Magnetic nanoparticle drug delivery systems for targeting tumor

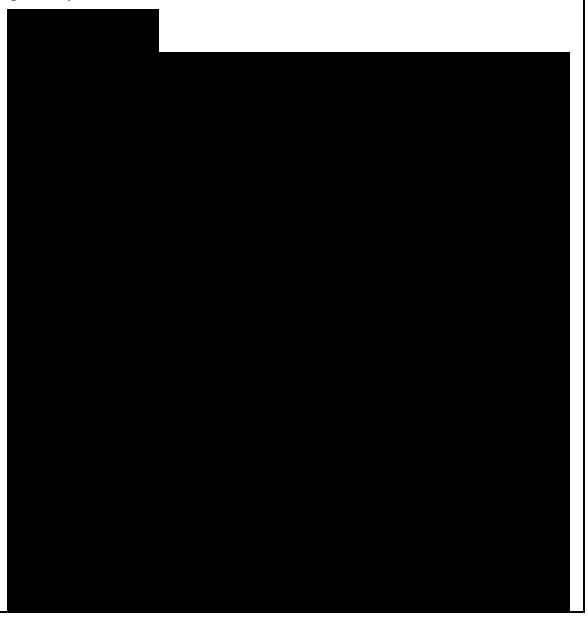
Abstract Tumor hypoxia, or low oxygen concentration, is a result of disordered vasculature that lead to distinctive hypoxic microenvironments not found in normal tissues. Many traditional anti-cancer agents are not able to penetrate into these hypoxic zones, whereas, conventional cancer therapies that work by blocking cell division are not effective to treat tumors within hypoxic zones. Under these circumstances the use of magnetic nanoparticles as a drug delivering agent system under the influence of external magnetic field has received much attention, based on their simplicity, ease of preparation, and ability to tailor their properties for specific biological applications. Hence in this review article we have reviewed current magnetic drug delivery systems, along with their application and clinical status in the field of magnetic drug delivery.

Introduction

Hypoxia is a pathological condition in which the whole body or specific tissues are deprived of an adequate oxygen supply. This mismatch between oxygen supply and its demand at the cellular level can be due to various reasons such as cardiac arrest, strangulation, high intake of carbon monoxide, exercise, or reduced vasculature as seen in tumor cells (Brahimi-Horn et al. 2007). Of various types of hypoxia discussed above, tumor hypoxia is

Các hệ thống dẫn truyền thuốc đến mô mục tiêu bằng hạt nano từ

Tóm tắt Giảm ôxy huyết khối u, hoặc nồng độ oxy thấp là hệ quả của hiện tượng rối loạn mạch máu dẫn đến sự hình thành các vi môi trường thiếu oxy đặc biệt (hiện tượng này không xảy ra trong các mô khỏe mạnh). Nhiều thuốc chống ung thư thông thường không thể xuyên qua những vùng thiếu oxy này, trong khi đó, các phương pháp điều trị ung thư thông thường dựa trên cơ chế ngăn chặn sự phân chia tế bào không thể điều trị hiệu quả các mô trong vùng thiếu oxy. Trong những trường hợp này, người ta đang suy nghĩ đến việc sử dụng các hạt nano từ làm hệ thống dẫn truyền thuốc dưới tác động của trường từ ngoài, do phương pháp này đơn giản, dễ chuẩn bị và có thể dễ dàng thay đổi các tính chất của chúng cho từng ứng dụng sinh học cụ thể. Do đó trong bài báo tổng quan này, chúng tôi sẽ trình bày về các hệ thống dẫn truyền thuốc từ tính hiện tại cùng với ứng dụng của chúng và các nghiên cứu lâm sàng trong lĩnh vực dẫn truyền thuốc từ tính.



