INTRODUCTION

The human body consists of trillions of cells, and each group of cells is designated for a specific function to sustain life. Healthy cells divide when they receive a chemical signal by various mechanisms, and the whole phenomenon is known as cell division. The cell division process is tightly regulated to maintain the normal homeostasis and is a critical issue in cancer due to the uncontrolled division process. Cells divide when they receive a chemical signal by various mechanisms, designated for a specific function to sustain life. Healthy cells divide when they receive a chemical signal by various mechanisms, and the whole phenomenon is known as cell division. The cell division process is tightly regulated to maintain the normal homeostasis and is a critical issue in cancer due to the uncontrolled division process.

Some of the approved chemotherapeutic drugs available for the treatment of cancer include doxorubicin (DOX), paclitaxel (PTX), gemcitabine, and cisplatin, to name a few. Unfortunately, chemotherapy in clinics fails mainly due to toxic side effects and the bioavailability at the different target sites other than the specific target site [6]. Studies on chemotherapy failure in clinics also suggest the diverse phenomenon of multi-drug resistance [7]. To overcome the limitations of bioavailability, multi-drug resistance, alternate treatment strategies such as radiotherapy (external beam therapy) and molecular radiotherapy (using beta and alpha rays) are emerging in the absence/presence of various drugs in clinical settings [8]. Instead, radiotherapy also has few limitations with its side effects associated with the use of alpha and beta radiation. The most common side effects during the radiotherapy treatment include the resistance, recurrence after initial treatment, and tumor lysis syndrome. The treatment of cancer in the clinics has to be more effective in the form of specific therapy such as chemo, immune, and radiotherapy. For clinical validation, there is a need for systematic clinical trials to provide opportunities and compelling goals for cancer treatment. However, various difficulties or challenges exist while executing clinical trials, including poor study design, poor trial execution, patient safety, dropouts, and reduced patients recruitment [9, 10]. Therefore, to overcome the challenges, especially with the treatment modalities carried out, cargo agents such as NPs for specific and versatile delivery platforms are needed to exploit the safety, efficacy, and effectiveness of the treatment. These treatment modalities should have strategies that rule out the consequences of bioavailability, tumor lysis syndrome, and multi-drug resistance.

The use of NPs in the field of nanomedicine acts as a versatile therapeutic platform for the synthesis and development of drug targeting cargos for the treatment of various types of cancers [11, 12]. The versatility in the use of NPs depends on the use of a variety of materials such as metals, inorganic and organic, due to their ease...
of synthesis, surface manipulations to carry desired functional groups, high binding affinity, ease of transport, which themselves act as therapeutic agents or carry the therapeutic agents and delivers especially to the tumor cells [13, 14]. NPs provide an efficient technology platform due to their flexibility and ease in tuning their biocompatible properties, synthesis of desired size and shape, tailoring various surface functional groups, and unique physio-chemical features [15, 16]. The conjugation of potential chemotherapeutic drugs with NPs has various advantages over the use of chemotherapeutic drugs such as transportation, specific targeting ability with reduced systemic toxicity, and enhanced drug accumulation inside the tumor [17-19]. The surface-modified-NPs also increases the absorption across the epithelial distribution and leaky membranes in the tumor to reach the optimal concentration very quickly in the tumor site as compared to chemotherapeutic drugs when used alone.

There are various types of NPs, such as lipid-based NPs, nanocapsule, polymeric NPs, metallic NPs, dendrimers, and LPs, emerging as useful tools in the clinical settings (fig. 2 [20, 21]. However, consideration of NPs based drugs in clinical practice remains unlikely due to various concerns such as possible toxicity issues, without exceptional regulatory guidance and compliance, cost-benefit attention, and decreasing interest for some health care staff. To date, different nanotechnology-based chemotherapeutic synthetic strategies are reported that could be considered for clinical use [22, 23]. Hence, we used different databases such as PubMed, Web of Science, Scopus, Ebesco for performing the search using the key terms such as lipid nanoparticles, polymeric nanoparticles, metallic nanoparticles, cancer, surface modifications to search for the relevant articles and considered.

