Sudan University of Science and Technology

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Modeling and Simulation of AuNPs based Drug Delivery System

نمذجة ومحاكاة نظام توصيل الدواء اعتمادا على جسيمات الذهب النانوية

This Thesis Submitted in Partial Fulfillment for the Requirement of the Degree of M.Sc. in Biomedical Engineering

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الآية

"وَهُوَ الَّذِي أَنْشَأَ لَكُمُ السَّمْعَ وَالْأَبْصارَ وَالْأَفْئِدَةَ قَلِيلًا ما تَشْكُرُونَ * وَهُوَ الَّذِي ذَرَأَكُمْ فِي الْأَرْضِ وَإِلَيْهِ تُحْشَرُونَ * وَهُوَ الَّذِي يُحْيِي وَيُمِيتُ وَلَهُ اخْتِلافُ اللَّيْلِ وَالنَّهارِ أَفَلا تَعْقِلُونَ "

المؤمنون(78-80)

Dedication

To my parents; who encourage, support, and believe on me to do the best.

To my brothers and sisters for standing by me.

To my friends, who motive and encourage me to be the best.

To Sofia Ali and Hassan Fadol for supporting and helping me.

Acknowledgement

Our grateful thanks to Allah for guiding and giving me the strength to complete this project with HIS mercy, kindness and blesses. Thanks are progressed specially to Dr. Fragoon Mohammed Ahmed for his wise supervisory and guidance. Thanks to Eng. Alsida Fatima and Eng. Saleh Elabase for helping me to finish this project.

Abstract

Drug delivery system is the method or process of introducing therapeutic substances into a body and improves efficiency and safety by controlling the rate, time and place of release of drugs in the body. In the past, the delivery of the drug faced many problems such as failure to reach the appropriate amount of specific cells. The drug delivery system using nanotechnology has limited or reduced these problems; despite some of the side effect problems of using this technology, such as the high cost of devices and the methods of manufacturing gold nanoparticles. In this study, COMSOL Multiphysics was used to illustrate the drug delivery system. Emphasis was placed on specific factors such as velocity, concentration and amount of drug delivered to the selected cells; from the results was observed that the concentration and amount of the drug delivered to cells using nanotechnology is appropriate according to compare with the previous studies and standard value of the concentration and amount of the drug delivered to cells.

المستخلص

نظام توصيل الدواء هو طريقة أو عملية إدخال المواد العلاجية الى جسم ويُحسِن الكفاءة والسلامة من خلال التحكم في معدل وزمن ومكان إطلاق الأدوية في الجسم. في الماضي كان توصيل الدواء يواجه الكثير من المشاكل مثل عدم وصول الكمية المناسبة للخلايا المحددة. نظام توصيل الدواء بإستخدام تقنية النانوتكنولوجي حد أو قلل من هذه المشاكل بالرغم من وجود بعض المشاكل الجانيبة من استخدم هذه التقنية كالتكلفة العالية للاجهزة وطرق تصنيع جسيمات الذهب النانوية. في هذا البحث تم استخدام برنامج COMSOL Multiphysics لتوضيح نظام توصيل الدواء تم التركيز على عوامل محددة مثل السرعة وتركيز وكمية الدواء التي يتم توصيلها للخلايا المحددة ; من النتائج تم ملاحظة أن تركيز الدواء وكميته التي يتم توصيلها الى الخلايا باستخدام تقنية النانوتكنولوجي مناسبة عند مقارنتها مع الدراسات السابقة والقيم القياسية لتركيز الدواء وكميته التي يتم توصيلها الى الخلايا.

