A Study of the Magnetic Nanocomposites with Natural Polymer Coating From the Perspective of the Targeted Drug Delivery

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ABSTRACT---- ***Recent research on the resistance of pathogenic bacteria to existing antibiotics has shown the rapid spread of this problem and has raised concerns in scientific circles and international organizations. The development of new antibiotics is still slow in the face of growing needs. In addition, the overuse of antibiotics in developing countries has exacerbated the problem. Therefore, the development of new and multidimensional strategies is necessary to address this global problem. One of the solutions that has been considered by researchers in recent years is the development of targeted drug delivery systems based on magnetic nanoparticles. Unique magnetic properties the physicochemical and physiological properties of magnetic nanoparticles have made them useful as carriers for delivering drugs to the target tissue. In this study, we try to provide a general study to some subjects such as synthesis of magnetic nanoparticles and coating of these nanoparticles with natural polymer to grain (mucilage to grain) as a biocompatible, non-toxic and oral polymeric agent for maximum loading of ciprofloxacin antibiotic on nanostructured nuclei Magnetite and shell to mucilage to grain, to study the effect of different parameters and fabrication conditions of samples on the structural, physicochemical, magnetic, colloidal stability and antibacterial properties of samples, and also to investigate the effect of pH on ciprofloxacin adsorption on magnet nanoparticles by mucilage to the grain and release of the drug from these nanoparticles.***

Keywords: ***Targeted Drug Delivery; Ciprofloxacin; Grain Mucilage; Magnetic Nanoparticles (Fe_3O_4)***

1. INTRODUCTION

Nanomaterials are types of materials with sizes smaller than micrometers (commonly defined between 1 and 100 nanometers) that are made of organic or inorganic biocompatible or non-biocompatible materials. The properties that make this material important and distinguish it from its large-scale counterparts are mainly related to the effects of size, magnetic properties, electron properties, and the role that these materials play in creating superficial phenomena due to their reduced dimensions. , related to. Common use of drugs causes them to spread through blood vessels throughout the body and affects the healthy and diseased cells of the body in a non-specific way, resulting in lack of targeted treatment and side effects of drugs. Nanoparticle-based targeted delivery systems have advantages due to advantages such as the ability to focus on target tissues (local function), stable drug release, and thus reduce the number of drug doses and frequency of drug use. Side effects of drugs and increase their effectiveness are treated and have many potentials and applications in the field of targeted drug delivery [1].

Targeted magnetic drug delivery can reduce the side effects of medications. This method is based on connecting drugs or therapeutic agents with magnetic nanocarriers and delivering the appropriate therapeutic dose of the drug to the target tissue by applying a magnetic field. Drugs can be embedded in the porosity of nanocarriers, or trapped in their internal matrix, or encapsulated in nucleus-shell nanostructures, or adsorbed on the surface of nanoparticles. It all depends on the type of system used for targeted drug delivery. Among the types of targeted nanoparticle drug delivery systems, magnetic nanoparticles with core-shell structure are one of the most common and widely used types of targeted drug delivery systems [2].

Some metals such as cobalt and nickel, despite having magnetic properties, are less considered for biological applications due to their toxicity, while iron oxides are non-toxic and have many biomedical applications [3]. Among these, iron oxide magnetic nanoparticles and in particular magnetite nanoparticles (Fe3O4) due to properties such as high saturation magnetism, biocompatibility, non-toxicity, cheap price, widely used for biological applications such as image sharpness in magnetic resonance imaging, thermotherapy , Targeted magnetic drug delivery, bio-isolates, bio-sensors, etc. are used [4].

Important factors influencing the behavior of magnetic nanoparticles in physiological conditions are related to the surface chemistry of nanoparticles, particle size (magnetic core size, hydrodynamic diameter and nanoparticle size distribution) and magnetic properties such as saturation magnetism, induction field and magnetosynthetic residue. Among these, nanoparticle surface chemistry is particularly important in the ability of nanoparticles to pass through the body's reticuloendothelial system (part of the immune system) and increase the half-life of particles in the bloodstream and reach the target tissue. Iron oxide magnetic nanoparticles with sizes less than 20 nm have paramagnetic properties [1, 5]. The property of paramagnetic cloud is one of the necessary properties for these nanoparticles for targeted drug delivery applications. Because in addition to the high saturation magnetization of these nanoparticles (due to the large number of magnetic moments of each particle), the absence of magnetic residue in these nanoparticles after removing the magnetic field, prevents them from sticking together and agglomerating and clogging blood vessels. On the other hand, the very small size of these nanoparticles increases their surface reactivity and the surface interactions in these nanoparticles increase their chemical activity, agglomeration and oxidation. Together, these factors can have negative effects on the magnetic properties and other physicochemical and physiological properties of these nanoparticles. Therefore, to improve the surface of nanoparticles to increase the hydrophilicity of nanoparticles, the possibility of binding drugs and biomolecules to their surface, increasing the colloidal stability of particles in the biological environment and increasing the half-life of nanoparticles in the bloodstream, strategies such as coating nanoparticles with hydrophilic and biocompatible polymers. Is followed [1]. In these targeted magnetic drug delivery systems, nanoparticles with core-shell structure, polymer shell by creating spatial repulsive forces and preventing nanoparticles from sticking together and agglomerating, in fact play the role of increasing the stability of nanoparticles and creating a place for drug adsorption and storage. This polymer coating also plays a role in protecting and preventing the oxidation of magnetic nanoparticles. If the magnetic core, due to its magnetic moment, gives these magnetic nanocarriers the ability to control and focus on the target tissue by applying an external magnetic field [2]. Natural polymers have a special place among them due to features such as high biocompatibility, cheap price and easy access. Natural granular polymer (mucilage to granular) is an example of natural, edible, biocompatible and non-toxic polymers that have many applications in the food and medical industries. This hydrophilic and biodegradable polymer in contact with water is separated from the granules and can be bonded with iron oxide nanoparticles [6].

