Nanoparticles and Nanospheres for Controlled Drug Delivery Systems

Abstract
Nanotechnology is a new field that engineers and scientists are vigorously researching because it has a great potential to improve the quality of life in multiple areas. One of the most promising fields of this cutting edge technology is the study of drug delivery systems. Engineering at the nanoscale can considerably improve bioavailability and disease treatment in general. Controlled nanoscale drug delivery systems are more efficient, reduce toxicity, and are more convenient than traditional methods. Nanoparticles can be manipulated to target areas of the body specified by the doctors. Once this technology transitions from the labs to the operating rooms it can bring hope and life to people dwindling at the edge of death.
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Introduction
Nanoparticles and nanospheres are the principal drug carriers proposed by nanotechnicians. Nanoparticles provide a new system to cure age-old health problems by delivering a concentrated amount of medicine to a specific area of the body. This revolutionary medical treatment goes beyond current methods of digestion or injection of drugs. Traditionally, patients have medicine distributed throughout their entire body which causes various side effects. In the near future, nanoparticles will enhance medical treatment by targeting individual cells and controlling drug distribution. Therefore the drug will not have to travel through the entire body. Instead, magnetic nanoparticles can be directed to the desired location through the application of an external magnetic field. The origin, types, synthesis, and physics behind this technology will be further discussed and explained followed by pros vs. cons and a critical analysis.
Origin of Nanoparticles
Technically speaking, nanoparticles have existed since the beginning of the world. However, they were first researched and studied for drug delivery systems around the 1970’s when they were devised as carriers for vaccines and anticancer drugs employing drug targeting to increase tumor uptake [8].

Types of Nanoparticles
There are various ways to classify nanoparticles. One of the most basic ways, found on the book written by chemists Mark and Daniel Ratner divides them into the following categories:

A. Polymer nanoparticles: These are particles made of polymeric materials, which have small cavities where a drug can be stored. Once swallowed by the patient, the enclosed drugs are released. This method facilitates a continuously smooth delivery over an extended period of time [7].

B. Nonpolar nanocoating: Many drugs cannot pass through membranes surrounding the cells due to their polarity. Polar drugs have difficulty reacting with nonpolar membranes. To fix this problem, non-polar nanoscale coatings can be devised to encapsulate and deliver the polar drug with no problem [7].

C. Smart materials and nanoparticles: The idea behind the development of these types of materials is to make them react only under certain conditions. For example, polymer nanoparticles can be equipped with bio receptors in their outer shell which can detect and respond to specific biochemical signals that will release the drug from inside the particle [7].
D. **Magnetic nanoparticles**: These are bound by molecular recognition of the cells which will cause the drug to be delivered. An applied external magnetic field can manipulate the position of the nano-dot; therefore it controls the delivery of the drug [7].

**Synthesis of Nanoparticles**

A. **Combustion** of iron pentacarbonyl and carbon monoxide is one method of producing nanoparticles. In this procedure a chain of iron oxide aggregate is produced [1].

B. **Fe3O4 nanoparticles** can be produced from a solution of ferric chloride (FeCl₃) and ferric sulfate (FeSO₄) under a magnetic influence. The mixture is prepared and kept under argon protection while an ammonia aqueous solution is quickly stirred into the mixture. The resultant is kept under a circular magnet; the magnetic field differs according to the location of the flask relative to the magnet. After aging for one day, the precipitate is filtered and washed with de-ionized water and ethyl alcohol. The result is Fe₃O₄ nanoparticles [2].

C. In **coprecipitation**, two methods are used to produce magnetic nanoparticles.

1. Ferrous hydroxide suspensions can be partially oxidized with different oxidizing agents. This method produces nanospheres with diameters of 30 to 100 nm [3].

2. The other method ages a mixture of ferrous and ferric hydroxides in an aqueous medium. In this method, the particle size can be controlled by
adjusting the pH or ionization of the medium. Size ranges from 2 to 15 nm [3].

