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Original Article

MAGNETIC DRUG TARGETING USING MAGNETIC NANOPARTICLES FOR CANCER THERAPY

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ABSTRACT

Globally, cancer is still among the most frequent causes of mortality.Traditional cancer treatment modalities, including surgery, radiotherapy, and chemotherapy, present limited selectivity and severe side effects. Chemotherapeutic agents target the growth and survival of rapidly dividing cancer cells, but they can also kill healthy cells through systemic circulation. Hence, the quest for specific drug-targeting systems for tumor-targeting agents in the therapeutic arm has attracted considerable attention in cancer therapy. Magnetic nanoparticles (MNPs) have attracted significant attention in biomedical research owing to their specific physical and features such as their small particle size and high surface-to-volume, and superparamagnetic behavior. Magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), which belong to the iron oxide nanoparticle family, are extensively investigated for biomedical because they are biocompatible and exhibit controllable magnetic properties. These nanoparticles can be functionalized with biocompatible coatings and anticancer agents to develop magnetic drug delivery systems. Magnetic Drug Targeting (MDT) is reliesed on the principle of magnetic nanoparticles conjugated with therapeutic agents directed to the cancerous tissue region by a magnetic field applied externall Such an approach makes increased drug accumulation within the targeted tissue possible, and a substantial impact has been achieved with systemic toxicity and side effects minimized. Furthermore, magnetic nanoparticles have been applied widely across biomedical fields, including magnetic resonance imaging (MRI), hyperthermia therapy, biosensors, and tissue engineering. The basic properties of magnetic nanoparticles, their biocompatibility, their application in cancer anticancer drug targeting using magnetic drug, and their properties in the context of the basic characteristics are investigated in this review as well. In addition, discussion has been provided on magnetic targeting dynamics, drug applications, and anti-cancer drugs with magnetic nanoparticles, as well as targeted drug system issues, based on the available literature. Drug delivery using magnetic nanoparticle systems is a promising strategy for optimizing cancer treatment while minimizing side effects.

Keywords: Magnetic Drug Targeting, MDT, Cancer Therapy, Magnetic Nanoparticles, MNPs, Targeted Drug Delivery

INTRODUCTION

Conventional cancer treatment methods mainly include surgical intervention, radiotherapy, and chemotherapy. Among these treatments, chemotherapy—literally meaning “treatment with drugs”—refers to the use of anticancer agents (chemotherapeutics) that primarily target cancer cells Perry (2008). In chemotherapy, both the type of drug and its dosage are critical factors. The lack of selectivity and dose-dependent toxicity of many anticancer drugs leads to significant challenges in chemotherapy treatment. One of

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the most important problems is that anticancer drugs destroy not only cancer cells but also all rapidly dividing cells in the body through systemic circulation, including healthy cells Pardee and Stein (2009). Furthermore, these treatments may lead to organ-specific toxicity and severe side effects, such as heart failure in breast cancer therapy Pugazhendhi et al. (2018), Carvalho et al. (2009), which may even result in life-threatening conditions Alexiou et al. (2011). The main goal of chemotherapy is to reduce or eliminate the side effects of anticancer drugs while maximizing the drug dose delivered to tumor tissue. Therefore, extensive research has focused on drug-targeting systems that deliver lower drug doses to patients while directing the drug specifically to cancerous tissue to achieve maximum therapeutic effect Alexiou et al. (2000). Magnetic drug targeting (MDT) systems using magnetic nanoparticles represent an important approach to overcoming these challenges in chemotherapy. In this strategy, chemotherapeutic drugs are attached to iron-oxide cores and directed to cancerous tissue using a magnetic field produced by an external source To prevent rapid elimination by the immune defense system and to allow drug attachment, biocompatible materials must be applied to the surface of magnetic nanoparticles Magnetic drug targeting (MDT) systems using magnetic nanoparticles represent an important approach to overcoming these challenges in chemotherapy. In this strategy, chemotherapeutic drugs are attached to iron-oxide cores and directed to cancerous tissue using a magnetic field produced by an external source To prevent rapid elimination by the immune defense system and to allow drug attachment, surface modification of magnetic nanoparticles with biocompatible materials is necessary.

Anticancer drugs generally distribute widely throughout the body. Since anticancer drugs can damage both tumor cells and healthy cells, the effectiveness of chemotherapy is frequently restricted by severe side effects Brigger et al. (2012). These side effects may range from relatively temporary conditions such as nausea and hair loss to more severe complications, including heart attacks. In some cases, treatment may even need to be discontinued due to these adverse effects. Moreover, the success of chemotherapy largely depends on the dosage of the administered drug. Unfortunately, increasing the drug dose is not a complete solution, as higher doses also lead to a significant increase in side effects. One of the major concerns is how much of the anticancer drug administered into the systemic circulation actually reaches the cancerous tissue. Drugs introduced into the systemic circulation travel throughout the entire body, and only a minor proportion of the therapeutic agent reaches the tumor region Consequently, healthy tissues are also exposed to the effects of anticancer drugs. The fundamental question that needs to be addressed is whether the administered anticancer drug can be specifically directed to the cancerous tissue and retained at that site. If this problem can be solved, much lower drug doses could be used for treatment, and a larger proportion of the administered drug could be delivered directly to the tumor region. At this point, the concept of drug targeting, which involves the use of delivery vehicles to transport drugs to particular sites in the body , becomes particularly important. In the early 1900s, the pioneer of immunology Paul Ehrlich introduced the concept of the “magic bullet”, proposing the idea of selectively targeting diseased cells without harming healthy tissues Perry (2008) Canefe and Duman (1994).