In this paper, objectives such as synthesis of magnetite magnetic nanoparticles and coating of these nanoparticles with natural polymer to grain (mucilage to grain) as a biocompatible, non-toxic and oral polymeric agent for maximum loading of ciprofloxacin antibiotic on nanostructured nuclei Magnetite and shell to mucilage to grain), to study the effect of different parameters and fabrication conditions of samples on the structural, physicochemical, magnetic, colloidal stability and antibacterial properties of samples and also to investigate the effect of pH on ciprofloxacin adsorption on magnet nanoparticles by mucilage to the grain and release of the drug from these nanoparticles, is desired.

2. MAGNETIC STATES AND PROPERTIES OF MATERIALS

Today, magnetic materials, as an essential and integral part of modern technologies, have wide applications in the field of manufacturing electronic and electromechanical devices and medical equipment. These materials are also widely used for biological applications such as image enhancement in imaging, magnetic resonance imaging (MRI), targeted drug delivery, thermotherapy, cell separation, and DNA extraction.

A. Magnetization

All matter is made up of atoms, and each atom contains electrons that move in electronic circuits. Because each of these circuits is limited to a single atom, they are called atomic currents. Atomic currents are complete rotational currents and do not lead to charge transfer, but this type of current can also generate a magnetic field. Atomic current is like a small closed circuit with atomic dimensions, so it can be considered as a magnetic dipole that has a magnetic dipole moment $\vec{m}_i$. Therefore, for a given volume of matter, magnetization is expressed as the sum of the magnetic dipole moments per unit volume with relation (1) [7-8]:

$$\vec{M} = \frac{1}{V}\sum_{\Omega_i}(\vec{m}_i) \quad (1)$$

Where Ω_i refers to volume of matter in which the magnetic dipole moments $\vec{m}_i$ are located. If the material is non-magnetic, the sum of the magnetic dipole moments $\vec{m}_i$ will be zero because of the catheters, and therefore the total magnetization will be zero.

B. Behavior of materials in the external magnetic field

The origin of magnetism in atoms is the magnitude of the orbital angular motion and the magnitude of the spin angular motion of the electrons, but the determination of the relative magnetic orientation of electrons in an ion placed in a crystal lattice depends on the interaction between the electrons. Accordingly, magnetic materials either oppose the external field and weaken it or intensify it. Therefore, the quantity of magnetic receptivity is defined as the reciprocal response of electrons and nuclei to an external magnetic field. In fact, magnetic susceptibility is a measure of a material's tendency to become magnetized when exposed to an external magnetic field. Magnetic materials are best classified according to their response (temperature dependent) to the external magnetic field. For ease of quantitative comparison of these responses as well as their classification in terms of magnetic properties separately, quantity χ is introduced. Magnetic susceptibility is defined as the ratio of the magnetization of a substance to the applied magnetic field H [9]. In the case of materials with linear behavior, the magnetization M is linearly related to the external field H and the acceptability χ is calculated using the following equation:

$$\chi = \mathrm{M}/\mathrm{H} \tag{2}$$

Accordingly, magnetic materials are divided into phases diamagnetic, paramagnetic, ferromagnetic, antipromagnetic and ferromagnetic [10].

C. Effect of particle size and shape on the induction field

In general, the structure of spheres in a ferromagnetic material determines the magnetic behavior that depends on the size and shape of the particles. Two of the most studied effects are the single-domain limit and the super-magnetic limit. When the particle size is large, the multi-domain structure is more desirable in terms of minimum energy. In this case, the competition between the magnetostatic energy and the wall formation energy leads to the formation of a multi-domain structure. As the particle size decreases, the proportion of different energies of the total energy of the ferromagnetic material changes; as the surface energy of the walls is greater than the magnetostatic energy. At sizes less than the critical diameter (D_c), the energy required to form the walls of the basins is greater than the energy of the single structure of the basin; thus the structure of the constituency is formed (Figure 1).

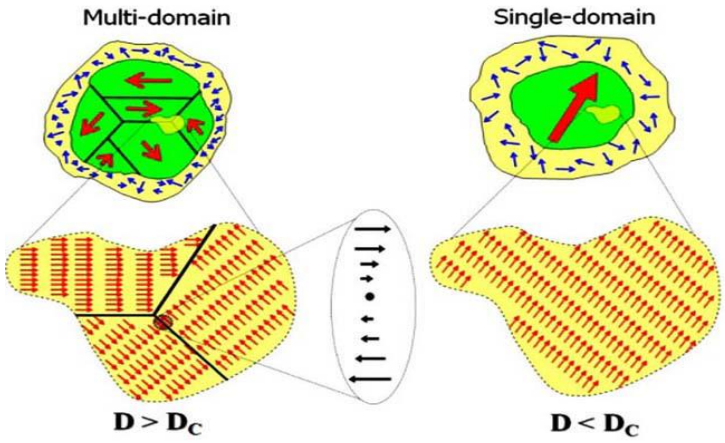

Figure 1. Schematic of a single-sphere and multi-sphere structure in particles smaller than and larger than the critical diameter [11]

The critical diameter at which the particles become single-sphere at smaller sizes is denoted by the following relation:

$$D_c \approx \frac{18(AK_u)^{1/2}}{\mu_0 M_s^2} \tag{3}$$

In this relation, A is the exchange constant, K_u is the uniaxial anisotropy constant, μ_0 is the magnetic susceptibility, and M_s is the saturation magnetization [12]. The size of the critical diameter varies for different materials. For example, the critical diameter is about 20 to 30 nm for magnetite and about 40 nm for cobalt ferrite [13]. In a single-domain structure, the spatial arrangement of the internal magnetization of a single-domain particle is highly dependent on size, so that as the particle size decreases to the critical diameter D_c, the coercive field initially increases to a maximum value; Then by reducing the size from the value of D_c to the critical level of superparamagnetism (Dp), its value reaches zero (Figure 2).

