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Review Article

FORMULATION OF MAGNETIC NANOPARTICLES AND THEIR APPLICATIONS

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ABSTRACT

Over the past three decades, there has been a considerable research interest in the area of developing drug delivery using nanoparticles (NPs) as carriers for small and large molecules. Targeting delivery of drugs to the diseased lesions is one of the most important aspects of drug delivery system. They have been used in vivo to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action. Various polymers have been used in the formulation of nanoparticles for drug delivery research to increase therapeutic benefit, while minimizing side effects. In order to see functionality and toxicity of nanoparticles in

various food and drug applications, it is important to establish procedures to prepare nanoparticles of a controlled size. NaturalControlled release of drugs from nanostructured functional materials, especially nanoparticles (NPs), is attracting increasing attention because of the opportunities in cancer therapy and the treatment of other ailments. The potential of magnetic NPs stems from the intrinsic properties of their magnetic cores combined with their drug loading capability and the biochemical properties that can be best owed on them by means of a suitable coating. This review was mainly focused on different techniques for the preparation of magnetic nanoparticles and their application in various field. In addition to that some of the applications in the field of biomedicine were also explained.

Keywords: Drug, Nanoparticles, NPs

INTRODUCTION

Nanotechnology is beginning to allow scientists, engineers, and physicians to work at the cellular and molecular levels to produce major advances in the life sciences and healthcare. Magnetic nanoparticles show remarkable new phenomena such as superparamagnetism, high field irreversibility, high saturation field, extra anisotropy contributions or shifted loops after field cooling. These phenomena arise from finite size and surface effects that dominate the magnetic behaviour of individual nanoparticles.[1,2]

Advantages

The main advantages of magnetic (organic or inorganic) NPs are that they can be: (i) visualized (superparamagnetic NPs are used in MRI); (ii) guided or held in place by means of a magnetic field; and (iii) heated in a magnetic field to trigger drug release or to produce

hyperthermia/ablation of tissue.

The other advantages of magnetic nanoparticles drug delivery sytems include (i) the ability to target specific locations in the body; (ii) the reduction of the quantity of drug needed to attain a particular concentration in the vicinity of the target; and (iii) the reduction of the concentration of the drug at non target sites minimizing severe side effects.

Different methods for the preparation of magnetic nanoparticles[1]

several popular methods including co-precipitation, microemulsion, thermal decomposition, solvothermal , chemical vapour deposition, combustion synthesis, carbon arc, laser pyrolysis synthesis have been reported for synthesis of MNPs.

LIQUID PHASE SYNTHSIS

The principles by which monodisperse (with a relative standard deviation of ~ 5%) particles can be prepared are readily presented in a diagram due to LaMer . As described in the LaMer diagram for homogeneous precipitation, as concentration increases to pass its saturation, it reaches a point where nucleation occurs. Particle growth most likely transpires by a combination of the diffusion of atoms onto the nuclei and with irreversible aggregation of nuclei. The requirements for monodispersity are evident from the LaMer diagram:

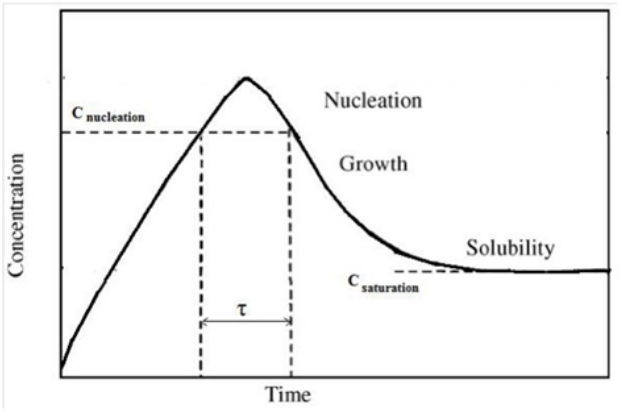

Figure 1 LaMer diagram

The rate of nucleation must be high enough so that the concentration does not continue to climb. Instead, a burst of nuclei are created in a short period (τ short).

The rate of growth of these nucleis must be fast enough to reduce the concentration below the nucleation concentration point, quickly. In this way only a limited number of particles are created.

The rate of growth must be slow enough, however, that the growth period is long compared with the nucleation period.

This usually narrows the size of distribution which results from finite nucleation period. So, by controlling these factors monodisperse MNPs with different sizes can be synthesized.