MAGNETIC NANOPARTICLES (MNP)

Across various scientific and technological disciplines, nanoscale materials with uniform morphology and narrow size distribution are widely required (Gubin, 2009; Gubin et al., 2005). Among these nanoscale materials, magnetic nanoparticles (MNPs) have gained substantial interest owing to their broad range of applications MNPs typically have very small diameters, generally ranging from 1 to 100 nm, which results in a surface-to-volume ratio. These nanoparticles can exhibit magnetic behavior and be manipulated by an external magnetic field Among various types of magnetic nanoparticles, magnetite (Fe_3O_4) exhibits superparamagnetic properties and is therefore extensively applied in applications such as biosensors, drug transport systems and magnetic hyperthermia therapeutic approach. In contrast, maghemite (γ-Fe_2O_3) is extensively used as a contrast agent in MRI applications and as a biosensor surface coating owing to its high biocompatibility Laurent et al. (2008),Gupta and Gupta (2005). The types of magnetic nanoparticles and their main properties are presented in Table 1

Table 1

Table 1 Magnetic nanoparticles and their main properties

Nanomaterial	Chemical Formula	Key Property
Magnetite	Fe_3O_4	Superparamagnetic behavior
Maghemite	γ-Fe_2O_3	High biocompatibility
Cobalt ferrite	$CoFe_2O_4$	High magnetic anisotropy
Nickel ferrite	$NiFe_2O_4$	Chemical stability
Manganese ferrite	$MnFe_2O_4$	Use as MRI contrast agent
Iron nanoparticles	Fe	High magnetic moment

Magnetic nanoparticles derived from iron oxide, especially magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), are commonly employed in biomedical fields owing to their unique physicochemical properties. Their nanoscale particle size and extensive surface-

to-volume ratio , and superparamagnetic behavior provide remarkable advantages in a variety of biomedical fields. As a result, these nanoparticles have attracted increasing attention, especially in cancer diagnosis and therapeutic applications, and are considered promising materials for both current and future biomedical technologies.

MAGNETIC DRUG CARRIERS

Following the development of the first magnetic polymer carriers in the 1970s, various magnetic nanoparticle and microparticle carriers have been designed to deliver drugs to specific sites in vivo. These carrier systems continue to be optimized. In most cases, the magnetic part of the particle is covered with biocompatible polymers including polyethylene glycol (PEG), polyvinyl alcohol (PVA), and dextran in recent studies, inorganic coatings such as silica have also been investigated the coating provides protection for the magnetic particle against the surrounding environment and can also be modified with molecules including carboxyl groups, biotin, avidin, carbodiimide, and other functional molecules. They provide binding sites that enable cytotoxic drugs or targeting antibodies to be attached to the carrier complex. Pankhurst et al. (2003)

Carriers generally display one of two structural configurations (i) a magnetic particle core, usually magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3), coated with a biocompatible polymer, or (ii) a porous biocompatible polymer matrix within which magnetic nanoparticles are embedded. Recent developments in carrier systems have largely focused on new polymeric or inorganic coating layers applied to magnetite and maghemite nanoparticles Pankhurst et al. (2009), Deng et al. (2003). Moreover noble metal coatings, particularly gold, have also been examined. Alternative magnetic particles, including iron, cobalt, and nickel nanoparticles, have also been explored in various studies, as well as materials such as yttrium aluminum garnet Grasset et al. (2001). Furthermore, cobalt/silica carriers have been investigated for potential applications in ophthalmic surgery for retinal repair Dahiya and Dureja (2016), Pugazhendhi et al. (2018).

The nanoscale size of magnetic nanoparticles (MNPs), generally ranging from a few to several tens of nanometers, represents one of their main advantages. This size range enables their use in studies involving biological structures such as cells with dimensions of about 10–100 μm, viruses with sizes generally between 20 and 450 nm, proteins (approximately 5–50 nm in size) , and genes (typically about 2 nm in width and 10–100 nm in length) Another important advantage of MNPs is their size-dependent superparamagnetic behavior. These nanoparticles are highly preferred because they can become magnetized when exposed to a magnetic field produced by an external source; however, they lose their magnetization once the external magnetic field is removed. Another advantage is that MNPs can be controlled by an external magnetic field, which enables numerous in vivo nano-bio applications, including magnetic drug targeting (MDT) Pankhurst et al. (2009), Bohara et al. (2016).

BIOCOMPATIBILITY

Magnetic carriers intended for biomedical applications should be water-based, biocompatible, non-toxic, and non-immunogenic Häfeli and Pauer (1999). The biocompatibility and potential toxicity of magnetic nanoparticles are largely influenced by their core composition and surface coatings. Iron oxide nanoparticles, particularly magnetite (Fe_3O_4) and its oxidized form maghemite (γ-Fe_2O_3), are the most widely utilized magnetic nanoparticles in biomedical applications. In contrast, strongly magnetic materials such as cobalt and nickel tend to be toxic and prone to oxidation, making them less appropriate for biomedical use. Tartaj et al. (2003)

The toxicity of the magnetic ions incorporated into the core is a crucial aspect that must be considered in the design of magnetic nanoparticles (MNPs)**.** Surface coatings provide two important protective functions: they inhibit the release of toxic ions from the magnetic core and protect the core against oxidation and corrosion. Among various nanomaterials, iron oxide nanoparticles are the most frequently utilized for in vivo biomedical applications, largely because iron is physiologically well tolerated by the human body. This is partly due to the body's natural ability to process excess iron and store it within the core of the iron-storage protein ferritin. Other elements such as manganese (Mn) and zinc (Zn) are also important components of the human body; however, their tolerable limits are significantly lower than those of iron. Therefore, appropriate surface modification strategies are required when these materials are used in nanoparticle systems. After administration in vivo, MNPs are recognized by the body's main defense mechanism, the reticuloendothelial system (RES). This system plays an important role in removing foreign substances from the bloodstream. During this process, MNPs interact with plasma proteins produced by the reticuloendothelial system (RES), which play a key role in the clearance of nanoparticles from the bloodstream. Appropriate surface coatings can inhibit the adsorption of these proteins, thereby extending the circulation time of MNPs and improving their chances of reaching the target tissue.