Types of nanoparticles

Iron oxide (IO)-NPs

Iron oxide NPs (IONPs) have improved super paramagnetic properties and are extensively considered for various clinical applications [24]. The different types of IO used for the NPs synthesis include Fe3O4 (magnetite), α-Fe2O3 (hematite or antiferromagnetic), c-Fe3O4 (maghemite, ferrimagnetic), FeO (wustite, antiferromagnetic), γ-Fe2O3 and β-Fe2O3. However, Fe3O4 and γ-Fe2O3 NPs are the favorable and most commonly used chemical forms that are specially designed for various biomedical applications such as imaging contrast agents for MRI, thermal therapeutic tools [25, 26] and as cargo vehicles due to their features of improved biocompatibility and easy formulation [27-30]. These are structurally constituted, having nanocrystalline magnetite Fe3O4 or γ-Fe2O3 with a polymeric coating. The Fe3O4 and γ-Fe2O3 NPs hold complex spinal crystal structure depending upon the cation distribution where oxygen ion atom occupies a tight packing in cubic lattice and iron ion atom positioned at interstices. Some studies provide insights and reveal that magnetization occurs due to the exchange of electrons between Fe2+ and Fe3+ atom ions that cohabit in the octahedral structure [31]. The properties that make the IONPs unique is due to their crystallizability, size, shape, super paramagnetic properties and magnetization induced heat generation. Since the size and shape of IONPs are related to their inherent properties, therefore synthesis is an important step. There are several optimized methods for the synthesis of IONPs, which comprise the co-precipitation, microemulsion, sonochemical methods, hydrothermal synthesis, and thermal decomposition. Furthermore, other methods of IONPs synthesis include electrochemical synthesis [32], laser pyrolysis techniques [33], microorganisms, or magnetotactic and iron-reducing bacterial synthesis. Considering the formulation of IONPs for clinical use is a significant challenging aspect. It requires specific surface modification that renders them high biocompatibility in the biological environment, reduces self-aggregation over longer duration preservation, reduces metal-related biological/clinical toxicity, multifunctional properties to hold the drugs for therapeutic effects and antibodies attachment for specific targeting while retaining the intrinsic superparamagnetic properties. The reactive shell properties of IONPs are used for various functional groups attachments such as a range of organic ligands (carboxylic acid, Phosphonic acid) [34, 35] polymers (PVA, PEG and PAA), sugars (Dextran, Chitosan) and zwitterionic ligand.

Further, other metallic/inorganic NPs (Gold, silica and Tantalum oxide), cross-linking besides engineering the surface coating layer is related to the nature of the NPs and their preferred biomedical applications [36, 37]. Besides, another group of researchers coated IONPs using small charged molecules, for example, folic acid to avoid macrophages uptake and enhance the heating to the cancer cell [36]. The in vivo kinetics and dynamics, and ultimately the fate of the IONPs, depends on the NPs and the type of the surface coatings, which determines the overall hydrodynamic size. Small NPs of approximately 20 nm with higher blood circulation half-life are usually excreted from the kidneys [38], and large NPs (150 nm) are quickly uptaken by the reticuloendothelial system (RES) predominantly by the liver and spleen. However, NPs with an intermediate size between 20-150 nm are mainly distributed in the heart, kidneys, and bone marrow [39].

Nanocrystalline magnetite (Fe3O4) cores have huge potential for biomedical applications in clinical cancer due to their properties that include biocompatibility, biodegradability, and simple and ease of synthesis [40]. There are two types of biocompatible layers that
can be considered to modify the surface of IONPs, i.e., organic and inorganic coatings [27]. The organic biocompatible based coating approaches are by either using a ligand exchange mechanism or physical assemblage/encapsulation [28]. Inorganic biocompatible coating involves the use of silica, Tantalum (V) Oxide. Gold NPs (GNPs) are inert and easily tailored by linking with the designed architecture of thiol (-SH) group ligands to render the best biocompatible properties [41]. Such types of coatings are used for therapeutic applications by attaching an antibody using the PEG linker to the Mag-GNP nanoshell [42]. IONPs coating with silica is performed by the Stober method or the reverse microemulsion [43].

