrasound imaging and intracelluar drug delivery
2	Song *et al.*[52]	2017	Ultrasmall superparamagnetic iron oxide/paclitaxel	Magnetic nanobubbles	Tumor-targeted therapy for breast cance
3	Marano *et al.*[53]	2016	Doxorubicin	Nanobubbles	Delivery of doxorubicin in anaplastic thyroid cancer
4	Deng *et al.*[54]	2014	Doxorubicin	Poly (lactic-co-glycolic acid) nanobubbles	Doxorubicin drug delivery into HeLa cells
5	Zhou *et al.*[55]	2019	Doxorubicin hydrochloride	Chitoson nanobubbles	Targeted drug delivery of doxorubicin

use in biomedical applications and coming into direct touch with tissues and cells.

Hemocompatibility

Applications in medication administration, gene delivery, and biosensing, all of which involve direct contact with blood, utilize nanocarriers as vectors. In this article, we look at the blood-compatibility behaviours of a few nanocarriers. Haemolysis is considered to be a simple and reliable measure for estimating blood compatibility of material, and studies on blood cell aggregation and haemolysis, as well as experiments on coagulation behaviours, have recently been carried out to evaluate the blood compatibility of nanocarriers *in vitro*.[66]

Histocompatibility

One of the areas of study that is being investigated to the greatest extent is that of targeted medication delivery, and the application of nanocarriers for diagnostic purposes has already reached the realm of biomedicine. The biocompatibility of numerous different types of nanomaterials, including superparamagnetic iron oxides, dendrimers, mesoporous silica particles, gold nanocarriers, and carbon nanotubes, is the primary emphasis of the present review.[67]

Cytotoxicity

The intensity of the toxicity may vary, depending both on the route of administration and the areas where it is deposited. For this reason, information on toxicity is presented using a system-based approach, with a focus on lung, cutaneous, liver, and nervous system targets. This helps to ensure that the information remains clinically relevant. The benefits and drawbacks of each of the possible routes are compared. Each compartment within a eukaryotic cell has its own unique function and is enclosed by its own membrane. The nucleus and the organelles, which comprise the mitochondria, endoplasmic reticulum, Golgi apparatus, peroxisomes, and lysosomes, are the primary types. Other types include endosomes and lysosomes.[68]

Neurotoxicity

The brain and spinal cord make up the central nervous system. Both of these organs are extremely sensitive and need special protection against xenobiotics. Multiple nanocarriers, including Polysorbate 80-coated PBCA nanocarriers and PEGylated PLA immunonanoparticles, have been shown in recent studies to cross the BBB after being administered intravenously and subsequently accumulate in the brain. However, once within the brain, the nanocarriers' unique physicochemical properties such as their enormous surface area may produce neurotoxicity. Consequently, it is necessary to assess the possible neurotoxic consequences of these nanocarriers on CNS function, as the precise mechanisms and pathways through which nanocarriers may exert their toxicity are as yet completely understood.[69]

SHORTCOMING, LIMITATIONS AND FUTURE PROSPECTS OF NANOCARRIERS

The use of nanoparticles has many advantages, including the elimination of side effects due to large doses, intestinal permeability, poor accessibility, the first pass effect, strong reactivity, instability, and fluctuations in plasma drug levels, among others. Using a nanocarrier raises the possibility of nanotoxicity. Bioaccumulation of nanocarriers is associated with elevated levels of reactive oxygen species within cells, which leads to oxidative stress and damages multiple body systems (respiratory, skin, liver, kidney, reproductive, central nervous, and immune). These adverse results are mainly attributable to the fact that nanocarriers are smaller than their bigger counterparts of the same composition, which means their characteristics are different.[70]

The malleability of nanocarriers in terms of both their composition and their design have attracted scientists from all over the world. The medicinal and diagnostic potential of nanocarriers is not limited to inorganic nanocarriers. Cancer therapy, iron replacement therapy, imaging agents, immunizations, anaesthetics, fungus therapies, and macular degeneration eye drops all involve nanocarriers. Today's scientific discoveries will undoubtedly influence the course of future events. Future scientific advances will be influenced by the present. The development of nanocarriers will be driven by nanotechnology and related industries. In the last ten years, biomedical research has made tremendous progress. Drug release from a nanoparticulate system can be controlled by environmental factors like as temperature, pH, osmolality, and enzyme activity. Potentially important in biomedical research advances in disease diagnostics are quantum dots, Raman probes, and real-time fluorescence or chemiluminescence detection. Expectations have shifted to the next attainable level as a result of therapeutic advancements including increased circulation duration and the capacity to focus drug release. Drug loading, targeting, conveying, releasing, barrier interaction, low toxicity, and safe environments for nanocarriers medications should be researched using higher animal models. Nanoparticles have the potential to improve cancer treatment by facilitating the detection of cancer cells, the delivery of multiple drugs at once, the visualization of the treatment site with imaging agents, the destruction of cancer cells with minimal side effects, and the simultaneous monitoring and treatment of the patient.[71–73]

Conclusion

The use of nanoparticles to deliver medications, such as anticancer and chemotherapeutic drugs, is a significant step forward made possible by nanotherapy. There are

many novel nanocarriers that have extraordinary benefits for drug delivery. Some examples of these nanocarriers include ultrabright nanocarriers, polymeric nanocarriers, ultrasound-mediated nanocarriers, smart nanocarriers, nanocomposites, protein nanocarriers, nucleic acid-based nanocarriers, carbon nanotubes, and nanobubbles. Other examples include self-nanoemulsifying drug delivery systems and nanobubbles. Many of the latest nanocarriers being developed as medication delivery systems have been detailed in this study. The research is still under process and many new nanocarriers are under study for the betterment of drug delivery. In addition to the other nanocarriers, the ones about which this paper is concerned play a significant part in the treatment of a wide range of diseases and disorders. This highlights the undeniable significance of nanocarriers in community health care and illness management.

Acknowledgments

We, thank you to the Suresh Gyan Vihar University, for their constant support and providing all facilities to complete this work.

Author contributions

Preeti Khulbe and Deepa Mohan Singh: Wrote and revised the first draft. Anshu Aman: English editing. Eknath D. Ahire and Raj K. Keservani: Proofreading and editing of final draft. All authors are agreed the final version and submitted the article.

Ethics approval

Not applicable.

Conflicts of interest

Eknath D. Ahire and Raj K. Keservani are Editorial Board Members. The article was subject to the journal's standard procedures, with peer review handled independently of these Members and their research groups.

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