MEDICAL AND TECHNOLOGICAL APPLICATIONS OF MAGNETIC NANOPARTICLES

Magnetic nanoparticles (MNPs) have gained significant interest in the scientific community because of their diverse applications They are particularly used in biomedicine Pankhurst et al. (2009), Pankhurst et al. (2003), drinking water purification Simeonidis et al. (2015), commercial applications Rai and Morris (2019), and magnetic storage media Sun et al. (2000), Ross (2001). In addition, MNPs are used in magnetic inks for inkjet printing Voit et al. (2003), biosensing technologies Dave and Gao (2009), Perez et al. (2002), and biosensor applications Rocha (2014), Miller et al. (2001). In biomedical fields, magnetic nanoparticles are important carriers for drug transport , drug delivery systems Jain et al. (2005) Chourpa et al. (2005), and as MRI contrast agents Boutry e t al.

(2006), Chouly et al. (1996). Furthermore, MNPs are widely used in magnetic hyperthermia treatments Ortega and Pankhurst (2013), Babincova et al. (2008), controlled fabrication of biomaterials Gupta et al. (2008), studies related to hearing Kuznetsov et al. (2001) and vision Voltairas et al. (2002), hippocampus research Schultheiss et al. (1999), Voltairas et al. (2002) gene therapy Scherer et al. (2002), Plank et al. (2003), magnetic twisting cytometry (MTC) Mijailovich et al.(2002), tissue engineering Dobson et al. (2002), Cartmell et al. (2002), and magnetic cell separation techniques Zborowski and Chalmers (2011).

Applications such as magnetic cell separation Zborowski and Chalmers (2011), Antfolk and Laurell (2017), magnetic hyperthermia Ortega and Pankhurst (2013), Schultheiss et al. (1999), Perigo et al. (2015), magnetic resonance imaging (MRI) Boutr et al. (2006), Chouly et al. (1996), and gene therapy Scherer et al. (2002), Plank et al. (2003) represent some of the biomedical fields in which magnetic nanoparticles (MNPs) are widely utilized Figure 1.

Figure 1

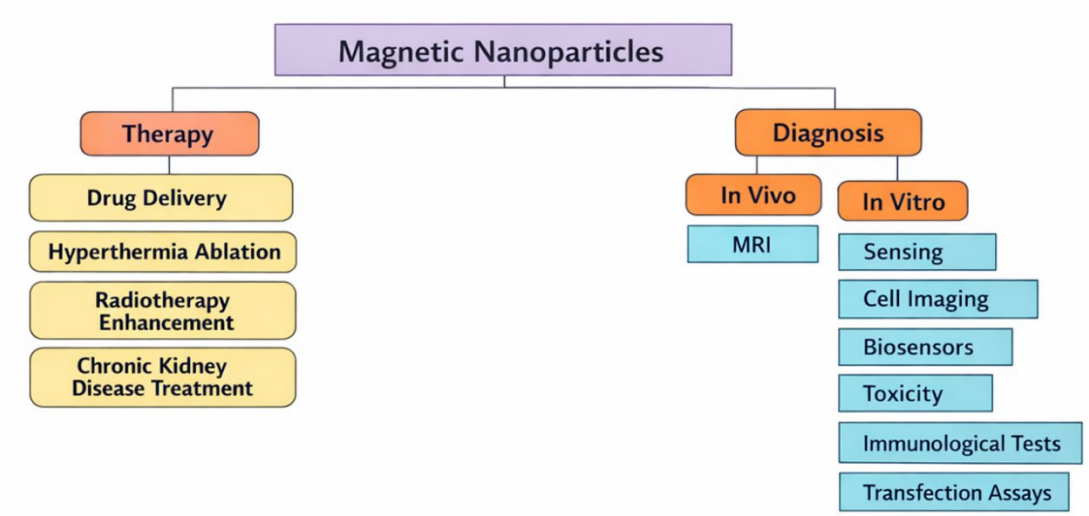

Figure 1 Role of Magnetic Nanoparticles in Biomedical Applications (MNPs)

Magnetic nanoparticles (MNPs) used in biomedical applications must possess several important properties, including strong magnetization, nanoscale particle sizes (<100 nm), and a uniform particle size distribution, non-immunogenicity, biocompatibility, water-based stability, and non-toxicity Laurent et al. (2008), Häfeli (2004).

MAGNETIC DRUG TARGETING

With the advancement of modern technology, nanotechnologies are now regarded as multimodal platforms capable of performing both diagnostic and therapeutic functions, commonly referred to as theranostics (Therapeutics + Diagnostics) Angelakeris (2017). Understanding the differences between normal cells and tumor cells is essential for the development of selective drug targeting strategies. The major reason for the failure in treating diseases like cancer is often associated with related not to drug discovery problems, but rather to drug delivery problems. Targeted delivery of the appropriate drug, at the correct place, time, and dosage, may greatly enhance treatment effectiveness for many diseases Since existing treatment options do not provide suitable solutions for every disease, advanced pharmacological technologies focus on developing patient-specific and targeted therapies designed to treat diseases effectively while minimizing toxicity Rai and Morris (2019). Advances in understanding the genetic alterations that transform normal cells into malignant cancer cells have led to the development of next-generation targeted therapies. By specifically targeting the biological abnormalities present in cancer cells, these therapies theoretically allow a greater number of normal cells to be spared from toxicity Pardee and Stein (2009).