The coated shells of IONPs allow performing various functions such as drug delivery vehicles in in vivo for the multimodal MRI and fluorescent imaging applications [42, 29].

In a Fe3O4 microemulsion of tantalum (V) oxide, a sol-gel reaction was carried out to obtain Fe3O4/TaOx core/shell multifunctional NPs [44]. Upon intravenous injection, such NPs exhibit long circulation half-lives. This rendered them as CT and MRI contrast agents to observe the changes associated with angiogenesis and the tumor microenvironment. Various researchers showed that multimeric ligand which can be bidentate or multidentate, for example, Dimecaptosuccinic acid (DMSA), containing bidentate-COOH groups provide excellent colloidal stability to IONPs in aqueous media and render water solubility and stability [43, 45]. These NPs exhibiting a hydrodynamic size of ~10 nm are highly stable between 6-8.5 pH ranges, do not self-aggregate in solution over long-standing, form highly homogenous solution, and are excreted by the kidneys. Natural ligands, like polysaccharides, can also interact with IONPs, which have many hydroxyl groups and carboxylic groups (-COOH), alginates, and amino acids [46]. Physical encapsulation of IONPs can also be achieved using LFs, micelles, and polymersomes via electrostatic interactions or van der Waals interactions. Such kind of biocompatible coatings is explicitly used in drug delivery for in vivo and in vitro therapeutic applications. Earlier anti-cancer drugs received much attention; due to the biocompatible nature of IONPs and are used as anti-cancer drug vehicles for the cancer therapeutic applications. Many anti-cancer drugs, for example, Doxorubicin (DOX), temozolomide (TMZ), and paclitaxel (PTX) are used with biocompatible coatings around IONPs and have been effectively validated in vitro and in vivo for their cancer treatment efficacy [47, 48].

Hequn Hao and colleagues [47] synthesized Fe3O4 nanocrystals using a co-precipitation technique in an alkaline medium with few modifications in which DOX-HCl aqueous solution was loaded onto Fe3O4 solution at room temperature in dark conditions followed by constant mixing at physiological pH for 12 h. Fe3O4 nanocrystals of size 10 nm were loaded onto BSA-DEX-FA NPs under high temperature, which triggers BSA gelation encapsulating the nanocrystals. Further, by diffusion technique, DOX was loaded onto BSA-DEX-FA, and the final formulation of NPs was obtained as DOX/Fe3O4/BSA-DEX-FA with an overall size of 100 nm that showed good solution homogeneity and stability. In vitro cytotoxicity studies using MTS assay in KB cells treated with DOX alone, and DOX loaded IONPs solutions having 1 μg/ml DOX at various intervals (24, 48 h and 72 h). These results showed a progressive decline in cancer cell proliferation in a dose and time-dependent manner. Furthermore, the tumor inhibition efficacy of DOX/Fe3O4/BSA-DEX-FA was evaluated in tumor mice models (18-22 g). Upon intravenous administration of DOX/Fe3O4/BSA-DEX-FA, and under the external magnetic field of 0.15T, the proper localization and accumulation of DOX loaded NPs into the tumor region was enhanced. Results obtained from these studies show the tumor inhibition rate of about 63%, respectively. In comparison, with DOX alone, it was 55%.

Temozolomide (TMZ) is a chemotherapeutic agent used for the management of glioblastoma. TMZ loaded IONPs functionalized with chitosan showed a hydrodynamic size of 50 nm [49]. Chlorotoxin (CTX) moieties are used as targeting ligands on these NPs. TMZ formulated IONPs exhibited higher stability at pH 7.4, followed by very long systemic circulation half-life, i.e., 7 times more than that of TMZ alone. A pre-clinical dose-response curve was analyzed in human U-118 MG cells by treatment with various concentrations [0-200 μg/ml] of TMZ, NP-TMZ, or NP-TMZ-CTX. This study showed great promise to convey a remedial dosage of NP-TMZ-CTX as compared to TMZ alone treatment at 72 h and showed 2-6 times much higher uptake into the cells and 50-90% reduction in the tumor cell proliferation.