Co-precipitation

Co-precipitation is a facile and convenient way to synthesize MNPs (metal oxides and ferrites) from aqueous salt solutions. There are two main methods for the synthesis in solution of magnetite spherical particles in the nanometre range. In the first, ferrous hydroxide suspensions are partially oxidized with different oxidizing agents . For example,

spherical magnetite particles of narrow size distribution with mean diameters between 30 and 100 nm can be obtained from a Fe(II)

salt, a base and a mild oxidant (nitrate ions). The other method consists in ageing stoichiometric mixtures of ferrous and ferric hydroxides in aqueous media, yielding spherical magnetite particles homogeneous in size. In addition, it has been shown that by adjusting the pH and the ionic strength of the precipitation medium, it is possible to control the mean size of the particles over one order of magnitude (from 15 to 2 nm) .The size decreases as the pH and the ionic strength in the medium increases . Both

parameters affect the chemical composition of the surface and consequently, the electrostatic surface charge of the particles. Under these conditions, magnetite particles are formed by

aggregation of primary particles formed within an Fe(OH)2 gel. This is an ordered aggregation that gives rise to spherical crystalline particles .The smallest particles can also be generated after adding polyvinylalcohol (PVA) to the iron salts.

Microemulsion

The water-in-oil (W/O) microemulsion, has been widely used to synthesize uniform sized MNPs .This is an isotropic and thermodynamically stable single-phase system that consists of three components: water, oil and an amphiphilic molecule, called surfactant. The surfactant molecule lowers the interfacial tension between water and oil resulting in the formation of a transparent solution. The water nanodroplets containing reagents, as a nanoreactor, undergo rapid coalescence allowing for a mixing, precipitation reaction and an aggregation processes for the synthesis of MNPs. The shape of the water pool is spherical and the surfactant molecules surround the nanodroplet wall. These walls act as cages for the growing particles and thereby reduce the average size of the particles during the collision and aggregation process. Thus, the size of the spherical nanoparticles can be controlled and tuned by changing the size of the water pool (*W*0 value, the water-to-surfactant molar ratio). Generally, the higher values of *W*0, give the larger particle size. By mixing two identical water-in-oil microemulsions containing the desired reactants, the microdroplets will continuously collide,coalesce and break again, and finally a precipitate forms in the micelles.

Thermal Decomposition[9]

Nanoparticles with a high level of monodispersity and size control can be obtained by high-temperature decomposition of organometallic precursors, such as [Mn+(acac)n], (M = Fe, Mn, Co, Ni, Cr; n = 2 or 3, acac = acetylacetonate), Mx(cup)x (cup = N nitrosophenylhydroxylamine) or carbolys (such as Fe(CO)5) using organic solvents and surfactants such as fatty acids, oleic acid and hexadecylamine. Thermal decomposition

of organometallic precursors which metal is the zero valent in their composition (such as Fe(CO)5) initially leads to a formation of metal NPs but if followed by oxidation can lead

to a high in quality mono dispersed metal oxides. On the other hand, decomposition of precursors with cationic metal centers (such as Fe (acac)3) leads directly to metal oxides NPs. Principally the ratios of the starting reagents including organometallic compounds, surfactants, and solvents are the decisive parameters for controlling the size and morphology of MNPs. The reaction temperature and time, as well as the aging period may also be crucial for the precise control of size and morphology.The effect of reaction temperatures and reaction times on size, morphology and magnetic properties of nanoparticles are schematically shown in the following figure. Metal oxide MNPs can also be synthesized by the thermal decomposition method. Up to date, two different approaches have been used for this purpose. First, thermal decomposition of metal carbonyl precursors followed by an oxidation step using air , or oxidation by using an oxidant at elevated temperatures .The second is decomposition of precursors with a cationic metal centre in the absence of reducing agents. The presences of reducing agents lead to metal NPs even by the use of cationic precursors .Thermal decomposition seems the best method developed to date for size and morphology control of NPs.

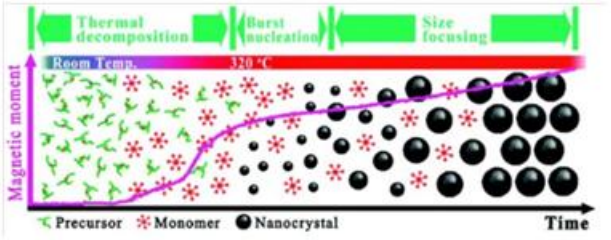

Figure 2

Effect of reaction temperature and reaction time on size, morphology and magnetic properties of MNPs of production is high and scalable. However, one of the major disadvantages of this method is the production of organic soluble NPs which limit the extent of application uses of them in biological fields besides surface treatment is needed after synthesis; also, thermal decomposition methods usually lead to complicated processes or require relatively high temperatures.