D. **Microemulsion** uses a mixture of water and oil to create microcavities that can control particle nucleation and growth [3].

E. **Polyols** in a solution with dissolved metallic salts can cause metal precipitation of fine metallic nanoparticles [3].

F. **High temperature decomposition of organic precursors** is a method in which iron precursors decompose in the presence of hot organic surfactants. It allows a good control of size and crystallinity of individual magnetic iron oxide nanoparticles [3].

**Magnetic Nanoparticles:**

A. **Size**

Magnetic nanoparticles have controllable sizes, ranging from a few nanometers up to tens of nanometers. This is comparable to the sizes of cells (10-100 micrometer), viruses (20-450 nm), proteins (5-50nm), and genes (2nm wide and 10-100nm long) [4]. Due to their size range and how they compare to those important biomedical parameters mentioned above, magnetic nanoparticles show great potential as targeted drug delivery mechanisms. They are small enough to travel through the body and big enough to encapsulate a drug to properly deliver it to the desired location.

B. **Physical Laws and implications**

To better understand magnetic nanoparticles, a little background on the basic physics behind their development is necessary. The physics is very simple. The study of
magnetism and how this phenomena interacts with different materials is key to understanding the nature of these nanoparticles.

1. Magnetism:

The study of magnetism and its effects on nanoparticles is key to the development of this technology. Both the nanoparticles and the biomolecules possess magnetic properties. When a material is placed in a magnetic field, this magnetic field is going to induce a response on the material, which follows the formula;

\[ B = \mu_0(H + M) \]  \[4\]

Where \( B \) is the magnetic field strengths, \( \mu_0 \) is the permeability of space, \( M \) is the magnetization (magnetic moment per unit volume), and \( H \) is the magnetic field moment \[4\].

2. Types of magnets

_Ferromagnets_ are materials which develop extremely strong magnetic properties when magnetic domains become aligned in the absence of an applied field. For example, iron, nickel, cobalt, and gadolinium are ferromagnetic at room temperature. Ferromagnetism is believed to be caused by magnetic fields generated by the electrons' spins in combination with a mechanism known as exchange coupling, which aligns all the spins in each magnetic domain \[5\].

_Ferrimagnets_ are materials whose atoms or ions tend to assume an ordered but nonparallel arrangement in the absence of a magnetic field below a certain characteristic temperature. A substantial net magnetization results from the antiparallel alignment of neighboring nonequivalent sub-lattices \[6\].
3. **Forces:**

The force applied on a point like magnetic dipole is given by the equation;

\[ F_m = (m \cdot \nabla)B \]  \[\text{[4]}\]

Where \( F_m \) is the force on the particle, \( m \) is the point-like magnetic dipole, \( \nabla \) is a mathematical vector gradient operator, and \( B \) is the magnetic field strength.

4. **Magnetic Separation**

Magnetic separation is one way to separate specific biological entities from their native environment. This is important to biomedicine applications so that concentrated samples may be prepared for subsequent analysis. It follows a two-step process where the desired biological entity is labeled with magnetic material and separated out through fluid based magnetic separation [4].

Labeling the entity is made through chemical modification of the surface of the magnetic nanoparticles. This is accomplished by coating the particles with biocompatible molecules. Specific binding sites on the surface of the cells are targeted by antibodies or other biological molecules like hormones or folic acid. These biological molecules specifically bind to their matching antigen. This provides a highly accurate way to label cells [4].

The magnetically labeled material is then separated from its native solution by passing the fluid mixture through a region in which there is a magnetic field gradient. This can immobilize the tagged material following the magnetic force equation [4].
C. Drug Delivery

Now that the basic physics laws have been covered, it is important to recognize how this actually affects nanoparticles and drug delivery systems. In order to achieve this, we must consider three steps.

1. Magnetic Guidance

Once the nanoparticles have entered the body, they need to be guided to the desired area. This is where the magnetic forces and interactions come to play. The concept is very simple. An outside magnet induces a magnetic field, which in turn induces a force on the nanoparticles directing them through the body [3][4].