Compared to bulk materials, nanomaterials possess distinct mechanical, electrical, optical, and magnetic properties. The utilization of these unique properties of nanomaterials helps address challenges related to the optimal location, timing, dosage, and delivery of therapeutic agents. Therapeutic approaches based on nanomaterials are designed to achieve improved treatment outcomes while requiring lower drug doses compared to conventional drug formulations Rai and Morris (2019).

In general, the main challenge in the cytotoxic approach commonly used in cancer therapy is how to minimize toxicity while maximizing anticancer activity Pardee and Stein (2009). To improve therapeutic outcomes without increasing toxicity, the drugs used should be relatively more specific to tumor cells than to normal tissues. Therefore, there is a growing need to develop new therapeutic strategies that may increase the efficiency of chemotherapy while limiting its side effect Developing strategies capable of selectively delivering drugs to diseased tissues while avoiding elevated concentrations in healthy tissues has become one of the

most active areas in cancer research. Among these approaches, Magnetic Drug Targeting (MDT) systems have gained significant attention as a promising strategy for cancer management treatment. In MDT systems, anticancer drugs are attached to magnetic nanoparticles (MNPs) Alexiou et al. (2011), Lübbe et al. (1996), Alexiou et al. (2002). The fundamental principle of this approach is to administer a lower dose of the anticancer drug to the patient while directing it to tumor tissue subjected to an external magnetic field , thereby maximizing the therapeutic effect. Thus, the primary objective of MDT is to reduce or eliminate the side effects of anticancer drugs while delivering the maximum possible drug dose to tumor tissues. One of the greatest advantages of MDT is its potential to minimize chemotherapy-related side effects by directing smaller drug doses directly to the target cancer tissue without prolonged systemic circulation Bilgili (2022).

The application of magnetic nanoparticles (MNPs) in biomedicine was initially reported by Gilchrist in 1957, who administered maghemite particles into the lymph nodes surrounding surgically excised tumors, thereby enabling selective inductive heating of the lymph nodes Gilchrist et al. (1957). However, in this study, Gilchrist did not propose the magnetic guidance or targeting of MNPs to specific sites. The first study related to magnetic targeting was conducted by Meyers in 1963, who demonstrated that small iron particles injected intravenously into the leg veins of dogs could be accumulated using an external magnet Meyers et al. (1963). Later, in 1975, Turner and Rand built upon Gilchrist's work and integrated this radiofrequency heating technique with embolization therapy Turner et al. (1975). These studies laid the foundation for research on the magnetic guidance of nanoparticles and magnetic hyperthermia, and they also inspired subsequent studies on drug targeting systems. The use of magnetic micro- and nanoparticles as therapeutic drug delivery carriers targeting specific areas of the body was first proposed in the late 1970s Senyei et al. (1978), Mosbach and Schröder (1979). Magnetic micro- and nanoparticles capable of binding cytotoxic drugs were developed by Widder and colleagues Widder et al. (1978). Lübbe et al. (1996) carried out the first clinical trials in humans on magnetic drug targeting, employing a ferrofluid (≈100 nm particle size) chemically attached to the anticancer drug epirubicin Lübbe et al. (1996). These studies are considered important milestones in the development of MDT applications.

Some of the anticancer drugs currently used in clinical practice have been successfully conjugated with magnetic components. Examples of studies in which magnetic nanoparticles (MNPs) are used in combination with anticancer drugs are presented in Table 2, along with their corresponding references. The table provides a non-exhaustive list of representative examples from the literature.

Table 2

Table 2 A Non-Exhaustive List of Studies İnvolving the İntegrated Use of Magnetic Nanoparticles (MNPs and Anticancer Drugs Bilgili (2022)

Antineoplastic Drug Group	MNP-Bound Drug Name	Reference
Cytotoxic Antibiotics	Doxorubicin	Liang et al. (2016) , Munnier et al. (2008)
(Anthracycline Group Drugs)	Mitoxantrone	Heidari Majd et al. (2013), Krukemeyer et al. (2012)
	Epirubicin	Xiong et al. (2017), Jalalian et al. (2013)
	Daunorubicin	Wang et al. (2011), Lai et al. (2009)
	Idarubicin	Gunduz et al. (2014)
Monoclonal Antibodies	Trastuzumab	Almaki et al. (2017)
	Rituximab	Song et al. (2020), Azadbakht et al. (2018)
	Cetuximab	Kaluzova et al. (2015), Zang et al. (2019)
	Bevacizumab	Lin et al. (2018), Savin et al. (2019)
Taksan	Paclitaxel	Chorny et al. (2010), Tarantash et al. (2018)
	Docetaxel	Ling et al. (2011), Panda et al. (2019)
Pilatin	Cisplatin	Babincova et al. (2008), Toro-Cordova et al. (2018)
	Carboplatin	Song et al. (2019), Davarpanah et al. (2018)
	Oxaliplatin	Jabalera et al. (2019), Liu et al. (2018)
	Vinblastine	Huang et al. (2019), Albermani et al. (2009)
Vinca Alkaloids and Analogues	Vincristine	Wu et al. (2016), Al-Musawi et al. (2021)
Other Cytotoxic Antibiotics	Bleomycin	Kavaz et al. (2010), Xu et al. (2013)
	Mitomycin	Ren et al. (2005), Yan et al. (2006)
Pyrimidine Analogues	Cytarabine	Shabani et al. (2019)
	Fluorouracil	Hashemi-Moghaddam et al. (2016), Ehi-Eromosele et al. (2017)
	Gemcitabine	Parsian et al. (2016), Viota et al. (2013)