Chemical Reduction

Among the various solution-phase chemistry routes developed for the preparation of metal NPs, the reduction of metal salts is the most common, and reducing agents such as NaBH4 have been commonly employed in the reactions. Nanoscale zero-valent iron (nZVI) which have been extensively used in the environmental remediation field, have commonly been prepared by mixing equal volumes of NaBH4 and FeCl3, the following reaction of:

$$4Fe3+ + 3NaBH4 + 9H2O \rightarrow 4Fe0 \downarrow + 3NaH2BO3 + 12H+ 6H2 \quad (5)$$

A key advantage of this method is its simplicity. It can be safely done in most chemistry labs with simple chemical reagents. Also, this reaction can be done at room temperature conditions.

Applications of Magnetic nanoparticles[8]

Industrial applications of magnetic nanoparticles cover a broad spectrum such as magnetic seals in motors, magnetic inks for bank cheques, magnetic recording media and biomedical applications such as magnetic resonance contrast media and therapeutic agents in cancer treatment. Each potential application requires the magnetic nanoparticles to have different properties. For example, in data storage applications, the particles need to have a stable, switchable magnetic state to represent bits of information, a state that is not affected by temperature fluctuations. For biomedical applications the use of particles that present superparamagnetic behaviour at room temperature is preferred. Furthermore, applications in biology and medical diagnosis and therapy require the magnetic particles to be stable in water at neutral pH and physiological salinity. The colloidal stability of this fluid will depend first, on the dimensions of the particles, which should be sufficiently small so that precipitation due to gravitation forces can be avoided, and second on the charge and surface chemistry, which give rise to both, steric and coulombic repulsions[4]. Additional restrictions to the possible particles that could be used for biomedical applications strongly depend on whether these particles are going to be used for *in vivo* or *in vitro* applications. For *in vivo* applications the magnetic particles must be coated with a biocompatible polymer during or

after the synthesis process to prevent the formation of large aggregates, changes from the original structure and biodegradation when exposed to the biological system. The polymer will also allow binding of drugs by covalent attachment, adsorption or entrapment on the particles .The important factors, which determine the biocompatibility and toxicity of these materials, are the nature of the magnetically responsive component, such as magnetite, iron, nickel, cobalt, neodimium–iron–boron or samarium–cobalt and the final size of the particles, their core and the coatings. Iron oxide particles such as magnetite (Fe3O4*)* or its oxidized form maghemite (*γ* - Fe2O3*)* are by far the most commonly employed for biomedical applications. Highly magnetic materials such as cobalt and nickel are toxic, susceptible to oxidation and hence are of little interest.Moreover, the main advantage of using particles of sizes smaller than 100 nm (so-called nanoparticles) is their higher effective surface areas (easier attachment of ligands), lower sedimentation rates (high stability) and improved tissular diffusion .Another advantage of using nanoparticles is that the magnetic dipole–dipole interactions are significantly reduced because they scale as *r*6 (*r* is the particle radius) .Therefore, for *in vivo* biomedical applications, magnetic nanoparticles must be made of a non-toxic and non-immunogenic material, with particle sizes small enough to remain in the circulation after injection and to pass through the capillary systems of organs and tissues avoiding vessel embolism. They must also have a high magnetization so that their movement in the blood can be controlled with a magnetic field and so that they can be immobilized close to the targeted pathologic tissues

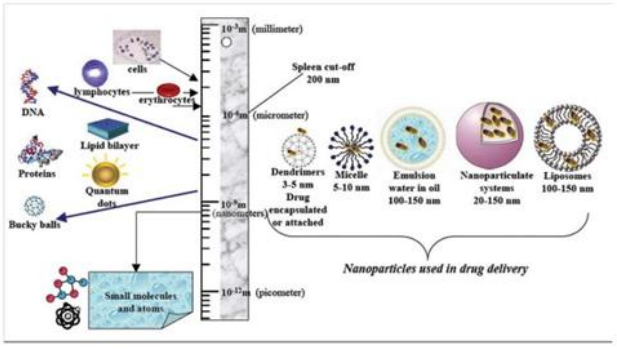

Figure 3 NP system for drug delivery applications

Drug delivery with magnetic NPs[13,14]

Different organic materials (polymeric NPs, liposomes, micelles) have been investigated as drug delivery nanovectors using passive targeting, active targeting with a recognition moiety (e.g. antibody), or active targeting by a physical stimulus (e.g. magnetism in magnetoliposomes). However, these organic systems still present limited chemical and

mechanic stability, swelling, susceptibility to microbiological attack, inadequate control over the drug release rate, and high cost. Polymer NPs also suffer from the problem of high polydispersity. Synthesis produces particles with a broad size distribution and irregular

branching, which could lead to heterogeneous pharmacological properties. One alternative is to use dendrimers, which have a monodisperse character and globular architecture resulting from their stepwise synthesis and can be purified at each step of growth. Visualization of dendrimers requires tagging with a specific moiety (i.e. a fluorophore or metal). A major drawback of dendrimers and dendritic polymers, however, is their high cost. The preparation

of dendritic polymers that circulate in the blood long enough to accumulate at target sites but that can also be removed from the body at a reasonable rate to avoid long-term accumulation also remains a challenge. Passive targeting using drug-conjugated dendrimers and dendritic polymers has been widely studied, mainly using the EPR effect. Therapies based on active targeting, such as antibody-conjugated dendrimers, constitute a promising alternative in view of the potential of antibodies for selective targeting. Because of the disadvantages of organic NPs for drug delivery, inorganic vectors constitute an interesting option and are the subject of intense research[15].