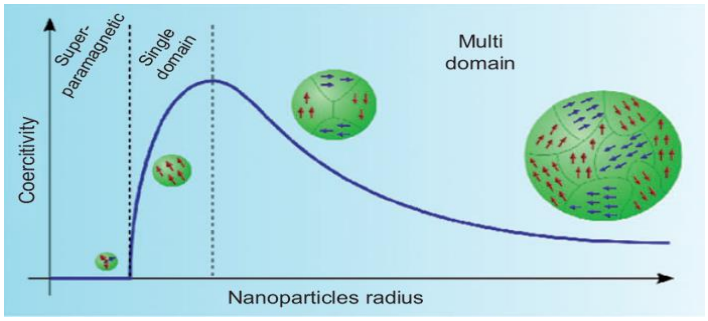

Figure 2. Coercion field change curve with particle size [13]

When the particle size becomes smaller than the superparamagnetic limit Dp, the coercive field becomes zero and the particles become superparamagnetic. At sizes smaller than Dp, the magnetic moment directions are not stable and change with time. This is one of the unique properties of superparamagnetic particles. Therefore, not every single sphere particle is superparamagnetic. Shape anisotropy is another factor affecting the coercive field. Deviation from the spherical shape of nanoparticles has a significant effect on their inductive field values.

Table 1. Investigation of the effect of shape on the induction field of iron nanoparticles by considering the ratios (c / a) [13]

Aspect ratio (c/a)	Coercivity (kOe)
1.1	820
1.5	3300
2.0	5200
5.0	9000
10.0	10100

As it is known, due to the changes in the length-to-width ratios, the shape of the nanoparticles changes and this deformation corresponds to the change in the values of the induction field for these nanoparticles. According to classical electrodynamics concepts, perfectly uniform magnetization is only possible for the ellipse, so an ideal single-domain nanoparticle should have an elliptical shape. The slightest deviation from the elliptical shape and deformation in the particles can cause the anisotropy of the shape and the change in the magnetic uniformity of the nanoparticles, and this plays an important role in determining the magnetic properties of the nanoparticles [13].

D. Iron oxides

Iron oxides are known compounds that are widely found in nature. Iron oxides have been used by humans for centuries; For example, about half a century ago, iron oxide nanoparticles have been used as a magnetic resonance imaging (MRI) imaging enhancer. In recent decades, the synthesis of iron oxides has received much attention from researchers not only for its scientific appeal but also for its many biological applications such as targeted drug delivery, magnetic resonance imaging (MRI), thermotherapy, bio-isolation and biosensor fabrication. Advantages such as physical and chemical stability, biocompatibility and non-toxicity and low cost of synthesis of these materials have made these materials as more suitable options for biological applications compared to some other materials.

So far, eight different types of iron oxides have been identified. However, the three compounds magnetite (Fe_3O_4), hematite (αFe_2O_3) and meghamite (γFe_2O_3) are more common for biological applications and have more uses. The structure of magnetite is different from most iron oxides because it contains both divalent and trivalent iron ions. Each of these three iron oxides has structural, biochemical, magnetic and other unique properties that make each suitable for specific applications in medicine and other fields [14].

D.1. Magnetite

Magnetite has an inverted spinel structure with the following structural formula.

$$(Fe^{3+})_A[Fe^{2+}, Fe^{3+}]_B O_4$$

Also, the skeleton of this structure is composed of 32 oxygen ions, which are narrowly packed in the direction [15] and form a FCC network (Figure 2-31).

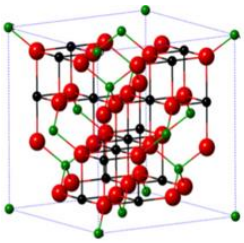

Figure 3. Demonstration of the magnetic crystal structure [14]

In this structure, all binary cations Fe^{2+}occupy half of the octagonal positions. Also, the trivalent cations Fe^{3+} are equally placed in the unoccupied quadrilateral and octahedral positions [14, 16]. Out of 64 quadrilateral positions in the spinel unit cell, only 8 positions are filled. Also, out of the 32 existing octagonal positions, only 16 positions are occupied by metal cations. Since the electronic structure of the binary cation Fe^{2+}ends in $3d^6$, therefore, each of these cations has 6 electrons in its last layer (3d), and according to the Pauli exclusion principle and Hound rules, how the spin of the electrons is oriented in The orbitals are such that the spins of 5 electrons out of 6 electrons of the last layer are in direct direction with each other and the spin of the sixth electron is opposite to the direction of the other electrons. Since the magnetic moment due to the electron spin is approximately equal to 1 Bohr magneton (μ_B), so the magnetic dipole moment of each Fe^{2+} is equal to $4\mu_B$. The electronic structure of trivalent cations Fe^{3+} also ends in $3d^5$; Therefore, according to the same principles, the magnetic dipole moment of each of the Fe^{3+} cations is $5\mu_B$. Since the orientation of the magnetic moments of the trivalent cations in subnets A and B with each other is antiparallel, therefore, the interaction of each other is neutralized and the magnetic moment of the whole lattice will be due only to the magnetic moments of the two-dimensional subunit B subunits. 8 is a cubic cell, so the total magnetization of each unit cell will be 32 μ_B [16, 17].