	Capecitabine	Ghadiri et al. (2017), Afzali et al. (2020)
	Azacitidine	Liu et al. (2010)
	Uracil	Medine et al. (2011)
Nitrogen Mustard Analogues	Chlorambucil	Yuan et al. (2010)
	Melphalan	Shanmugavel and Karthikeyan (2014)
	Ifosfamide	Kong et al. (2015)
	Methotrexate	Attari et al. (2019), Kohler et al. (2006)
Folic Acid Analogues	Pemetrexed Disodium	Ak et al. (2020), Mohapatra et al. (2014)
	Imatinib	Karimi Ghezeli et al. (2019), Dahiya and Dureja (2016)
Protein Kinase Inhibitors	Gefitinib	Borg et al. (2020)

In addition to the antineoplastic drugs listed in Table 2, certain drugs such as tamoxifen, which is widely used in hormone therapy for breast cancer as an adjuvant treatment to prevent disease recurrence after breast surgery, have also been conjugated with magnetic nanoparticles (MNPs) Majd et al. (2013).

Compared with conventional chemotherapy, targeted nanomedicines provide reduced non-specific cytotoxicity and can be engineered to exhibit multiple functionalities Such delivery systems are designed to transport adequate amounts of the relevant drug, often toxic, to specific regions of the body while shielding it from the surrounding biological environment . Drug targeting systems facilitate the use of more effective diagnostic and therapeutic strategies for improved disease management, while also contributing to the reduction of overall healthcare costs Rai and Morris (2019). A common problem encountered in cancer therapy is low specificity, meaning that the drugs used lack selectivity and destroy not only cancer cells but also all rapidly dividing cells in the body, including normal cells Pardee and Stein (2009). This situation leads to several challenges associated with chemotherapy treatment. From a clinical effectiveness perspective, the focus of anticancer drug development in recent years has shifted toward targeted drug delivery, due to limitations of cytotoxic therapies such as dose-limiting toxicity and drug resistance. To improve therapeutic outcomes without increasing toxicity, strategies aimed at overcoming drug resistance and inhibiting tumor growth should be relatively more specific to tumor cells than to normal tissues. Therefore, numerous strategies have been developed to achieve high therapeutic efficacy with reduced toxicity and/or overcome multidrug resistance, including the use of adjuvant or neoadjuvant therapies, combination therapies with other drugs and treatment modalities, and more recently, the use of specific and selective targeting approaches Pardee and Stein (2009), Baykara (2016). Cancer cells may fail to respond to one or more anticancer drugs, or they may initially respond to treatment but later develop resistance. Drug resistance in cells is primarily associated with mutations occurring in cancer cells. Reduced activity in membrane transport mechanisms or mutations in proteins responsible for mediating the intracellular action of drugs can lead to the development of drug resistance Ullah (2008). Such unfavorable outcomes that limit treatment efficacy have necessitated the development of new approaches for cancer therapy.

Since organs are located deep within the body cavity (around 8 ± 12 cm away from the body surface , concentrating the magnetic flux density on the tumor region region becomes significantly more complex. To overcome this challenge, two main approaches have been proposed: (a) the use of larger particles, or (b) the use of a stronger magnetic field Alexiou et al. (2000).

Magnetic Drug Targeting (MDT) studies generally involve two multidisciplinary components. The first focuses on the synthesis of magnetic nanoparticles (MNPs) and drug conjugation, while the second involves the transport and delivery of the drug-loaded nanoparticles. The synthesis of MNPs includes several stages such as selection of synthesis methods and their reproducibility, management of particle size and size distribution, stabilization of the synthesized particles, evaluation of toxicity, and surface coating with biocompatible and stealth materials to prolong systemic circulation in the body. The final step in this process involves drug conjugation to the nanoparticle surface. The drug transport component involves studies related to the generation of high-gradient magnetic fields, he interaction between the applied magnetic field and particle size , the transport profiles of MNPs within blood vessels, magnetohydrodynamic effects, blood rheology, and the physiology of cancer cells Bilgili (2022).

The difference between the success and failure of chemotherapy depends not only on the drug itself but also on how effectively it is delivered to its target. Due to the relatively non-specific effects of chemotherapeutic agents, even under optimal conditions there is almost always a certain degree of toxicity in normal tissues. Hence, the ability to accurately deliver the antineoplastic agent to the tumor site is critically important , as it can reduce systemic toxic side effects resulting from general systemic distribution and allow the use of much lower drug doses Alexiou et al. (2000). One of the major disadvantages of most chemotherapeutic agents is their lack of specificity. After intravenous administration, therapeutic drugs circulate systemically and are distributed across the body. As a result, the drugs affect not only the target tumor cells but also normal, healthy cells, causing harmful side effects. As an example, the toxic effects associated with anti-inflammatory drugs used in patients suffering from chronic arthritis may result in the discontinuation of therapy However, if these treatments could be directed to a specific site, such as an individual joint it would be

possible to continue using these highly potent and effective agents without causing widespread systemic toxicity Pankhurst et al. (2003).