one of the most important pathological conditions for tumor therapy and diagnosis. In general, a tumor environment is characterized by a highly proliferating mass of cells that grows faster than the vasculature creating an avascular environment deficient in oxygen (Brahimi-Horn et al. 2007). Such hypoxic zones have been postulated to have a reduced response to radiotherapy due to a decrease in oxygen free radicals that are required to produce enough DNA damage result in cell death (Moeller et al. 2007). In addition, cells of these regions are considered to be chemotherapy-resistant due to limited delivery of drugs via the circulation (Brahimi-Horn et al. 2007). In such cases, the delivery of nanoparticles or drug loaded nanoparticles via angiogene- sis is also not much effective due to the formation of neovessels which are often distorted and irregular and thus less efficient in oxygen, nutrient transport and drug delivery. This lack of efficient transport system in the body to deliver drug to the tumor cells has recently attracted lot of consideration and lot of delivery vehicles has been postulated. Of which magnetic nanoparticles as a drug delivery system has received considerable attention.

Magnetic drug delivery system works on the delivery of magnetic nanoparticles loaded with drug to the tumor site under the influence of external magnetic field (Fig. 1). However, development of this

delivery 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. Fortunately, such magnetic properties are usually acquired by very small nanoparticles within the size range of less than 10 nm, due to the presence of single domain state. In contrast, large magnetic particles are well known for their multidomain structure. These multidomain states are separated by domain walls, as depicted in Fig. 2. This formation of the domain walls is energetically favorable if the energy consumption for the formation of the domain walls is lower than the formation of single domain states (Gubin 2009). As the dimensions of the particles are reduced, it costs more energy to create a domain wall than to support a

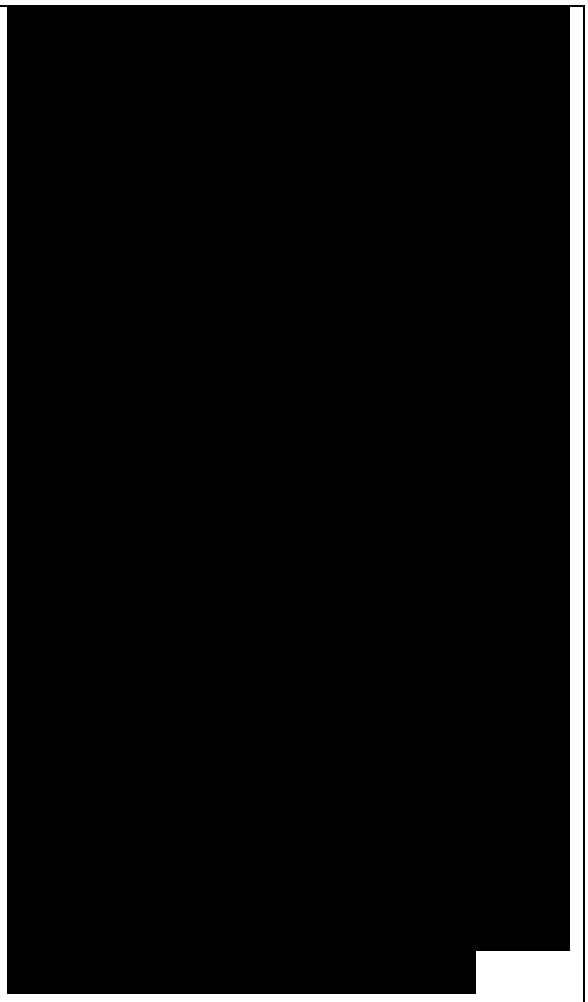
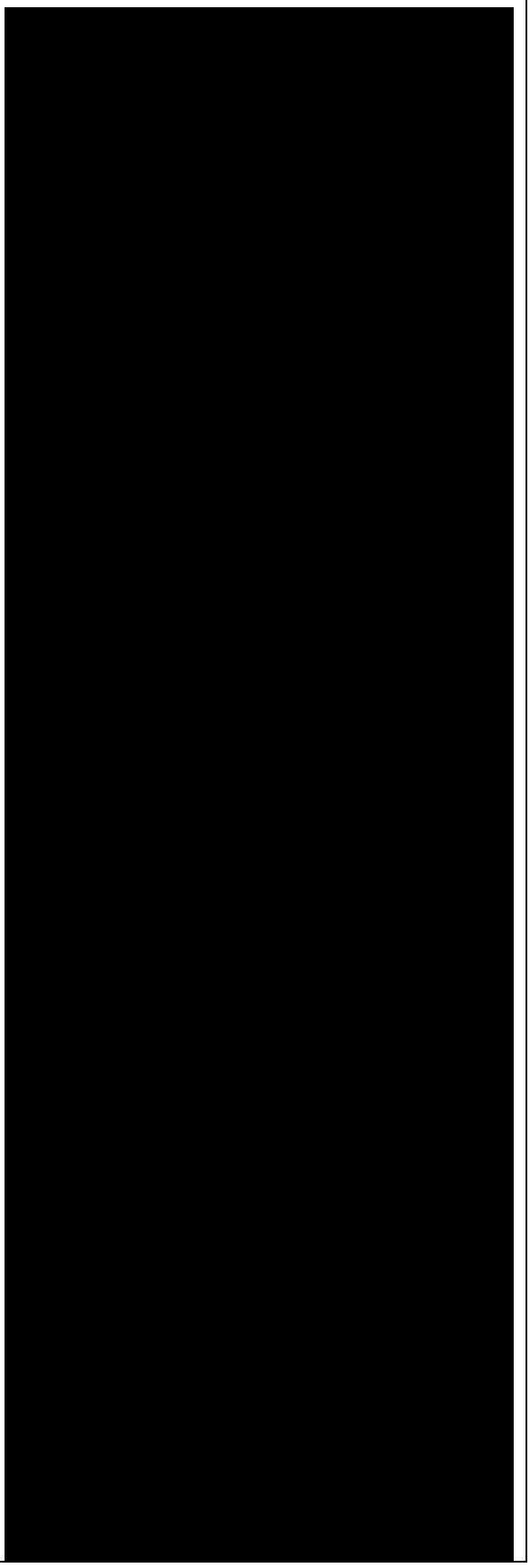