A schematic representation is shown below on figure 1.

![Figure 1: Schematic representation of the magnetically driven transport of drugs to a specific region. A catheter is inserted into an arterial feed to the tumour and a magnetic stand is positioned over the targeted site.][3]

In the figure above, a magnet applies a magnetic field which is represented by the oval-shaped lines. This field imposes a force on the magnetic carriers (nanoparticles) which then move through the artery until they reach the organ.
Since the nanoparticles are traveling through the bloodstream, they experience a drag force. Therefore, it is important to design the magnet and nanoparticles to overcome this force and be able to move through the blood. This also plays an important role when sizing the nanoparticle, since larger diameter nanospheres are able to withstand flow dynamics better than smaller size ones [4].

2. **Target location**

The second step is to get the particle to recognize the specific targeted cell. This could be achieved in various ways. One possibility is to place chemicals in the nanoparticles that are in an inactive state. These chemicals would “wake up” when they encounter a signal or chemical that they would react to, thus releasing the drug [7]. Another way to achieve this would be to coat the nanoparticles with enzymes or proteins. Once they reach their target, the cells recognize them and allow them to pierce their membrane, thus “swallowing” the drug [7].

3. **Drug Release**

Once the nanoparticles have reached and recognized their target, they can release the drug because of the chemical signals. Also, when the nanoparticles pierce through the membranes of the cell they carry the drug along with them.

**D. Advantages and Disadvantages**

As we have discussed throughout this paper there are various advantages to this new technology. The ratio of the amount of drug to which a person is exposed to the actual dose of the substance the body receives (bioavailability) is greatly increased because of the specific targeting that this technology allows doctors to employ. This, in turn,
decreases the amount of drugs needed to achieve the goal, as well as the amount of drug or chemicals the body is exposed to. Also, it localizes the action of these external chemicals, minimizing their effect on other cells or organs within the body. This also decreases the side effects a medicine may produce on patients. Targeted delivery assures doctors that the treatment is delivered to the location in the desired amount.

However, everything comes at a price, and this technology does offer some minor disadvantages. The fact that these particles have not been tested on humans yet means that we do not know for certain how our bodies will react to them. Because they are an external agent they could be toxic to the human body. Also, nanoparticles may cause embolization of the veins. This means that the veins close up and obstruct blood flow through them, which could cause serious health problems to the patient.

**Critical analysis**

Drug delivery through nanoparticles is a promising technology that needs to be further researched. While all the work and research currently being done by nanotechnologist is excellent and ingenious, there is still room for improvement. One consideration that has been overlooked is the possibility of a remotely controlled drug delivery system through nanoparticles or a self-guided smart nanoparticle. A remotely controlled nanoparticle would not need the application of an external magnetic field to the body, and some of the possible toxic hazards caused by the magnetic materials would be avoided. If more research is made in the area, this could even further revolutionize drug delivery. Also, smart nanoparticles could be created by encoding in them a map of the circulatory system that guides them through the veins until they reach the desired cell. This technology
involves a lot of nanoelectronics and imagination, but there is nothing stopping man from reaching these goals in the future. If researchers focused on these proposed techniques, they may become a reality. Another important aspect to consider researching is that transition from animals to humans. This technology can not be employed massively until it is proven how the human body will react to the nanoparticles. Therefore, this area is critical to its future. Also, nanoparticles need to be produced more massively in order to cover the demand for treatments. The transition from laboratory experiments to mass production will create a big impact on the economy.
Conclusion
Contrary to what one might believe before researching the topic, there are various kinds of nanoparticles and ways to synthesize them. Drug delivery through nanoparticles has the promising potential to cure diseases that have troubled humanity for centuries. They also revolutionize the field of biomedicine by increasing bioavailability and minimizing drug scattering on the body. It is almost impossible to believe that the physics behind this technology is very simple and easy to understand. The simplest explanation is generally the best explanation; this might be the reason why such a simple technology is so cutting edge and promising to the advancement of science and humanity.
References


