TARGETED DRUG DELIVERY USING MAGNETIC NANOPARTICLES: A REVIEW

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Abstract: Continuing improvement in the pharmacological and therapeutic properties of drugs is the driving force of the revolution in novel drug delivery systems. Amongst the plethora of avenues explored for the new ways of targeted drug delivery, magnetic nanoparticles (MNPs) grabbed foremost attention offering local drug delivery, reduced toxic reactions and controlled drug release for prolonged period of time addressing problems of healthy tissue damage and drug wastage. Due to their unique purposes, magnetic nano-particles have been of great interest. An attempt is made herein to review the concept of MNPs, their advantages, methods of preparation, characterization, applications in drug delivery. Usage of MNPs depends largely on the preparation process to select optimal conditions and election of agents to modify their surface. This review deals with use of MNPs in Tumor hypoxia or tumors in low oxygen concentration as well as magnetic drug targeting using core–shell magnetic carrier nano-particles (Iron and Gold nano-particles) loaded with anti-cancer drugs. This review deals with the disadvantages of MNPs and how they can be overcome. It focuses on exemplifying different drug formulations formulated into MNPs. Future prospective, challenges in drug delivery and scope of MNPs are briefly discussed.

Keywords: Magnetic nanoparticles (MNPs), controlled drug release, drug wastage, Tumor hypoxia, core–shell, magnetic drug targeting, super-paramagnetic iron oxide nanoparticles (SPIONs)

1. Introduction

Magnetic drug delivery system works on the delivery of magnetic nanoparticles (MNPs) loaded with the drug, controlled by magnetic field which is applied externally, to the site of action. However the development of this system mandates that the nanoparticles behave magnetic only under the influence of external magnetic field and are rendered inactive once the external magnetic field is removed. These properties are acquired by very small nanoparticles in the range less than 10 nm. The large magnetic particles possess multi domain structure. Below a critical size, the energy cost to produce domain walls increases than to support a single domain state. Magnetic nanoparticles show phenomena such as super-paramagnetism, irreversibility in high field, high saturation field etc. There are varied industrial and biomedical applications. They are used in vivo as well as in vitro applications. The use of MNPs is a very upcoming field in targeted drug delivery systems and we shall first look at the mechanism and formulation of MNPs and

later their applications and advantages and disadvantages. [4]

2. Synthesis of magnetic nanoparticles

Over the past decades much research has been done on synthesis of iron oxide magnetic nanoparticles, and many approaches have described efficient synthetic routes to produce the shape-controlled, stable and bio-compatible magnetic nanoparticles. The most common methods include co-precipitation, thermal decomposition, polyol synthesis, micro emulsions, vapour method and frame spray synthesis. In addition to this, these nanoparticles can also be prepared by the other methods such as sonochemical and electrochemical synthesis, microorganism or bacterial synthesis (magnetotactic and iron reducing bacteria). There are two major steps involved in MNP synthesis: a) MNP core fabrication, followed by b) Coating of SPIONs.

2.1. MNP core fabrication

The magnetic functionality of MNPs for magnetic resonance imaging is dictated by the composition, size, and shape of magnetic cores. These nanoparticle cores are made from different materials and are of various sizes, shapes, uniformities, and magnetic properties. Specifically, MNPs have been formed from pure iron and cobalt metals, alloys such as cobalt-platinum ($CoPt_3$), iron-platinum (FePt), iron-zinc (FeZn) and from iron oxides, including magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3). The iron oxides have also been doped to enhance their magnetic properties to form M-Fe_2O_4 structures where M is a metal ion of oxidation state +2, such as manganese, iron, cobalt or nickel. While these magnetic nanoparticles make very good magnetic resonance contrasting agents. Nanoparticles, which contain Cobalt, Nickel and Manganese, are potentially toxic in nature. This makes them poor candidates for clinical use until they are coated with advanced coatings and chelating agent. Alternatively, the non-doped iron oxides degrade to their non-toxic iron and oxygen components, making them particularly attractive as nanoparticle cores. Superparamagnetic iron oxide nanoparticles (SPIONs) can be fabricated by either top-down (mechanical attrition) or bottom-up (chemical synthesis) approaches. For uniform composition and size of nanoparticles chemical routes are preferred [7]. Different chemical methods of SPION synthesis:

2.1.1. Co-precipitation

This is one of the most promising methods because of its simplicity and productivity. It is widely used for biomedical applications because of the ease of implementation and need for less hazardous materials and procedures. The reaction principle is simply as follows:

$$Fe^{2+} + 2Fe^{3+} + 8OH^- \longleftrightarrow Fe(OH)_2 + 2Fe(OH)_2$$

$$Fe(OH)2 + 2Fe(OH)_2 \longrightarrow Fe_3O_4 + H_2O$$

There are two main methods for the synthesis in solution of MNPs. First method makes use of oxidation of ferrous hydroxide solutions. For eg. MNPs of narrow size distribution in the range 30-300 nm can be obtained from

Fe(II) salt, a base and a mild oxidant like nitrate ions. The other method consists of complexing ferrous and ferric ions in aqueous media yielding homogenous spherical magnetite particles. By adjusting the pH and the ionic strength, the particles size can be controlled. The size decreases as the pH and ionic strength increases. Both the parameters affect the chemical composition of the surface and consequently the electrostatic surface charge. Under these conditions, magnetite particles are formed by aggregation of primary particles formed within a $Fe(OH)_2$ gel. This ordered aggregation gives rise to crystalline particles. The difficulties in preparing Fe_3O_4 MNPs by chemical co-precipitation are the agglomeration tendency of particles because of extremely small particle size leading to great specific surface area and high surface energy.

2.1.2. High temperature decomposition of organic precursors

The decomposition of organo-iron compounds in the presence of hot organic surfactants has yielded markedly improved samples with better control of size, narrow size distribution and better crystallinity of individual and dispersible magnetic iron oxide nanoparticles. Biomedical applications like MRI, magnetic cell separation or magneto-relaxometry strongly depend on particle size and thus magnetic nanoparticles produced by this method could be potentially used for these applications.

2.1.3. Polyols

Fine metallic particles can be obtained by reduction of dissolved metallic salts and direct metal precipitation from a solution containing a polyol. Liquid polyol acts as the solvent for the metallic precursor, reducing agent and as a complexing agent for the metallic cations.

2.1.4. Microemulsions

Water in oil micro-emulsion systems, fine micro droplets of the aqueous phase trapped within assemblies of surfactant molecules dispersed in a continuous oil phase. Average size in the range of 4 to 12 nm can be obtained from this method.

2.1.5. Aerosol/Vapour methods

This includes spray and laser pyrolysis. Spray and laser pyrolysis have been shown to be excellent techniques for the direct and continuous production of well-defined magnetic nanoparticles under exhaustive control of experimental conditions. Spray pyrolysis is a process in which solid particles are obtained by spraying a solution into a series of reactors. In these reactors aerosol droplets undergo evaporation, causes evaporation of the solvent and solute gets condensed within the droplet. Then precipitated particles are subjected to higher temperatures for drying and thermolysis. This results into formation of microporous solids, which finally aggregate to form dense particles. This method is used to obtain finely dispersed particles of predictable shape, size, and composition. The resulting powders consist of spherical particles. Their final diameter can be predetermined from diameter of the original droplets. The method is simple, rapid, and continuous, so it offers certain advantages over other techniques. Laser pyrolysis involves heating of flowing mixture of gases with a continuous wave CO_2 laser, which initiates and sustains a chemical

reaction. Above a certain pressure and laser intensity, a critical concentration of nuclei is achieved and it leads to homogenous nucleation of particles. Advantages are

- Small particle size
- Narrow particle size distribution
- Nearly absence of aggregation.
- Rapid, continuous method.
- Simple precipitation from a homogenous solution [9].