Studies also suggest the preparation of IONPs using double emulsion technique (DEC) stabilizers in the presence of surfactants such as PVA forming the DEC-IO complex. Paclitaxel (PTX) anti-cancer drug was loaded onto DEC-IO to form a complex of DEC-IO-PTX with a hydrodynamic size range of 75-200 nm. In vivo cell viability experiments in HeLa and MCF cells with DEC-IO-PTX treatment for 24 h showed IC50 values of 65±7% less as compared to DEC-IO i.e.90±15%. They have also explored a targeting ligand like peptide IV024 by DEC using EDC linker against several xenograft cancer models of lungs, breast, prostate, liver, and oral cancer. When the cells were targeted using IV024 with a DOX, and PTX loaded IONPs, cell viability of only 10% was observed within 24 h of treatment with DOX and 5% with PTX in HeLa and MCF-7 cancer cells. These results explored the role of IV024 peptide using IONPs loaded anti-cancer agent for targeting the cancer cells. Similar studies were also performed using anti-cancer drug DOX, DEC-IO-DOX and targeting peptide ligand IV024, IV024–DEC-IO-DOX, in the same cancer cells and the cell viability was effectively reduced with peptide ligand IV024 [50].
Liposome nanoparticles (LP-NPs)

LPs are prepared from lipids, generally composed of phospholipids, and cholesterol as components [51]. LPs are chemically made up of phospholipids and cholesterol. Furthermore, these LPs have multiple concentric bilayers with each lipid bilayer separated by aqueous media [52]. Primarily, LPs were implied to understand the substantial properties of cell membranes, which include lipids alignment in the bilayer, their physiochemical properties, and ion transportation through the biological membrane. There are various type of LPs such as multilamellar vesicles, constituted with phospholipid bilayer membrane unplugged by aqueous medium up to 5 µm size. Small unilamellar vesicle made up of aqueous partition enclosed with a mono lipid bilayer and the size of such LPs range from 20-100 nm [51, 52]. We know the majority of LPs components are chemically phospholipids and cholesterol, which make the majority proportion of the biomembranes. Such chemical characteristics of lipids regulate the major behavior of LPs. LPs preparations involve the use of phospholipids and the most commonly used phospholipids include egg or soya, phosphatidylcholine, and synthetic phosphatidylcholine [53, 54]. Since naturally occurring phospholipids like egg or soya bean phospholipids have a significant extent of polyunsaturated fatty acid, they render the vesicles less stability than their synthetic equivalents. The molar proportion of phospholipid ranges from 55 to 100 % of total LPs constituents. The 2-distearoyl-sn-glycero-phosphocholine (DSPC) is known to be the most common phospholipid of the LP's lipid region of DSPC is used to coordinate with other functional charged groups of other polymers such as polyethylene glycol (PEG) [55, 56]. However, phospholipid components alone of LPs make the sieve-like properties; therefore, the ratio of cholesterol determines the LPs formulation and their stability. The molar proportion of cholesterol, if varied between 30-45% of the total LPs component, determines the rigidity, elasticity, permeability, stability, and fluidity of the bilayer [54, 57, 58]. Furthermore, cholesterol also strengthens the LPs in terms of the rigidity and thereby influences the lipid bilayers phase transition properties. The increased rigidity influences encapsulated drug leakage from the vesicles. Some of the research groups also revealed that cholesterol avoids hydrolytic degradation of the lipid bilayer. Depending on the application of LPs, various other components also have been used in addition to phospholipid and cholesterol. The overall liposomal surface charge plays a crucial role in the cellular uptake mechanism. Studies show that the process of endocytosis mechanism easily takes positively charged or cationic LPs, whereas negatively charged and neutral LPs show low endocytosis uptake. However, negatively charged LPs are frequently used in drug delivery applications because negative surface charges can be recognizable by receptors present on various cells, including the RES. The charge on the liposomal surface also plays a crucial function in deciding the fate of the LPs intracellularly [59, 60]. While using the LPs in the clinical settings, PEG is the most widely used surface modifier to amplify blood circulation time due to its stealth properties (escaping the engulfing process and rapid clearance through the RES) and has demonstrated widespread application in the drug delivery applications for effective cancer treatment. The various synthetic techniques adopted for the preparation of LPs include-solvent removal, ethanol injection methods, emulsion, and detergent removal [59-61]. From these methods, the size distributions of LPs obtained are in the range of 25-1000 nm depending on the LPs method adopted. However, typical sizes between 50 to 200 nm are commonly used for a variety of biomedical applications. LPs are implied to understand the hydrophilic, hydrophobic, and amphiphilic carrier, and accordingly, the hydrophobic or hydrophilic drugs can be used to entrap or encapsulate within the LPs resulting in effective cancer cell therapeutics [53, 55]. Therefore, both hydrophobic and hydrophilic drugs can be used to entrap or encapsulate within the vesicles. The hydrophobic drug gets intercalated within the lipid layers of the LPs, whereas hydrophilic drugs encapsulate in the central aqueous core. However, the encapsulation of chemotherapeutic drugs into LPs is commonly brought about into two different ways (1) passive loading–encapsulation of the drug at the time of vesicle formation and (2) dynamic loading–vesicle formation followed by drug trapping. LPs are known to be the most organic NPs approved for cancer treatment and usually have a great potential for targeting as delivery vehicles for chemotherapeutic drugs. Other applications of LPs include reduced transferrin (TF) elimination, enhance targeting specificity and reduce the chemotherapeutic agent’s non-specific side effects [34, 62, 63].