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Chapter one

Introduction

1.1 General review:

Cancer is a disease which occurs when changes in a group of normal cells within the body lead to uncontrolled growth causing a lump called a tumor [1]. Cancer also is difficult and complex to determine and detect it; and that are a lot of things causes the cancer including tobacco use, certain infections, radiation, lack of physical activity, fatness, and environmental contamination. It was found that five to ten people with cancer had a genetic cause. Recently cancer is become common and a lot of people around the world are suffering from; and it is usually treated with chemotherapy, radiation therapy and surgery [2]. The researchers are presently focusing on the improvement, development and investigations of new methods that can help them on treatment without destroy or affect the health cell. One of this methods use the nanotechnology as carrier of drug; it was discovered recently and used in many fields one of this is medical field. In medical field it is used also in many areas such as sensors and drug delivery. Nanotechnology is the study of extremely small structures, having size of 0.1 to 100 nm. Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect. That is a special form of drug delivery system where the medicament is selectively targeted or delivered only to its site of action or absorption and not to the non-target organs or tissues or cells called targeted drug delivery system. A drug carrier is any substrate used in the process of drug delivery which serves to improve the selectivity, effectiveness, and/or safety of drug administration. Drug carriers are primarily used to control the release of a drug into systemic circulation.

1.2 Problem statement:

In conventional drug delivery system there are a lot of problems faces drug till deliver to specific cell such as poor solubility, rapid clearance, a lack of targeting, and often poor translocation ability across cell membranes. Lack of devices used to monitor drug delivery also lack of teams who have experience in laboratory experiments.

1.3 Objectives:

1.3.1 General objective:

The general objective of this research is to model and simulate of AuNPs based drug delivery system.

1.3.2 Specific objectives:

The specific objectives of this research are to:

- Model the drug delivery system as software by using COMSOL Multiphysics.
- Simulate the model to ensure that is easy to work and make change.
- Design low cost drug delivery system based on nanotechnology to use in medical application.

1.4 Methodology:

To design the desired model and simulate it, firstly the data was collected from previous theories and experiences. Secondly the mathematical calculations (mathematical model) that are needed in the model have been done. Finally a design simulation by using COMSOL Multiphysics software was done to make sure the model works well.

1.5 Thesis layout:

The first chapter outlines the general view of the project followed by the problem definition and the objectives behind this design. The second chapter gives a back ground study and literature review about research. The third chapter states the theoretical fundamental of the drug delivery system, nanotechnology and COMSOL Multiphysics. Chapter four explains the method and the steps followed to design model. Chapter five shows the results and their discussions. Finally the conclusion and recommendations are given in chapter six.

Chapter two

Literature review

2.1 Introduction:

Nanotechnology originally came into existence in 9th century by Mesopotamian people for giving lustrous effect in pots. For the first time in 1857, Michael Faraday discovered the ruby gold nanoparticles (AuNPs), which became the foundation for the modern nanotechnology. Forty years later, Zsigmondy merged his technology with Faraday's discovery and introduced the procedure called, 'seed mediated method', which would still be used in the present day for the synthesis of various NPs. Zsigmondy also invented an ultramicroscope for characterizing the structure, shape, and size of NPs. Another scientist, Svedberg introduced ultracentrifuge and showed that the motion of macromolecules (colloids) depended on their shape and size. In the similar period, G. Mie tried to find out the reason for various colors of gold (Au) colloids. Recently, the applications of AuNPs expanded into various biomedical fields, such as biosensors, clinical chemistry, immunoassays, genomics, photothermolysis of cancer cell, microorganisms detection and control, targeted drug delivery, optical imaging and monitoring of biological cells and tissues by exploiting resonance scattering, or in vivo photo acoustic techniques [3].