3. INTRODUCTION TO NANOMATERIALS

Nanomaterials are usually classified based on factors such as size, morphology, composition, coating and agglomeration. In terms of spatial dimensions, nanomaterials can be placed in four groups: 0-D, 1-D, 2-D and 3-D. The first group (0-D) consists of nanomaterials whose size in all three dimensions is in the range of nanometers. These particles are also known as artificial atoms or quantum dots because of their discrete energy levels. Metal nanoparticles, including gold and silver nanoparticles, are examples of this type. The second group (1-D) includes materials whose size in two dimensions is in the range of nanometer dimensions and their third dimension size is comparable to the other two dimensions. Carbon nanotubes, nanofibers, and nanorods are examples of such materials. These nanomaterials have a high surface area and length to width ratio and are therefore suitable for making nanocomposites. The third group (2-D) consists of nanomaterials, one dimension of which is in the range of nanometer dimensions and the other two dimensions are comparable to the third dimension. Graphene, nanofilms, nanofibers, nanosheets and nanofilms are examples of this. These types of plate structures have a thickness in the range of 1 to 100 nm. The fourth group (3-D) consists of materials whose dimensions are all outside the nanometer range, but whose overall structure is composed of a set of nanoparticles or nanocrystals. The best examples of this type of material are mass nanostructures that contain components with sizes ranging from about 1 to 100 nanometers. These types of nanostructures are in fact a multiple arrangement of specific nanocrystals with different orientations, which makes these materials have a nanocrystalline structure with nanoscale properties. In other words, nanomaterials (3-D) can include a set of nanoparticles, nanorods, nanotubes, or nanofibers that are embedded in a network [18].

3.1. Magnetic nanostructures

The term nanostructure is used to describe materials with small structures ranging in size from 1 to 100 nanometers. Nanostructures usually have unique physical, chemical, electrical, structural, and magnetic properties. The study of nanostructures and magnetic materials encompasses a wide range of synthesis methods and characterization techniques, as well as studies in physics, chemistry, and materials science. These studies not only provide information about the structure and magnetic properties of materials, but also develop knowledge and skills in the techniques and methods of synthesis of these nanostructures [19].

Magnetic nanostructures can exist in various forms such as thin films, nanoparticles, nanowires, clusters, and so on. As the size of the magnetic material decreases, strong surface effects become more pronounced due to the increase in surface-to-volume ratio and the increase in energy of the exchange interactions between the magnetic atoms, so that by reducing the size of the magnetic material, unique properties Appear [19-20].

To describe the structural properties and morphology of magnetic nanostructures, there is a kind of classification based on the physical mechanisms affecting the magnetic behaviors of these nanostructures. Accordingly, magnetic nanostructures are classified into four different groups. Group A consists of very fine particles that are ideally non-interacting and completely separated from each other. Ferrofluids in which magnetic nanoparticles are surrounded by surfactants to prevent interaction between particles and their stability are included in this group.
Group B is very fine nanoparticles with core-shell structures. Group C is a composite consisting of fine magnetic particles that are embedded in a heterogeneous lattice, which may be magnetic or non-magnetic. Group D is a material containing fine crystals inside a Nanocrystalline networks are distributed. This type of magnetic nanostructure may also consist of two separate phases so that the phase of the nanocrystals is separate from the phase of the lattice or the crystals and the lattice are both composed of the same material. Figure (4) shows the classification of these magnetic nanostructures [19].

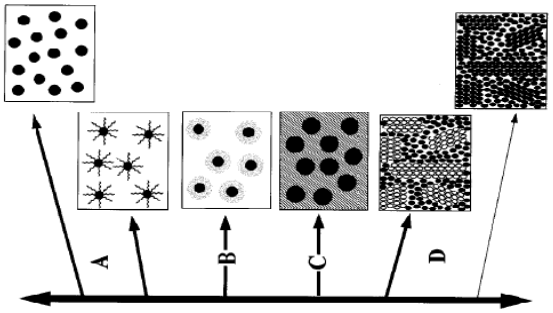

Figure 4. Types of magnetic nanostructures [19]

3.2. Methods of synthesis of nanomaterials

The first and most necessary step to study the different properties of nanomaterials and use them in different technologies is their production. Since nanomaterials often exhibit different electrical, chemical, magnetic, and optical properties than their larger counterparts, and since the emergence of these changes in material properties depends on particle size, there have been extensive efforts in recent decades to develop methods of synthesis of nanomaterials with uniform morphology and sizes for scientific and industrial applications [21].