Several liposomal based drugs are now available in market such as Doxil® (caelyx® (DOX), myocet® (DOX), lipodox® (DOX), daunoxome® (daunorubicin), depocyt™ (cytarabine) marqibo®, (vincristine), onivyde® (vincentine), onyxyde®, doceAqualip and visudyne®. Usually, most of the liposomal formulations are used as intravenous injections, and their systemic administration leads to the rapid clearance from the circulation due which most of them show very short circulating half-lives. However, the circulation half-lives could be increased, if needed, in some cases of treatment strategies by using branched or long chains of PEGylation. The first example of liposomal NPs drug is DOX-PEGylated LPs (Doxil®), which has shown reduced cardiotoxic side effects [22, 64]. Doxil® is approved for numerous solid tumors, such as Kaposi’s sarcoma, ovarian cancer, multiple myeloma, and metastatic breast cancer [38, 65]. Various studies revealed that PEGylated LPs-DOX enhances about 4 to 16 fold of drug efficacy in cancer cell treatment in comparison to free DOX. Some of the complex LPs systems have also been reported and are in the clinical trial.

Cyclic RGD and TF were also used to enhance specific binding to the tumors and efficient cellular uptake since TF is a possible ligand for effective delivery as it can cross the blood-brain barrier (BBB) easily. Studies have shown the introduction of multiple functional groups onto the LPs to create RGD/TF-Lpas cargo systems. This system is used for linking the PTX drug to form a new complex system that precisely targets the gliomas. Recently, varieties of monoclonal antibodies have been tagged to LPs for targeting various types of cancer (anti-HER2 long-circulating LPs are used to target HER2-expressing tumors). Antibody CC52 against an in vivo model of rat colon adenocarcinoma CC531 conjugated with PEGylated LPs had high uptake levels in cancer. Studies have also shown that i. v. administration of (TAG)-72 conjugated with PEG-LPs effectively targeted and accumulated in LS174 T human colon cancer cells [66].