In magnetically guided therapy, a cytotoxic drug is linked to a biocompatible magnetic nanoparticle carrier. The drug–carrier complexes are administered intravenously and distributed through the circulatory system Upon entering the bloodstream, the particles are guided by externally applied high-gradient magnetic fields to accumulate at a specific target site in the body Figure 2 Once localized at the target region, the drug–carrier complex can release the drug through enzymatic activity or changes in physiological factors such as osmolality, temperature or pHor Alexiou et al. (2000), and can then be internalized by tumor cells Pankhurst et al. (2003).

Figure 2

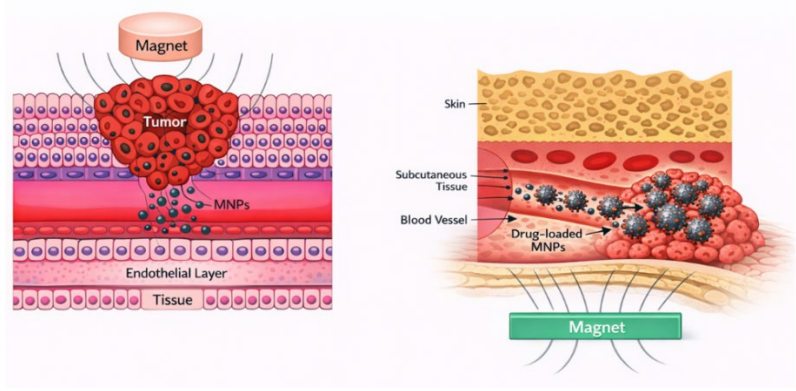

Figure 2 Cross-Sectional Schematic Representation of a Hypothetical Magnetic Drug Delivery System Bilgili (2022)

Magnetic drug delivery using particle carriers represents a highly effective method for delivering therapeutic agents o a targeted disease site. Very high levels of chemotherapeutic or radiological agents can be concentrated near the target region, such as a tumor, without producing toxic effects in nearby normal tissues or elsewhere in the body. Figure 3 demonstrates the concept of magnetic targeting by contrasting systemic drug distribution with magnetically guided delivery In magnetic drug targeting, a drug or therapeutic radioisotope is conjugated to a magnetic compound, administered into the patient's bloodstream, and subsequently localized at the target site by a strong magnetic field (see the arrow in Figure 3). Based on the type of drug used, the therapeutic agent may either be gradually released from magnetic carriers (e.g., chemotherapeutic drugs from MNPs) or induce a localized therapeutic effect, such as irradiation from radioactive microspheres or hyperthermia generated by magnetic nanoparticles. Consequently, large amounts of systemically circulating drugs can be substituted with substantially smaller doses specifically targeted to magnetically localized disease sites makes it possible to achieve effective treatment with significantly increased local drug concentrations, sometimes several times higher than conventional systemic delivery Häfeli and Pauer (1999).

Figure 3

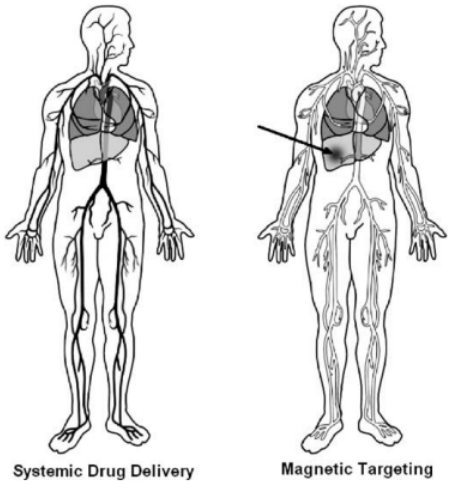

Figure 3 Concept of Magnetic Drug Targeting Häfeli (2004)

The therapeutic effectiveness is influenced by several physical parameters, such as magnetic field strength, magnetic field gradient, and the volumetric and magnetic characteristics of the particles. Since the carriers, namely ferrofluids, are generally administered through intravenous or intra-arterial injection various flow-related parameters also play an important role, such as blood flow velocity, circulation time, the level of ferrofluid concentration, and route of administration. In addition, physiological characteristics, including the depth of the target tissue, defined as the distance from the magnetic field source , the reversibility and binding strength between the drug and carrier, and tumor volume also significantly influence the efficiency of the therapy Pankhurst et al. (2003), Lübbe et al. (1996).

BARRIERS TO DRUG TARGETING

Administered drugs must first overcome the barriers encountered within the circulatory system . The amount of drug that reaches the appropriate target region through circulation subsequently encounters cellular barriers at the target site. As a result, only a small fraction of the drug is internalized by the cells, contributing to the therapeutic effect.

Following intravenous administration, nanoparticles are quivkly surrounded by circulating molecules, including plasma proteins once they enter the bloodstream. This process is termed opsonization and significantly influences the fate of the injected particles Davis (1997). Under normal conditions, opsonization facilitates recognition of the particles by RES, which constitutes the primary defense system of the body. The RES consists of specialized phagocytic cells related to the connective tissue network of organs such as the liver, spleen, and lymph nodes Kreuter (1994). Kupffer cells in the liver, along with macrophages in the spleen and circulating macrophages to a lesser extent, play an important role in the removal of opsonized particles from the bloodstream. Physicochemical characteristics that affect the opsonization process including particle size, surface charge density, and the hydrophilic–hydrophobic balance have been thoroughly examined in both liposomal and polymer-based nanoparticle systems Generally, carrier surfaces that are smaller, more neutral, and more hydrophilic show prolonged plasma half-lives. Considering the size effect, it has been suggested that changes in surface curvature can affect the level and/or type of opsonin adsorption Mornet et al. (2004). In intravenous administration, colloidal drug carriers are typically cleared from the bloodstream within a few minutes, and their final biodistribution is generally 80–90% in the liver, 5–8% in the spleen, and 1–2% in the bone marrow Mornet et al. (2004). Consequently, the in vivo or ex vivo application of nanoparticles requires appropriate surface functionalization to ensure that the particles remain non-toxic, biocompatible, and stable against clearance by the reticuloendothelial system (RES) Berry and Curtis (2003).