Hossein Jahangirian, et al., (2017): used nanoparticles (NPs) to treatment diseased cells because it improves efficiency, decrease the side effects and enhance healthcare of human. In addition to that explained the use of nanodrug delivery also have side effect and should be not ignored. Furthermore discussed the impact of green chemistry (includes all branches of chemistry and all ways to produce new substances) on the field of nanotechnology drug delivery and it creates new field called green nanomedicine. Besides that the main goals of green chemistry were been defined such as design of reactions of the greatest efficiency. Also green nanotechnology was defined as the application of the 12 principles of green chemistry to design new nanomaterial to achieve economic, social health and

environmental benefits. One of the examples for the applications of green chemistry for nanodrug carriers depends on gold NPs (AuNPs). In addition to that demonstrated production NPs by green chemical reactions. Finally it was reported that the green chemistry methods are more efficient for synthesis or product of nanomaterial compared to other method and also helped to obviate one of which largest involvement faced with today's NP drug delivery systems is toxicity [4].

M. Ramezanpour, et al., (2016): explained that the importance of drug delivery is the same of the drug itself and the some challenges are facing the drug delivery like endo or epithelial membranes. The Drug Delivery System (DDS) as a capsule that it content the drug and could been said DDS is an ideal cause it is easy to run, non-toxic and transfers the drug to the specific area and practically the advantages for an ideal DDS are a cheap and simple to make. The aim for DDS is to optimize NPs and the small DDS (NP) is better than larger DDS. The different types of NPs those are exist such as liposomes, dendrimers, carbon nanotubes (CNTs), inorganic and polymer-based NPs. Also the physiochemical properties of NPs and explained the physical characteristics of NPs are a significant step in designing DDS. In addition to that some research has encountered practical and substantial difficulties in spite of the practical and technological development in measuring, designing and improving the structures and dynamics of nanoparticles; and most of DDSs success in vitro but fail in vivo. The computer modeling techniques provided detailed information about interactions and some other physical properties. Then described the main experimental approaches to characterize NP-based DDSs and concentrate in more detail on present applications of computer simulations aimed at understanding molecular sides of DDSs in this review. The common biophysics and computer approaches used to understand the DDSs. Although concentrated specific computational studies of many major types of NPs used in drug delivery research. In general computer

simulation has ability to give a lot of details of NPs structure and their interactions with drugs. The DDSs efficiency depend on many parameters such as stability in the bloodstream, targeting to the desired tissues, uptake by endocytosis or other mechanisms, and final release of the drugs [5].

Xiaojiao Yu, et al., (2016): started by explaining the properties of NPs and how it improves and their uses as drug carrier. The method that used to create or manufacture the medical NPs is called bottom-up method. The ways of transport drug-loaded nanoparticles into three main categories: passive targeting; which relies on the permeability and retention (EPR) effect, active targeting; which uses ligand-receptor interactions for more selective drug delivery, and physical targeting; which uses external sources or fields to guide NPs to the target site and to control the release process and it is still at the clinical trial stage. NPs can self-assembly as many compositions such as amphiphilic micelles and liposome, and also more exotic rotaxanes, dendrimers, and metal core particles. Any particles of these have a specific advantages and disadvantages and it is compatible to deliver many therapies into many areas. Micelles and liposomes are the most typical NPs that have been used as drug delivery carrier, as for the other particles there are a lot of research on it. Rotaxanes can release cargo in response to a tailored stimulus, while dendrimers can sometimes maximize surface area and cargo capacity when compared with simple spherical structures. In addition, metal-core particles are a good choice for physical and combination physical-active or physical-passive targeting. There are many challenges of experimental development of NPs such as size, shape, and surface charge must all be controlled to carry drugs to the target site. Unsuitable physical parameters and environmental differences sometimes have effects on drug delivery efficacy and that maybe cause side effects. NPs should be firstly tested in both living cells and tissue and after that moved it into vivo tests [6].