2.1.6. Flame spray synthesis

Magnetic iron oxide nanoparticles have been prepared by flame spray pyrolysis (FSP) under controlled atmosphere. Synthesis of Fe_2O_3 (Hematite), Fe_3O_4 (Magnetite) and FeO (Wustite) particles is possible by this method. The oxidation state of iron is controlled by changing the fuel to air ratio during combustion as well as by controlling the valence state of the applied iron precursor. Maximum magnetisation was achieved for a mixture of maghemite and magnetite. [11]

2.2. Coating of SPIONs

SPIONs are stable at higher and lower pH solutions, but to use in vivo it requires that SPIONs to be coated. These surface coatings typically composed of polymers. Functions of these coatings are as follows:

1. To protect against iron oxide core agglomeration.
2. To provide chemical vehicles for the conjugation of drug molecules, targeting ligands, and reporter compounds
3. To limit non-specific cell interactions. Additionally, polymeric coatings have been engineered to enhance SPION pharmacokinetics, endosomal release, and tailored drug loading and release behaviors.

Following group of polymers have been used to serve these coating functions [29]:

- Polyethyelne Glycol (PEG)
- Dextran
- Chitosan
- Polyethyleneimine (PEI)
- Liposomes and Micelles
- Copolymers

Coating materials and immobilization strategies each influence the magnetic properties of MNPs in different ways.

3. Mechanism of action of magnetic nanoparticles

The superparamagnetic properties of the magnetic micro and nanoparticles have opened promising new perspectives for in vivo application. The magnetic nanoparticles as drug carriers provide huge opportunities in cancer treatment. The use of such carriers in targeted therapy considerably reduces the side effects of conventional chemotherapy. A novel carrier system allows for intravenous drug delivery and the local accumulation of chemotherapeutic agents which is comparable to that achieved by the administration of a 100-fold higher dose of the drug. The magnetic drug targeting enables precise location of drug in the body with the use of external magnetic field. After the vascular injection, the particles can be transported and concentrated at desired location with the help of an external magnet. For drug delivery application the optimal size of nanoparticles should be in the range from 10 to 200 nm. The size below 200 nm allows for systematic

administration in circulation system and also into targeted tissue. It enhances the ability of nanoparticles to evade the biological particulate filters, such as blood brain barrier or reticuloendothelial system. To date, magnetic drug targeting has been studied mostly in pre-clinical models for cancer therapy with intravascular administration of chemotherapeutics. The "magnetic epirubicin" with doses in the range of 5-100mg/m^2 was infused intravenous over 15 min into a vein located contra laterally to the tumor in patients with advanced and unsuccessfully pretreated metastatic breast cancer, chondrosarcoma and squamous cell carcinoma. The neodymium magnets were large 8x4x2cm or 3x3x1cm and were kept at a distance of 0.5 cm to tumor surface [33]. The clinical trials provided the important information about the conditions of drug release, distribution and mechanism of action. It was concluded that the size of magnetic particles should be close to 1μm to increase of their accumulation in tumor site and, consequently, the concentration of the drug. The better optimization of ionic binding epirubicin on to the surface of magnetic nanoparticles also can improve the drug release in physiological parameters. Hence, a new group of novel nano- and micro magnetic particles consisting of various synthetic and natural matrices were investigated. The magnetic dug targeting approach offers a new opportunity to treat malignant tumors locoregionally. The treatment of squamous cell carcinoma in rabbits with nanoparticles covered with modified starch to which the mitoxantrone was ionically bound, caused complete and permanent remission of the cancer compared with control group. The advantage of ionically bound mitoxantrone is that the anticancer agent is able to desorb from the magnetic caries after the 30 min (half-time). Determination of time of desorption is very important because the ferro-fluids have to be transferred to the tumor region by the magnetic field. Next, the drug must dissociate to act within the tumor. Generally, the total release of drug from the magnetic carriers is recommended at less than 1 hour. The 100 nm particles size and strong magnetic field (1.7 Tesla) are optimal for efficient treatment of smaller animals such as mouse or rat. However, the appropriate magnetic field strength and particle size for treatment of deep body cavities and human cancer has to be optimized.