Nanostructures with different shapes can be obtained by various methods such as dispersion and homogenization of a substance in a liquid medium or by condensation or synthesis of low molecular weight particles, so the methods of making nanomaterials can be classified according to their formation mechanism. . Accordingly, nanomaterial synthesis methods are divided into two very general approaches, top-down and bottom-up. Also, by considering other properties such as the energy required for the nanomaterial formation process, synthesis methods can be divided into two categories: high energy and low energy methods. On the other hand, considering the effective physical and chemical mechanisms in the process of nanoparticle synthesis, nanomaterial synthesis methods can be divided into two categories: physical and chemical [22] .
Due to the overlap of the features of different categories, it seems appropriate to rely on the main features of these methods. Accordingly, in the nanotechnology world, nanomaterial synthesis methods are usually divided into two main approaches, bottom-up and top-down, and chemical and physical. Both top-down and bottom-up methods play a very important role in nanotechnology. Both have advantages and disadvantages.
The main problem of top-down methods is damage to the surface structure of the material, and other disadvantages include impurities and crystal defects in the synthesized material. In contrast, bottom-up methods have advantages such as greater control over particle size and morphology, and materials synthesized by this method usually have fewer crystal defects, more homogeneous chemical composition, smaller size, and better structural order than top-down methods [18]. So far, many physical and chemical methods have been developed for the synthesis of nanomaterials, such as mechanical methods such as mechanical milling, laser pulse deposition, sequential delay density, and chemical methods such as co-precipitation and sol-gel methods [23].

3.3. Stabilization of nanoparticles

Most targeted drug delivery systems consist of nanoparticles that are homogeneously dispersed in a liquid to form a suspension. For these two-phase systems, the stability of nanoparticles is of fundamental importance and one of the major challenges in this field of technology is the stability of nanoparticles in biological suspensions [14]. The very small size and large surface area of the nanoparticles cause strong van der Waals interactions between them, and these nanoparticles tend to stick together and agglomerate in order to reduce energy and reach a steady state [24]. Agglomeration of nanoparticles not only causes them to settle and clump, but also alters some of their properties, such as thermal conductivity and magnetic properties. Therefore, research in the field of nanoparticle stability requires knowledge of physicochemical

properties and factors affecting the stability of nanoparticles. The first factor affecting the stability of particles is their size. Fine particles are usually more resistant to deposition due to brown motion and overcoming gravitational forces. Another important factor affecting the stability of particles is their electric charge, so that the stability of nanoparticles in suspensions is directly related to their electrostatic properties. The electric charge of particles usually acts as an electric potential at the interface of a double layer composed of opposite electric charges, causing repulsive forces between the particles and causing their colloidal stability. This electrical potential is called the zeta potential, which we will explain in the next section. Another important and influential factor on the particle stability is spatial repulsion forces, the nature of which is related to the surface properties of nanoparticles [25]. In general, two important factors of electrical charge of particles and surface properties play an important role in their colloidal stability (Figure 5).

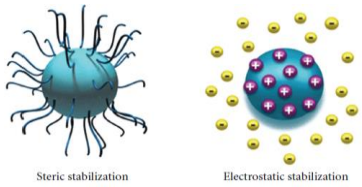

Figure 5. Scheme of electrostatic stability and spatial stability [25]

In order to increase the stability of particles and prevent agglomeration, precipitation, oxidation, erosion and change of their magnetic properties, stabilizing agents and techniques of nanoparticles are usually used. One of the simplest and most widely used techniques for stabilizing nanoparticles in suspensions is the use of ultrasonics or homogenizers. The use of these tools is considered as a powerful technique to stabilize particles by crushing and homogenizing them. Other stabilizing agents of nanoparticles include surfactants. The use of surfactants in aqueous suspensions can help stabilize the particles by affecting their electric charge. Their mechanism of action is that by modifying the surface of nanoparticles by converting hydrophobic to hydrophilic surfaces for aqueous liquids and converting hydrophilic surfaces to hydrophobic for non-aqueous liquids, as a result of the opposite charge on the surface of nanoparticles and increase zeta potential, their stability [24-25] . Other important stabilizing factors of nanoparticles include polymers that affect the surface properties of nanoparticles and create spatial repulsive forces to cause colloidal stability of nanoparticles. In the following sections, we will explain polymers in detail.

3.4. polymer

The word polymer is derived from the Greek words poly meaning many and meros meaning part or part, and refers to very large molecules made up of a very large number of smaller units called monomers [26]. Polymers are classified according to different physical, chemical and structural properties and their nature; but in terms of skeletal structure, they can be divided into three categories of linear or elongated polymers, branched and lattice. Linear polymers are a polymer filament with two ends, figure (6-a); If the branched polymers have side polymer chains branched, figure (6-b). Mesh polymers have a three-dimensional structure; Each polymer chain is connected to the other chains by a string of connecting points, figure (6-c) [27].

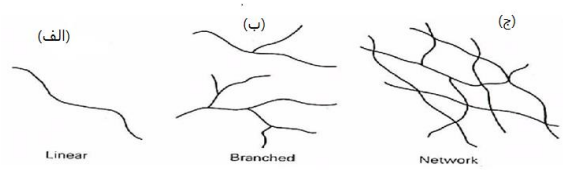

Figure 6. Demonstration of classification of polymers according to skeletal structure [62]

Naturally derived polymers, such as DNA, RNA, proteins, and polysaccharides, have been around since the beginning of life and play a vital role in plant and animal life. Humans have long used natural polymers to make clothing, cosmetics, shelter, tools, hunting tools, writing instruments and other necessities; However, the origins of today's industrial polymers have changed dramatically with important discoveries made in the nineteenth century in the production of polymers by modifications made to specific natural polymers [27].
Natural polymers are widely used for a variety of applications due to their desirable properties such as abundant availability, biocompatibility, biodegradability and renewability. These polymers are less toxic than synthetic polymers, so they are suitable for biological and medical applications such as targeted drug delivery, gene therapy, pharmacy, and the like. These polymers are primarily of plant, animal, and microbial origin and are chemically subdivided into polysaccharides, proteins, polyesters, and polyamide-based polymers (Figure 7). Careful examination of these polymers reveals their flexible nature to modify these polymers for a variety of applications. Also, the chemical bonds in these polymers are such that they can

be easily degraded by biological agents (biodegradability) in these polymers and thus increase the biocompatibility of these polymers [28].