S. Bhatia (2016): illustrated that the a lot of emerging department in pharmaceutical sciences known as " Pharmaceutical nanotechnology " presents new tools, chances and field, which are predictable to have considerable applications in disease diagnostics and therapeutics. Now days nanopharamceuticals show massive potential in drug delivery as carrier for spatial and temporal delivery of bioactive and diagnostics. Beside that it also supplies smart materials for tissue engineering. This field is now well-established for drug delivery, diagnostics, prognostic and treatment of diseases through its nanoengineered tools. Pharmaceutical nanotechnology includes nano sized products which can be modified in numerous methods to enhance their characteristics. Drugs that are transformed into nano range display some unique features which can lead to prolonged circulation, improve drug localization and enhance drug efficacy. Several pharmaceutical nanotechnology based systems which can be described as nanopharmaceuticals like polymeric nanoparticles, magnetic nanoparticles, liposomes, carbon nanotubes, quantum dots, dendrimers, metallic nanoparticles, polymeric nanoparticles. With help nanopharmaceuticals, Pharmaceutical nanotechnology could have a profound impact on disease protection to support better insights into the molecular basis of disease. However some recently set health risk evidences limits their utilization in pharmaceutical industry. With regard to some issues like safety, bioethical issues, toxicity hazards, physiological and pharmaceutical challenges obtained to be intent by the scientists. Current researchers are yet lacking enough data and guidelines related to safe use of these nanotechnology based devices and materials. Thus pharmaceutical nanotechnology is still in infancy. His research summarized the types of nanopharmaceuticals with the most important applications and nanoparticles associated health risk related information available till present [7].

Sean McGinty, et al., (2015): presented a general model of drug release from a drug delivery device (DDD) and the subsequent transport in biological tissue. The model of drug delivery from a DDD comprises a challenging problem from a mathematical and computational view. Any model should be established on equilibrium between generality (flexible and able to describe a number of different cases), reliability (able to capture the qualitative behavior) and simplicity (only include the important features and be easy to use). The fact is that biological systems are very complex and some degree of simplification is require if any development is to be made. In this paper they have presented a general and integrated model of drug release and tissue distribution that may be forced to a number of drug delivery systems. The model regards for the built up effects of diffusion, dissolution and solubility in the polymer coating and can model many different types of binding in the tissue, ranging from nonlinear saturable reversible to linear irreversible binding. By presenting the case of a drug-eluting stent, the able to demonstrate that the model can provide results which are consistent with in-vivo experimental data, and moreover, provides added value over experiments in that concentration profiles can be calculated for the drug in each phase - this is virtually impossible to do by experiments alone. The model will be beneficial to better understand the drug release kinetics of existing DDD, and in designing those of the future [8].

Faheem, et al., (2014): explained that the nanoparticles are increasingly being necessary tool of recent day research in most every field of science. Application of gold nanoparticles, especially in cancer imaging and therapy is remarkably promising over the recent surge of scientific communications from all around the world. Apart from being biocompatible and non-toxic, surface plasmon resonance enhanced light scattering and absorption, and their ability to convert absorbed light into localized heat makes them more suitable as agents for photothermal cancer

therapy resulting in thermal ablation of the cancer cells. Furthermore, the high surface-to-volume ratio of the gold nanoparticle supports the bio-functionalization of their surface with ligands that can specifically target the cancer cells and also with biocompatible polymers, making them more suitable for in vivo applications. Their review focused on overview of characteristic features, synthesis and potential applications of gold nanoparticles in cancer therapy and diagnosis [9].

2.2 Summary:

The studies mentioned above are concern in the methods that are used to synthesis the NPs, the advantages and disadvantages of NPs rather than improve the method for deliver drug to the cells and use of GNPs material for this purpose.

Chapter three

Theoretical background

3.1 Introduction:

Nanotechnology is relatively new, and although the full scope of contributions of these technological advances in the field of human health care remains unexplored, recent advances suggest that nanotechnology will have a profound impact on disease prevention, diagnosis, and treatment [10].

3.2 Nanotechnology:

The prefix "nano" is a Greek word which means "dwarf". The word "nano" means very small or miniature size. The term nanotechnology was first used in 1974 by the late Norio Taniguchi (University of Tokyo) to refer to the ability to engineer materials precisely at the scale of nanometers. Nanotechnology is the study of extremely small structures, having size of 0.1 to 100 nm. Also it can be defied as the design and fabrication of materials, devices and systems with control at nanometer dimensions [11, 12].