Fig. 4: Liposome based nanoparticles
Polymeric based NPs

Polymeric NPs are one of the most studied across all aspects of the field, including biomedical applications. In particular, PLGA is a commonly used synthetic polymer and widely preferred for the drug-loaded NPs preparation. Such NPs play a vital role as a carrier and suitable for the chemotherapeutic drug. Utilization of a single polymer chain of PLGA is a commonly used synthetic polymer and widely because of their biodegradability and bio-compatibility properties. Furthermore, hyaluronic acid (HA) has been extensively used and widely studied for cancer treatment. The finding from various groups also suggests that the PEGylated-HA NPs reduces the uptake in the liver and shows extended blood circulation half-lives and enhanced the tumor accumulation in cancer cells. In vivo studies indicates that the PEGylated-PAC NPs loaded with DOX showed a more significant chemotherapeutic effect with reduced toxicity as compared to the DOX alone treatment.

Fig. 5: Polymeric micelle

Challenges

NPs provide great opportunities in cancer therapy, leading to an improvement in cancer survival cases due to their high sensitivity and specificity. NPs based drug delivery in cancer therapy is a expanding field of research with the new technological advancements that has revolutionized medical research in the recent years. Though current scientific evidences shows promising results, however, there are few challenges of concern when it comes to the development of biocompatible NPs and their mode of treatments. Toxicity of utmost importance and might occur due to various reactions taking place within the biological systems. Another critical challenge that limits the use of NPs-based drugs in clinical settings is the lack of adequate guidelines. Therefore, significant complications in the clinical application of nanomaterials are the estimation of the toxicities and mimicking the in vivo effects of nanoformulations. However, future advancements and research in this field will provide promising benefits in cancer treatment.

CONCLUSION

The cancer therapy that is available these days is not able to accurately target tumors and metastasis. Moreover, drug-resistance towards the clinically available and use of chemotherapeutic strategies is a major challenge. There is a need to develop strategies that could help target tumors more effectively and with reduced side effects. NPs such as 10NPs, LPS based NPs and polymeric NPs can act as therapeutic tools for targeting cancers. However, the most recent strategies for making use of NPs as cargo agents for drug delivery in chemotherapeutics includes their ease of design and synthesis of desired sizes and shapes. The versatile nature and use of various types of NPs include the flexibility of surface modification by multifunctional agents/ligands as cargo agents for drug delivery. These surface-modified NPs shows potential in accumulating at the tumor target site (both in vitro and in vivo) with high efficacy and efficiency, can be modulated in the circulation for desired time durations and overcomes the phenomenon of drug-resistance. Such NPs design strategies are evolving and the recent evidences suggest that NPs are promising tools for cancer chemotherapeutics.

ABBREVIATION

Blood-brain barrier (BBB), Bovine serum albumin (BSA), Computed tomography (CT), Double emulsion capsule (DEC), Docetaxel (DEX), Dynamic light scattering (DLS), Doxorubicin nucleic acid (DNA), Doxorubicin (DOX), Folic acid (FA), Food and drug administration (FDA), Glycosaminoglycan (GAG), Good manufacture practice (GMP), Hyaluronic acid (HA), N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA), Intravenous (I.V.), Iron oxide nanoparticles (IONPs), Liposomes (LPS), Magnetic nanoparticles (MNP), Magnetic resonance imaging (MRI), Nanoparticles (NPs), Paclitaxel (PTX), Polyacrylic acid (PAA), Polyethylene glycol (PEG), Polylactic acid (PLA), Poly(lactide-co-glycolic acid) (PLGA), Polyvinyl alcohol (PVA), Retinolendothelial system (RES), Transferrin (TF), Temozolomide (TMZ), Ultrasoundography (US)

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AUTHORS CONTRIBUTIONS

Arushi Chauhan (AC) and Ravi Ranjan (RR) equally contributed in performing the search, collecting the data, drafting the manuscript and references. Pramod Avti (PA) and Arvind Gulbake (AG) conceived the idea, written and edited the manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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