Fig. 1 Schematic representation of Magnetic drug delivery system under the influence of external magnetic field. Fmag is direction of external magnetic field are targeted. Copyrighted from reference (Park et al. 2010)

Fig. 2 Magnetic moment in both ferromagnetic and superparamag-netic materials. On application of the magnetic field the domain walls in ferromagnetic materials are washed away and aligned to the direction of the magnetic field. Whereas, in a superparamagnetic materials usually defined as the single domain structure has no domain walls, but magnetic moments align to the direction of the applied external

magnetic field. The domain structure of the magnetic materials has been drawn for simplicity. Copyrighted from reference (Mody et al. 2013)

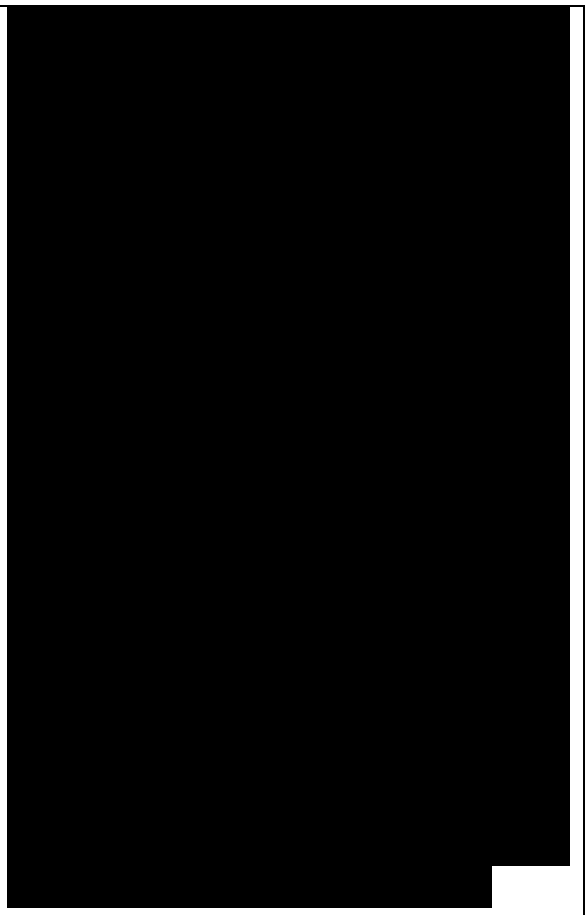


single-domain state. Thus below a critical size all the domain walls are washed away and the particle becomes a single domain particle (Lu et al. 2007). In practice, as the particle size is reduced, the coercivity increases to a maximum and then decreases toward zero. Below a critical diameter the coercivity becomes zero. Such particles are termed superparamagnetic (Fig. 3) (Jun et al. 2007). Here coercivity is defined as the force applied to reduce the residual magnetic field left in the magnetic particles to zero after the removal of an external magnetic field (Fig. 4). Therefore, when the particle size is small the spin-flip barrier for the reversal of the magnetic moments is very small, and the energy at the room temperature for small particles is enough for simple magnetization reversal energy i.e. Ms2V * kBT * 25 meV at room temperature (Gubin 2009; Krishnan 2010). Thus when typical ferro- magnets obtain a critical diameter of about 5-10 nm it paves the way to become superparamagnetic nanoparticle. The superparamagnetism of any magnetic nanomaterial is basically caused by thermal effects where the thermal fluctuations are strong enough to spontaneously demagnetize a previously saturated assembly; therefore these par-ticles have zero coercivity and have no hysteresis (Krishnan 2010). As a result, superparamagnetic nanoparticles

become magnetic in the presence of an external magnet, but revert to a nonmagnetic state when the external magnet is removed. This avoids an 'active' behavior of the particles when there is no applied field. This behavior of superparamagnetic materials results in potential advantages to deliver therapeutics onto specific sites under the influence of external magnetic field and can be reverted to their nonmagnetic states by removing external magnetic field to allow them to be excreted (Park et al. 2010).

Ferrite oxide—magnetite (Fe_3O_4) is the naturally occurring minerals on earth which is widely used in the form of superparamagnetic nanoparticles for diverse biological applications, such as MRI, magnetic separation, and magnetic drug delivery. However, the use of magnetic nanoparticles in vivo needs lot of surface modification so as to protect them from reticuloendothelial system and increase the stability of molecule in vivo. Organic ligands such as polyethylene glycol, dextran, aminosilanes are commonly used to stabilize the magnetic nanoparticles (Laurent et al. 2008; Reddy et al. 2012). Unfortunately, these surface protectants modulate the magnetic properties by modifying the anisotropy and decreasing the surface magnetic moment of the metal atoms located at the surface of the particles (Paulus et al. 1999; van Leeuwen et al. 1994). This reduction has been mainly associated to the existence of a magnetically dead layer on the surface of particles (Kodama 1999). Thus the effect of

size and surface coating of magnetic nanoparticles are both very important for the fabrication of nanomaterials for their role as diagnostic and therapeutic agents (Liu et al. 2011; Pal- iwal et al. 2010). Any change in size and surface coating will modulate the magnetic properties such as Coercivity (Hc) of these nanospheres of the nanoparticles and hence can vary the effectiveness of these diagnostic as well as therapeutic agents. It is imperative to mention that the design of novel MNPs for biomedical application requires careful evaluation of the effect of surface modification, size, shape on its magnetic properties. A thorough consideration of each design parameter must be evaluated to produce MNPs that can overcome biological barriers and