Figure 4

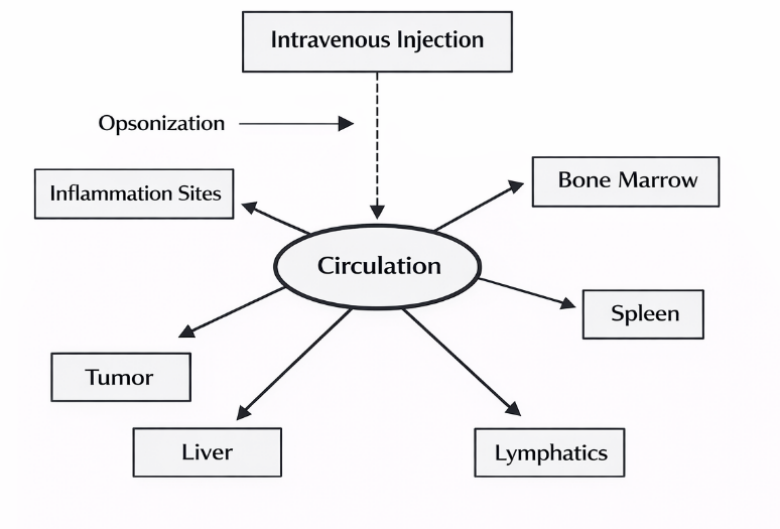

Figure 4 Following Administration, the Particles are Quickly Coated by Plasma Proteins Through Opsonization Berry et al. (2003)

Nanoparticles with hydrophobic surfaces are efficiently coated by plasma components and are therefore quickly eliminated from circulation, whereas more hydrophilic particles can resist this coating and are removed more slowly from the bloodstream According to the literature, the most frequently used coatings include dextran derivatives, polyethylene glycol, polyethylene oxide, poloxamers, and polyoxamines Lacava et al. (2001). Dense polymer brushes serve to inhibit opsonization, which allows nanoparticles to remain in the bloodstream for longer periods Brigger et al. (2012), Shen et al. (1996), Gref et al. (1994). Another strategy to avoid uptake by the reticuloendothelial system is to minimize particle size Gref et al. (1994), Moghimi et al. (2001). However, despite these

approaches, coated nanoparticles are still not able to completely avoid uptake by the reticuloendothelial system Gaur et al. (2000) Berry and Curtis (2003).

The major challenges associated with systemic drug administration and the barriers that anticancer drugs must overcome to reach cancer cells in vivo can be summarized as follows Brigger et al. (2012), Torchilin (2000):

- physiological barriers (cell-independent mechanism),
- cell-based drug resistance mechanisms
- resistance to drug therapy resulting from the biodistribution, biotransformation, and elimination of anticancer drugs within the body,
- lack of drug-specific affinity toward pathological sites,
- the requirement for a large quantity of drug doses to accomplish the goal of sufficiently elevated local concentrations, and
- non-specific toxic effects and other adverse reactions associated with dosages

The effectiveness of anticancer drugs can also be considerably influenced depending on the route of administration. For instance, orally administered therapeutics may lose activity in acidic environments or undergo absorption and metabolism in the liver and gastrointestinal tract, which can significantly reduce systemic bioavailability. When nanoparticles larger than 10 nm are administered intravenously (i.v.), they may lead to non-specific deposition of therapeutic agents in the reticuloendothelial system of the liver and spleen , which reduces the quantity of circulating therapeutic agents in the body. In contrast, therapeutic agents with sizes smaller than 5 nm, similar to small-molecule drugs, can be rapidly cleared from the bloodstream through renal and hepatic elimination. Interactions between therapeutic agents and serum proteins can influence their biodistribution, pharmacokinetic behavior, bioactivity, and targeting efficiency of therapeutic agents and nanoparticle drug. Large macromolecules such as proteins and antibodies, as well as viral vectors and nanoparticles are not readily cleared by the kidneys and thus display longer circulation times in the bloodstream, allowing greater delivery of the drug to tumor sites. The bioavailability of nanoparticle-based therapeutics is also affected by macrophages. However, when the size of the therapeutic agent exceeds approximately 200–400 nm, the particles can be rapidly cleared from circulation due to enhanced macrophage uptake. One of the most important challenges in chemotherapy often causes severe systemic toxicity, which restricts the maximum dose that can be given to patients and often leads to harmful side effects that affect patient health and well-being. In addition, small-molecule chemotherapeutic drugs are rapidly cleared from the bloodstream, typically exhibiting short circulation half-lives of approximately 15–30 minutes. Drug specificity can be improved by delivering therapeutics to tumors using antibody-based targeting strategies. Due to their relatively large size, antibody-based therapeutics generally have longer half-lives and higher delivery efficiency to tumors compared with conventional chemotherapeutic drugs. Therapeutic agents may also be administered via nanoparticle-based delivery systems. Nanoparticle drug carriers, typically smaller than 100–200 nm, can accumulate in tumor tissues via the enhanced permeability and retention EPR effect, which allows nanoparticles to pass through leaky tumor vasculature and accumulate in the perivascular region (the area surrounding blood vessels) Rai and Morris (2019).