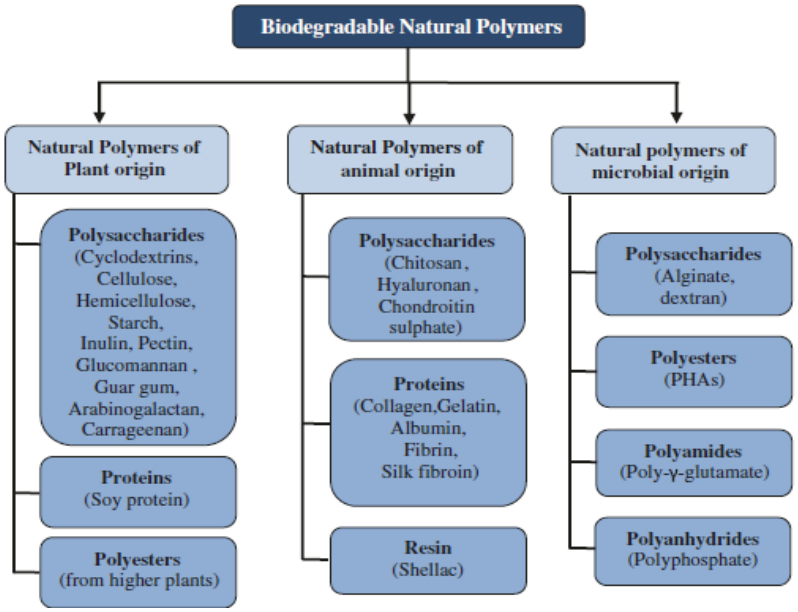

Figure 7. Classification of biodegradable natural polymers [28]

Polysaccharides, which are a class of natural polymers; They are actually carbohydrates made up of a large number of small molecules called monosaccharides. Polysaccharides are structurally divided into two main categories. The first group, called hemopolysaccharides, are made up of one type of monomer, while the second group, made up of two or more monomers, are called heteropolysaccharides. Hemopolysaccharides include starch, glycogen, cellulose and chitin [29]. Modification of nanoparticles with polymers compared to small molecules and surfactants, in addition to providing multiple functional groups and greater stability, plays a more effective role in relation to biological aspects such as distribution and mechanisms of nanoparticles adsorption and disposal in the biological environment. In addition, a wide range of biodegradable natural and synthetic polymers such as polysaccharides, polyspartates, gelatin, starch, alginate, polyacrylic acid, chitosan, and polymethyl methacrylate are commonly used to modify nanospheres.

3.5. Targeted magnetic drug delivery

In conventional drug delivery systems, such as oral and ingestable drugs or injectable drugs, drugs are distributed systemically throughout the body through the bloodstream and, in addition to diseased tissues, affect healthy organs; therefore, the side effects of drugs increase. On the other hand, due to the restrictions imposed by the immune system and the body's biological barriers, only a small portion of the drugs reach the target tissue, and this reduces the therapeutic effects of the drugs. The purpose of targeted drug delivery is to deliver the appropriate dose of drug to the target tissue and maintain the desired concentration of drugs in the body for a certain period of time (keeping the drug dose in the treatment window), in order to reduce drug side effects and increase drug effectiveness and accelerate treatment [14].

The initial ideas for targeted drug delivery came from Paul Ehrlich. Ehrlich argued that if an agent could selectively target pathogen receptors, drugs could be selectively delivered to the target tissue by that target agent, minimizing damage to healthy tissue. They had selective target cells. Ehrlich was awarded the 1908 Nobel Prize in Medicine for his research in immunology. The idea for Eric's magic bullets was not until 1940. Various strategies were then proposed based on the use of a physically stimulus-sensitive carrier with the ability to selectively bind to tumor tissue in order to deliver the drug to the target tissue by others [1].

Today, various strategies are pursued in the field of targeted drug delivery. These strategies can be divided into three general categories: active targeting, passive targeting and physical targeting. Physical targeting is based on the use of physical factors such as magnetic field, electric field, light and ultrasound. Targeted magnetic drug delivery follows such a strategy. Targeted magnetic drug delivery is one of the most effective and practical methods for delivering drugs, proteins and other therapeutic agents to specific areas of the body using magnetic materials and controlling them by applying a magnetic field. In targeted magnetic delivery, a drug or therapeutic agent attaches to a magnetic carrier and, as the magnetic carrier enters the body, focuses on the target tissue by applying an external magnetic field. The process of concentrating magnetic carriers in the target tissue is based on the competition between the forces due to blood flow and the magnetic

forces exerted by the magnetic field. Blood flow velocity is about 10 cm / s in arteries and about 0.05 cm / s in capillaries. When the force exerted by the external magnetic field on the nanocarrier overcomes the forces due to blood flow, the magnetic carriers focus on the target tissue [1, 30].