We refer to NPs when the drug is covalently attached to the surface or entrapped or adsorbed within the pores of the magnetic carrier (polymer, mesoporous silica, etc.). Nanocapsules ('reservoirs') designate magnetic vesicular systems where the drug is confined to an aqueous or oily cavity, usually prepared by the reverse micelle procedure, and surrounded by an organic membrane (magnetoliposomes) or encapsulated within a hollow inorganic capsule. The key parameters in the behavior of magnetic NPs are related to surface chemistry, size (magnetic core, hydrodynamic volume, and size distribution), and magnetic properties (magnetic moment, remanence, coercivity). The surface chemistry is especially important to avoid the action of the reticuloendothelial system (RES), which is part of the immune system, and increase the half-life in the blood stream. Coating the NPs with a neutral and hydrophilic compound increases the circulatory half-life from minutes to hours or days. Another possibility is to reduce the particle size; however, despite all efforts, complete evasion of the RES does not seem feasible and unwanted migration to other areas in the body could cause toxicological problems[5,6]. In addition to cancer treatment, magnetic NPs can also be used in anaemic chronic kidney disease and disorders associated with the musculoskeletal system (i.e. local inflammatory processes, side effects). For those disorders, superparamagnetic Fe oxide NPs (SPION), in conjunction with external magnetic fields, seem a suitable alternative for drug delivery to inflammatory sites by maintaining appropriate local concentrations while reducing overall dosage and side effects[16].

A list of some other applications of nanomaterials to biology or medicine is given below:[10,17]

- Fluorescent biological labels
- Drug and gene delivery
- Bio detection of pathogens
- Detection of proteins
- Probing of DNA structure
- Tissue engineering
- Tumour destruction via heating (hyperthermia)
- Separation and purification of biological molecules andcells
- MRI contrast enhancement

Limitations of magnetic drug delivery[12]

Since the magnetic gradient decreases with the distance to the target, the main limitation of magnetic drug delivery relates to the strength of the external field that can be applied to obtain the necessary magnetic gradient to control the residence time of NPs in the desired

area or which triggers the drug desorption. Permanent Nd-Fe-B magnets in combination with SPION, which have excellent magnetic properties, can reach effective magnetic field depths up to 10-15 cm in the body. However, it must be noted that the magnetic carriers accumulate not only at the desired site but also throughout the cross section from the external source to the depth marking the effective field limit. Obviously, the geometry of the magnetic field is extremely important and must be taken into account when designing a magnetic targeting process. As a means to elude the limitations of using external magnetic fields, internal magnets can be located in the vicinity of the target by using minimally invasive surgery. Several studies have simulated the interaction between a magnetic implant and magnetic NPs, enabling drug delivery. In addition, work in several laboratories is addressing targeted drug delivery with magnetic implants. Another limitation relates to the small size of NPs, a requisite for superparamagnetism, which is in turn needed to avoid magnetic agglomeration once the magnetic field is removed. A small size implies a magnetic response of reduced strength, making it difficult to direct particles and keep them in the proximity of the

target while withstanding the drag of blood flow. Targeting is likely to be more effective in regions of slower blood velocity, and particularly when the magnetic field source is close to the target site. As for all biomedical applications, limitations also arise in extrapolating from animal models to humans. There are many physiological parameters to consider, ranging from differences in weight, blood volume, cardiac output, and circulation time to tumor volume/location/blood flow, complicating the extrapolation of data obtained in animal models. Related to this point is the fact that studies on toxicity and the fate of magnetic carriers are insufficient and, in many cases, there is insufficient characterization. Finally, state-of-the-art magnetic drug delivery seems mainly applicable to well-defined tumors, as treatment of metastatic neoplasms and small tumors in the early stages of their growth still remains a challenge. Treating emerging tumors will involve the development of a new generation of seek-and-destroy NPs, which specifically recognize small clusters of cancer cells and carry the necessary elements (drugs or hyperthermia agents) for their destruction. A strong interest continues in this field given the capability of NPs to access tumors in regions where conventional surgery cannot be applied.

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