MAJOR CHALLENGES ASSOCIATED WITH MAGNETIC DRUG TARGETING

The major problems related to systemic drug administration include the biological distribution the systemic distribution of pharmaceuticals, the lack of specificity toward pathological sites, the need for high drug doses to obtain adequate local concentrations, and non-specific toxicity with additional adverse effects. Targeted drug delivery strategies seek to overcome many of these limitations Torchilin (2000). One of the fundamental approaches to drug targeting is magnetic targeting, which involves guiding a drug immobilized on magnetic materials using an external magnetic field Berry and Curtis (2003).

For magnetic drug targeting (MDT) to be successful, it must be both safe and effective, meaning that the maximum therapeutic effect should be achieved with a minimal amount of magnetic particles, enabling the drug to be efficiently delivered and transported to the target site.

From a biophysiological perspective, several parameters related to the ferrofluid-bound drug complex and the applied magnetic field plays a critical role including:

1) size of the particles
2) surface properties of the nanoparticles,
3) ferrofluid particle concentration,
4) properties of the carrier fluid,
5) the reversibility and binding strength between the drug and ferrofluid (desorption properties)
6) administration route to the organism
7) injection/infusion dutation time and rate,
8) the magnetic field configuration and strength

9) He time period of magnetic field application

The patient's physiological parameters also play an important role and include:

1) body size, body weight, and body surface area
2) the volume of circulating blood
3) cardiac output and overall vascular resistance,
4) blood circulation time, (etumor dimensions and anatomical location
5) tumor volume and location,
6) vascularization of the tumor, and
7) blood flow within the tumor.

Since Physiological parameters are influenced by the size of the organism, the type of the characteristics of the ferrofluid–drug complex, the type of the characteristics of the ferrofluid–drug complex parameters for the effectiveness of MDT are the ferrofluid bioavailability and the in the in vivo drug release time Lübbe et al. (1996).

To understand this new pharmacological approach and its mechanism of action, several factors must be considered, which can be grouped into different categories. First, there are ferrofluid-related parameters, including the particle dimensions, surface characteristics, the concentration and volume of the carrier, together with magnetic field strength, which influence the characteristics of the drug–particle interaction. Second, there are factors related to delivery into the organism, including the pathway of administration of administration, as well as the injection rate and duration or infusion. Finally, the physiological characteristics of the organism must be considered, encompassing factors such as body weight, blood volume, cardiac output, circulation time, tumor volume, tumor location, and tumor blood flowLübbe et al. (1996), Lübbe et al. (1996). Therefore, moving from animal experiments to human clinical trials is a complex process and presents significant challenges Berry and Curtis (2003).

Several challenges are related to magnetically targeted drug delivery Pankhurst et al. (2003), Tartaj et al. (2003), Lübbe et al. (1996), Häfeli (2004). These challenges include:

1) The risk of blood vessel embolization at the target site caused by the accumulation of magnetic carrier,
2) Challenges associated with scaling up from animal models, resulting from the larger distance between the target site and the external magnet,
3) following release, the drug is no longer guided by the magnetic field,
4) potential adverse toxic effects of magnetic carriers,
5) forces acting on the particles within the bloodstream,
6) magnetic forces created by the externally applied magnet,
7) Concentration of magnetic nanoparticles (MNPs),
8) Tumor volume,
9) Reversibility of the drug–carrier binding,
10) Tissue depth,
11) Circulation time, and
12) Route of administration (e.g., intravenous (i.v.) or intra-arterial (i.a.)).

Nevertheless, recent experimental and preclinical research suggests that these limitations may still be addressed, improve drug retention through magnetic targeting, and simultaneously address potential safety concerns Pardee and Stein (2009), Lübbe e t al. (1996).

CONCLUSION

The treatment of cancer, primarily with chemotherapy, has proven to be difficult and often not only has poor selectivity but also has serious side effects. Chemotherapeutic drugs are administered in a systemic manner, through the circulatory system, damaging healthy cells in the body and is a key contributor to the limited efficacy of therapy. As the field of cancer research has emphasized controlled drug delivery systems in recent years, the design of such systems has increasingly been important. Due to their small size, high surface-to-volume ratio and controllability using external magnetic fields, magnetic nanoparticles have gained increasing importance in biomedical applications. Notably, nanoparticles based on iron oxides, such as magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), are frequently employedin magnetic drug targeting applications due to their biocompatibility and superparamagnetic character. The functionalization of such nanoparticles with biocompatible polymers or inorganic coatings yields stability in biological environments, thereby making their surface friendly to the application of anticancer drugs. MDT (Magnetic Drug Targeting) technique enables the targeted application of drugs loaded with to the targeted sites of tumor with assistance of an external magnetic field. By this approach, high concentrations of drug can reach the target site and systemic toxicity and side effects are diminished to

an extremely small extent. Magnetic NPs not only represent drug delivery devices but also find applications in other several biomedical applications, including magnetic resonance imaging (MRI), magnetic hyperthermia, biosensors, gene therapy, and tissue engineering But numerous technical and biological obstacles need to be surpassed to ensure the translation of magnetic drug-targeting technology into clinical application. Specifically, the feasibility of nanoparticle biocompatibility, toxicity, rapid clearance by the reticuloendothelial system, penetration of magnetic fields into deep tissues and amount of nanoparticle accumulation at the specific target are issues that need ongoing research. These findings demonstrate the remarkable potential of magnetic nanoparticle-based drug delivery systems that could lead to the development of targeted and more effective therapeutic strategies to address the issues of cancer. Thanks to the latest trends in nanotechnology, materials science, and biomedical engineering, it is anticipated that using magnetic drug targeting systems can play an increasingly important role in producing safer, more effective, personalized treatments for cancer.

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