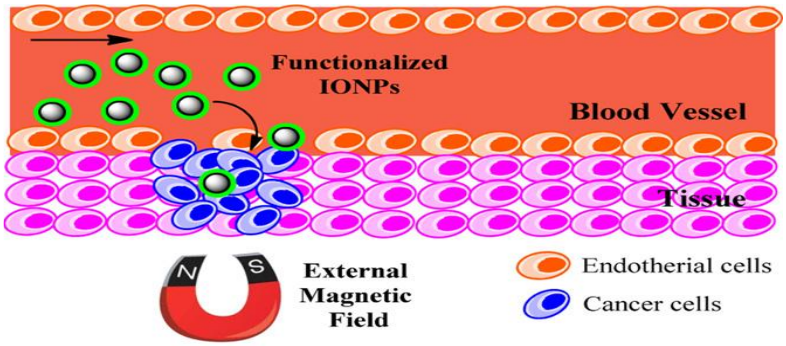

Figure 8. Schematic of magnetic nanocarriers and their concentration in the target tissue by applying an external magnetic field [14]

3.6. Properties required for magnetic nanoparticles for clinical use

For biological applications, magnetic nanoparticles need to be stable in water, the normal pH of the blood, and other physiological conditions of the body. Colloidal stability of nanoparticles is closely related to particle size as well as surface charge and particle surface chemistry. In order to apply magnetic nanoparticles in vivo, it is necessary that these nanoparticles be coated with biocompatible and biodegradable agents such as polymers to prevent them from agglomerating and agglomerating. One of the important factors that affect the biocompatibility of these nanoparticles is the degree of toxicity of magnetic nanoparticles used for biological applications. Materials such as magnetite, iron, nickel, cobalt, etc. have magnetic properties, but some of them, such as cobalt and nickel, are toxic, so there is little interest in biological applications. In addition, one of the important factors for using these nanoparticles is their small size (below 100 nm). The small size of the nanoparticles brings advantages such as high specific surface area and consequent better binding to ligands, lower sedimentation rate in liquids and thus better colloidal stability and facilitate better diffusion and distribution in body tissues. Since the dipole-dipole interaction between nanoparticles is related to the sixth power of the nanoparticle radius (r^6), further reduction of the nanoparticle size significantly reduces the bipolar-dipole interaction between them, and this is another advantage of using nanoparticles. Small in biological applications. Small particles can remain in the bloodstream for a long time after injection, and their small size increases the chances of hiding and passing through the reticuloendothelial system (part of the immune system) and also increases the half-life of nanoparticles in blood plasma. The small size of the nanoparticles makes it easier to pass through the walls of the capillaries and penetrate more effectively into the tissues of the body, facilitating their spread and preventing embolization and blockage of the arteries. Also, the physiological design of nanoparticles used in vivo should be such that it does not lead to severe reactions of the immune system [30].

Having high saturation magnetism is another necessary factor for these nanoparticles; this is because these nanoparticles must be able to respond to the external field when the magnetic field is applied and overcome the forces applied by the bloodstream and focus on the target tissue. The finite size distribution and the uniform shape and size of nanoparticles is another important factor for nanoparticles with biological applications, because nanoparticles with uniform size distribution have uniform and homogeneous colloidal properties as well as more uniform physical, chemical and physiological properties. Provides more accurate characterization, easier application, and increased efficiency of these nanoparticles in biological applications [30].

In general, the fate of nanoparticles after entering the body may face different scenarios. One of the most challenging issues when placing nanoparticles in the biological environment is the success of these nanoparticles crossing the biological barriers of the body and reaching the target tissue. In the biological environment of the body, and especially in the blood, there is a set of ions and biomolecules such as fats, metabolic agents, sugars and proteins, and after nanoparticles enter the body, these agents are formed by van der Waals, electrostatic, hydrogen and hydrogen bonds. They adhere to the surface of nanoparticles. Binding of these factors to the surface of nanoparticles leads to the formation of a coating on the surface of nanoparticles called the corona protein. Regardless of the nature of the corona protein, the formation of this coating on the surface of nanoparticles has important effects not only on the physicochemical properties of nanoparticles, but also on their physiological and biological properties and even on their colloidal stability. Therefore, the properties of nanoparticles coated with corona protein will be different from the properties of nanoparticles before entering the body's biological environment. In general, the interactions between the molecules that make up the biological environment and the

nanoparticles that are placed in this environment affect their surface properties and thus their colloidal stability. In such cases, standardized characterization can be very useful in determining the physicochemical and physiological properties of nanoparticles in the biological environment. In the first step, it is necessary to measure the colloidal nature of the synthesized nanoparticles as well as their physical and chemical properties in a solution (at least in water). Performing these tests provides information about the surface charge, hydrophilicity, hydrophobicity, and agglomeration status of the synthesized nanoparticles. In the next step, physiological characterization of the nanoparticles in the biological environment is performed. In this method, in order to fully characterize, nanoparticles are dispersed in a real biological environment and their physiological properties and interactions with the environment are investigated. In the final stage, nanoparticles are tested in vivo on an organism and then clinical trials are performed [31].

3.7. Types of magnetic drug carriers

The ability to deliver drugs and other therapeutic agents to the target area as well as control drug release in targeted drug delivery systems is very important. One of the most important challenges in targeted drug delivery systems is the very rapid and explosive release of drugs. Scientific observations show that in many cases a large amount of drug loaded on magnetic nanoparticles is isolated from magnetic nanoparticles with a very high release rate shortly after injection into the body, resulting in a very small amount of drug loaded into the tissue. Is achieved and the effectiveness of treatment is reduced. To solve this problem, magnetic nanoparticles in medical applications are designed with different shapes such as core-shell structures, liposomes, micelles and polymer carriers such as hydrogels or polymer nanoparticles (Figure 8).