The use of magnetic particles can significantly improve hyperthermia cancer treatment. This therapy involves raising the temperature of the target tissue to 43-46°C. In this conditions its sensitivity to chemo- and radiotherapy increases and may additionally stimulate activities of the host immune system. The problem with hyperthermia therapy is the heating of large area of tissue or body in general, not only the tumor region. The healthy tissues adsorb microwave, laser and ultrasound energy which can cause burns and blisters. Magnetic hyperthermia is one of the anti-cancer approaches based on the introduction of ferro - or superparamagnetic particles into the tumor tissue.

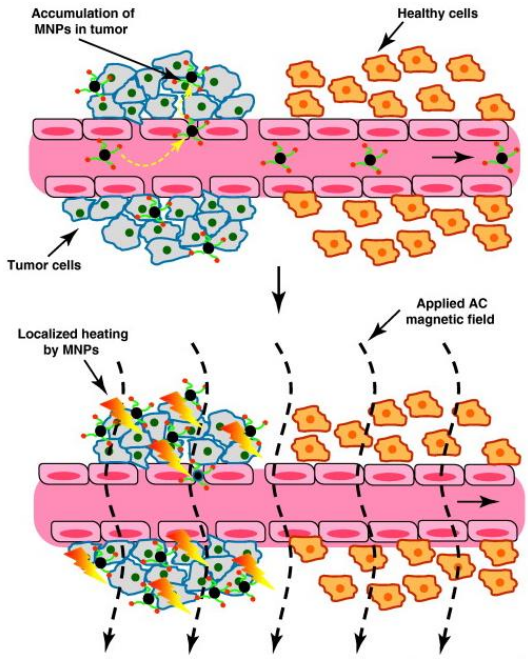

Figure 1: Scheme of magnetic hyperthermia treatment of affected tissue; (a) accumulation of magnetic nanoparticles (MNPs) by the magnet at the tumor site; (b) exposition of tumor cells to an altering current (AC) magnetic field

Aerosol drug delivery system allows for the pulmonary drug administration delivery of therapeutic agents [32]. The non-invasive drug delivery is mainly used for treatment of lung disorders such as asthma, chronic obstructive pulmonary disease [31] and lung cancer. The high and effective drug concentration at disease site in standard chemotherapy in lung cancer with cytotoxic drugs is particularly difficult. The problem is that the cytotoxic potency of chemoterapeutics is not limited to cancer region. The high efficiency of aerosol droplets comprising SPIONs in combination with external magnetic gradient field was confirmed by computer aided simulation and demonstrated experimentally in mice. The anatomy of human lung also allows for the implementation of magnetosols in targeted therapy. The concept of targeted delivery of magnetic aerosol droplets to the lungs is given in Figure 2.

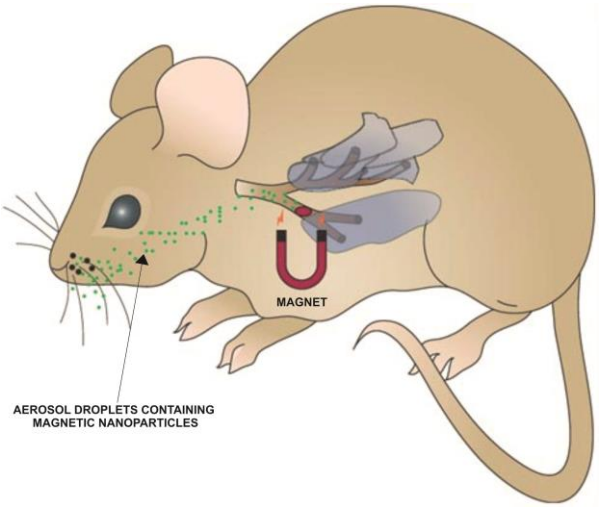

Figure 2: The concept of non-invasive delivery of magnetic aerosol droplets to the lungs and concentrated to the target site (tumor) with the help of magnet