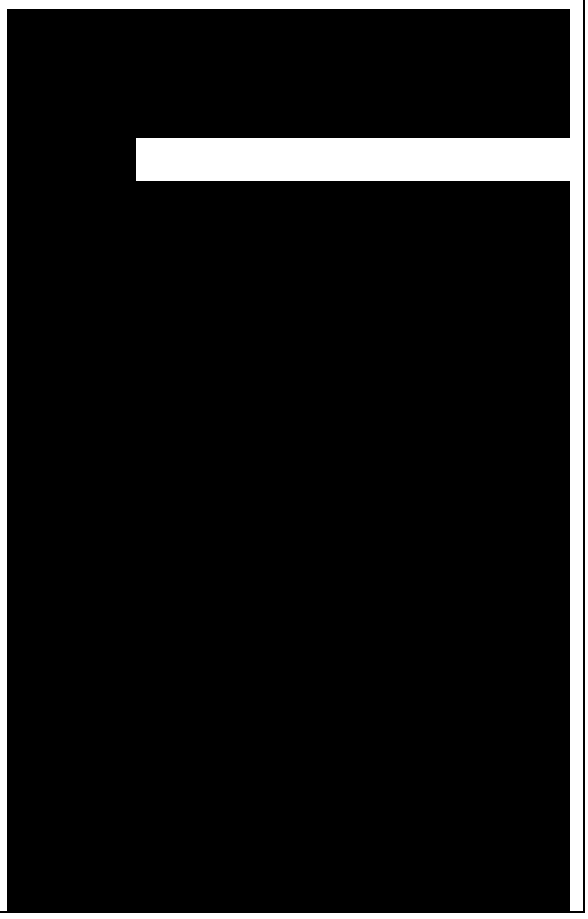


Fig. 3 Schematic illustration of the coercivity-size relations of small particles. Copyrighted from reference (Jun et al. 2007)

carry out its function. Additional information on the effect of change in shape, size, and surface coating of nanoparticles on its magnetic properties is beyond the scope of this review and readers are requested to refer book titled ‘‘Magnetic Nanoparticles’’ by Dr. Sergey P. Gubin and a review by Krishnan (Gubin 2009; Krishnan 2010). In particular, it must be concluded that the magnetic response of a nanoparticle to an inert coating is rather complex and system specific; the effect of coating cannot be predetermined before the actual magnetic measurements have been

performed. Even with limited information on the behavior of these systems various attempts have been made to bioengineer magnetic nanoparticles so as to utilize them for magnetic drug delivery. In the following section, we have tried to outline few of these applications followed by their current status in clinical trials.

Magnetic nanoparticles for drug delivery

Magnetic nanoparticles offer the possibility of being systematically administered but directed towards a specific target in the human body while remaining ultimately localized, by means of an applied magnetic field. Even though the concept of using magnetic particles for drug delivery was proposed as far back as 1970, the field of magnetic drug delivery has only recently received much attention (Senyei et al. 1978; Widder et al. 1978). Usually therapeutic agents are attached to the surface of magnetic nanoparticles or encapsulated within a nanocomposite mixture of a polymer and magnetic nanoparticle. In this case they can be operated under the influence of very low values of applied magnetic field. Ideal properties for the nanocomplexes which are to be used must be those with high values of magnetization at the operational temperature. Magnetic particles from iron, cobalt, and nickel are favorable in such situations due to their specific magnetic properties but the control of the particle size and shape, and the matrix or medium in which the particle is embedded is also critical. More commonly, these

particles may have magnetic cores with an external coating of a polymer or other metals and nonmetals such as gold or silica. They can also be nanocomposite mixtures consisting of magnetic nanoparticles encapsulated within a porous polymer. Presence of the polymers or various metal/nonmetal coat-ing provides an opportunity to anchor various therapeutic drugs or DNA for targeted gene delivery (McBain et al. 2008b). Another approach lies in encapsulating a cytotoxic drug along with magnetic nanospheres inside the polymer matrix. Once targeted to the site of action, the sustained delivery of the drug molecule at the site of action will provide its therapeutic effect.	Chúng cũng có thể là các hỗn hợp nanocomposite bao gồm các hạt nano từ được đóng gói trong polymer xốp. Vì có thể sử dụng polymer hoặc các lớp phủ kim loại/phi kim khác nhau, nên chúng ta có thể tích hợp các loại thuốc điều trị khác nhau hoặc DNA để dẫn truyền gen mục tiêu (2008b McBain và các cộng sự). Một phương pháp khác nữa là đóng gói thuốc gây độc tế bào cùng với các hình cầu nano từ bên trong nền polymer. Một khi đã nhắm đến một vị trí hoạt động, việc cung cấp liên tục phân tử thuốc tại vị trí hoạt động sẽ phát huy hiệu quả điều trị của nó.