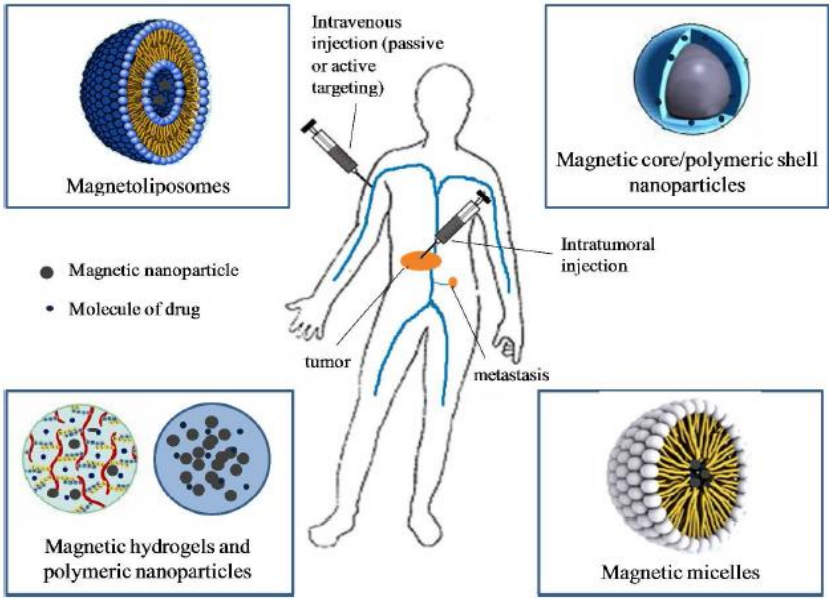

Figure 8. Types of magnetic drug carriers for biological applications [32]

Of all these structures, liposomal structures are one of the most attractive systems for targeted drug delivery applications. Liposomes are composed of a dual structure of hydrophobic and hydrophilic and have the ability to simultaneously load two types of hydrophobic and hydrophilic drugs in their structure; In such a way that hydrophilic drugs can be placed inside them and hydrophobic drugs can be placed between their two lipid layers. Another of these targeted drug delivery systems is micelles, which arise from the community of surfactants in an aqueous medium. They are formed in such a way that the polar heads of the surfactants are placed next to each other in an aqueous environment and are surrounded by water and hydrophobic parts of the surfactants. Such structures have the ability to load hydrophobic drugs in their central structure. Drug molecules can be attached to the polymer structure through a fissile bond. Micelles, like liposomes, increase the circulation time of the drug in the body and increase the accumulation of the drug in the target tissue through inactive targeting and also have the ability to escape from the reticuloendothelial system [32-33].
Another targeted drug delivery system is polymer nanoparticles, which are of great interest due to the possibility of controlling and regulating their composition, structure and some properties such as shape, size and surface charge by controlling the polymerization process. Some magnetic nanoparticles and drugs can be embedded uniformly in polymer nanoparticles and have the potential to be used as a target for targeted drug delivery as well as heat therapy for cancer. These systems have the ability that by changing some parameters such as selecting different ratios of the polymer or changing the type of polymer, special capabilities can be given to the system and based on this, systems can be designed

that use some physiological parameters such as temperature and PH. Release an optimal release rate specifically in the target tissue [32-33].
Core-shell systems are also widely used as one of the most common targeted drug delivery systems for targeted drug delivery applications and cancer thermotherapy and other biological applications. In these systems, a metal core or metal oxide usually gives the system magnetic capacity, while an organic coating can trap drugs within its structure as a drug-retaining agent. The shell also has other capabilities such as protecting the magnetic core from oxidation and agglomeration [32]. Also some recent researches have presented new approaches that can be developed for the considered subject [33-39].

4. CONCLUSIONS

1. Since nanomaterials often exhibit different electrical, chemical, magnetic, and optical properties than their larger counterparts, and since the emergence of these changes in material properties depends on particle size, there have been extensive efforts in recent decades to develop methods of synthesis of nanomaterials with uniform morphology and sizes for scientific and industrial applications.
2. Most targeted drug delivery systems consist of nanoparticles that are homogeneously dispersed in a liquid to form a suspension. For these two-phase systems, the stability of nanoparticles is of fundamental importance and one of the major challenges in this field of technology is the stability of nanoparticles in biological suspensions.
3. The polymers that are less toxic than synthetic polymers, so they are suitable for biological and medical applications such as targeted drug delivery, gene therapy, pharmacy, and the like.
4. Due to the restrictions imposed by the immune system and the body's biological barriers, only a small portion of the drugs reach the target tissue, and this reduces the therapeutic effects of the drugs. The purpose of targeted drug delivery is to deliver the appropriate dose of drug to the target tissue and maintain the desired concentration of drugs in the body for a certain period of time (keeping the drug dose in the treatment window), in order to reduce drug side effects and increase drug effectiveness and accelerate treatment.
5. For biological applications, magnetic nanoparticles need to be stable in water, the normal pH of the blood, and other physiological conditions of the body.
6. Colloidal stability of nanoparticles is closely related to particle size as well as surface charge and particle surface chemistry.
7. Another targeted drug delivery system is polymer nanoparticles, which are of great interest due to the possibility of controlling and regulating their composition, structure and some properties such as shape, size and surface charge by controlling the polymerization process.
8. One of the most important challenges in targeted drug delivery systems is the very rapid and explosive release of drugs. To solve this problem, magnetic nanoparticles in medical applications can be designed with different shapes such as core-shell structures, liposomes, micelles and polymer carriers such as hydrogels or polymer nanoparticles.

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