Nanotechnology recently has become one of the very important and existing fields in Physics, Chemistry, Engineering and Biology [13].

3.2.1 History of nanotechnology:

The development in the field of nanotechnology started in 1958 and the various stages of development have been summarized in Table (3.1) [11].

Table 3.1 Periodical development in nanotechnology

Year	**Development in nanotechnology**
1959	R. Feynman initiated thought process
1974	The term nanotechnology was used by Taniguchi for the first time.
1981	IBM Scanning Tunneling Microscope
1985	"Bucky Ball"
1986	First book on nanotechnology Engines of Creation published by K. Eric Drexler, Atomic Force Microscope
1989	IBM logo was made with individual atoms

1991	S. Iijima discovered Carbon Nano tube for the first time.
1999	1st nanomedicine book by R. Freitas “Nano medicine” was published
2000	For the first time National Nanotechnology Initiative was launched
2001	For developing theory of nanometer-scale electronic devices and for synthesis and characterization of carbon nanotubes and nano wires, Feynman Prize in Nanotechnology was awarded
2002	Feynman Prize in Nanotechnology was awarded for using DNA to enable the self-assembly of new structures and for advancing our ability to model molecular machine systems.
2003	Feynman Prize in Nanotechnology was awarded for modeling the molecular and electronic structures of new materials and for integrating single molecule biological motors with nano scale silicon devices.
2004	First policy conference on advanced nanotech was held. First center for nanomechanical systems was established, Feynman Prize in Nanotechnology was awarded for designing stable protein structures and for constructing a novel enzyme with an altered function.
2005-2010	3D Nano systems like robotics, 3D networking and active nanoproducts that change their state during use were prepared.
2011	Era of molecular nanotechnology started

3.2.2 Types of nanotechnology:

Nanotechnology is divided to two basic types:

1. **Nanomaterial**
2. **Nano devices**

The types and sub classified of nanomaterial and nano devices are shown in the schematic diagram (Figure 3.1) [12].