4. Applications

Magnetic nanoparticles have attracted the attention of scientific community as potential materials for carriers of drug, gene delivery, DNA, biomolecules separation, hypothermal treatment of tumours, contrast agents for magnetic imaging, information storage, catalysis and biomedical uses. They can be used both *in vivo* and *in vitro* to great effect. Endomagnetics has real promise for oncology, hematology, drug delivery and stem cells therapies. The different applications of magnetic nanoparticles include:

- Use of superparamagnetic iron oxide nanoparticles, coated with polyvinyl alcohol (PVA–SPION), and its fluorescently functionalized analogue

can be used in treatment of inflammatory joint diseases.

- Non-invasively targeting respiratory tract deposition of high aspect ratio aerosols loaded with magnetic nanoparticles by controlling particle orientations through magnetic field alignment to specific locations within the lung.
- Effective targeting of selective tissue markers has been demonstrated using derivatized SPIONs [4].
- Development of hyaluronic acid-Fe_2O_3 hybrid MNPs for targeted delivery of peptides.

Conventional methods of cancer therapy such as surgery, radiation and chemotherapy are either invasive or have undesirable side effects. Magnetically directed drug delivery using MNPs, optionally combined with hyperthermia is a very attractive technique to improve the performance of current methods of cancer treatment. The strategy is to concentrate the drug loaded MNP carriers at the tumor site by using an external magnetic field. The drug can be released from the carrier either via enzymatic activity or changes in physiological conditions such as pH, osmolality, temperature etc [34]. If the MNPs are coated with a golden shell, the shell can provide advantages such as computed tomography (CT) contrast. It can be heated by near infrared (NIR) light radiation; the resulting heat can destroy tumour cells without damaging healthy tissues. This is known as hyperthermia. The MNPs are injected into the body and guided to the site of action by an external magnet. Then a strong external magnetic field (alternates 10,000 times per second) is applied which leads to production of heat. This heat thus generated kills the tumor cells, however leaves the healthy cells unharmed. Thus, MNPs can prove to be of great use in cancer therapy. However, it is still at a very nascent stage and a lot has to be done before this can actually be put to practical use.

5. Disadvantages

The small size of the particles brings in the problem of toxicity, due to smaller sizes, their action becomes uncontrollable as they tend to accumulate at site of action. In regenerative medicine cells have to be labeled with specific cell receptors only after which they can be implanted within the body. Their prolonged use reduces the efficiency of the therapy due to degradation of carriers. Toxic cellular effects are observed and manifested into many metabolic disorders which further jeopardies the efficiency. Migration of nanoparticles could pose major threat due to risk of affecting the major organs which could trigger an immunological or an inflammatory response by the body. These are all highly undesirable consequences. [35].

6. Conclusion

The use of magnetic nanoparticles as drug delivery system is still defined by its biocompatibility and selective targeting to the desired cell or tissue, externally applying a constant magnetic field. Magnetic Nanoparticles offer to open new vistas in the area of drug delivery, and they promise as a prudent tactic to drug delivery problems when

the problems of toxicity, localization and cost are addressed. This technology will not only minimize invasive procedures, but also reduce the side effects to healthy tissues, which are the two primary concerns in conventional cancer therapy. The gold coated nanoparticles are promising candidates as magnetic drug carriers for tumour targeted delivery. The field of magnetic drug delivery is still at infancy and there is still a lot of scope so as to carry it from the bench top to the clinic, addressing all issues facing it.

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