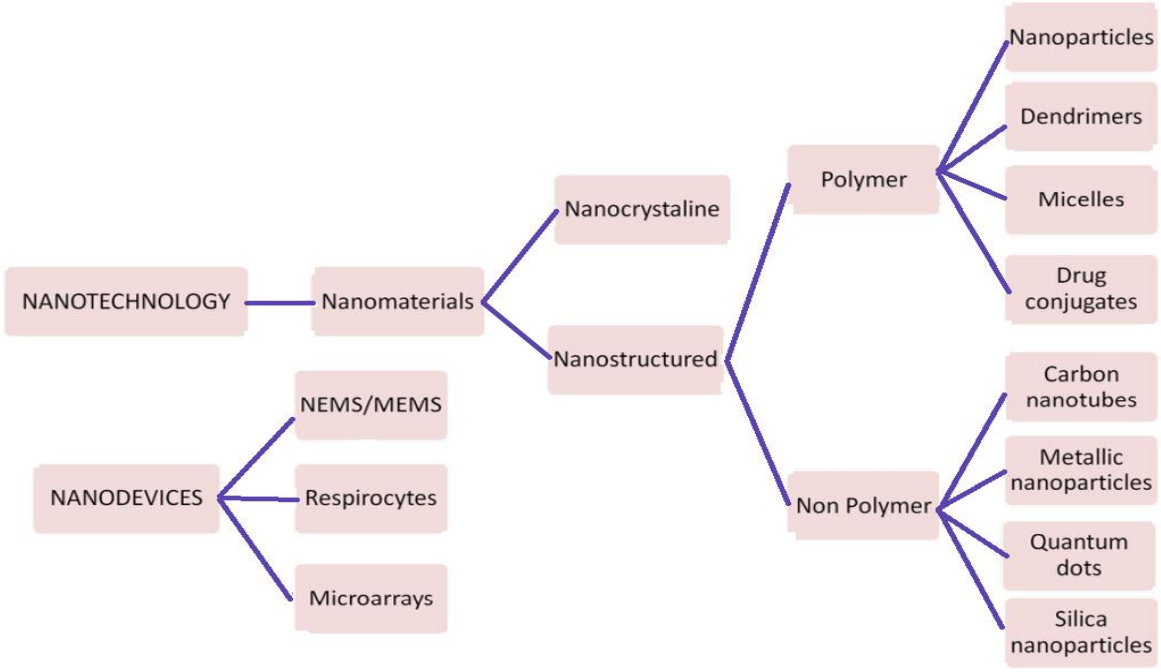

Figure 3.1 Schematic diagram of various types of nanotechnology

3.2.3 Nanotechnology uses in Medicine:

National Institute of Health in USA defines nanomedicine as "highly specific medical intervention at the molecular scale for diagnosis, prevention and treatment of disease" [13].

3.2.4 Advantages of Nanotechnology:

- Nanotechnology-based delivery systems can also protect drugs from degradation.
- Improved products may be available with a change in the physical properties when their sizes are shrunk.
- Reduce the number of doses required.
- Make treatment a better experience and reduce treatment expenses.
- Nano-based systems allow delivery of insoluble drugs.
- Allowing the use of previously rejected drugs or drugs which are difficult to administer.

- Drug targeting can be achieved by taking advantage of the distinct pathophysiological features of diseased tissues.
- An ideal targeting system should have long circulating time; it should be present at appropriate concentrations at the target site.
- It should not lose its activity or therapeutic efficacy while in circulation.
- Tumors allow an enhanced permeability and retention effect.
- Passive targeting of drugs to the macrophages present in the liver and spleen.
- Nanotechnology offers a solution for using the numerous chemical entities for treating brain disorders that are not clinically useful because of the presence of the blood-brain barrier.
- Improve the oral bioavailability of the agents that are not effectively used orally [10].

3.2.5 Applications of Nanotechnology:

- Health and Medicine.
- Electronics.
- Transportation.
- Energy and Environment.
- Space exploration [14].

3.3 Nanoparticles (NPs):

According to American Society for Testing and Materials (ASTM international 2006), nanoparticles are those particles which have two or more than two dimensions and are in the size range of 1 – 100 nm . These particles have special and enhanced physical and chemical properties as compared to their bulk materials due to their large reactive and exposed surface area and quantum size effect as a result of specific electronic structures. These particles have been widely used in many fields such as electronics, photochemical, biomedicine and chemistry.

Regardless of the nature of nanoparticles, their most important physical properties are the following:

- Surface area. It has been found that properties vary with particle size. In sub-micrometer particles, forces that govern the atomic or molecular universe dominate to the detriment of statistical aspects, which are revealed at the macroscale.
- Optical properties. Nanoparticles often have particular optical properties, as they are small enough to limit the thickness of the common electron layer of metals; this phenomenon generates quantum effects. Although it is common knowledge that gold is yellow and silicon is grey, gold and silicon nanoparticles are bright red to black. Moreover, gold nanoparticles melt at a much lower temperature (~ 300ºC, 2.5 nm size) than gold slabs that melt at 1064ºC. Solar energy absorption in photovoltaic cells made of silicon-based nanomaterials is much higher than in thin films of the same materials. The smaller the particles, the higher the absorption efficiency.
- Uniformity. Clusters, aggregates or filaments, in other words, the molecular or atomic assemblies that form nanoparticles, are defined by the interaction of forces among the molecules or atoms of a particle and the interaction forces among particles.
- Functionalization. Nanoparticles of any type can be linked to microbiological entities randomly, through natural processes occurring in atmosphere, water or at the surface of the Earth. Nanoparticles are then directed to living organisms, organelles within the cells and individual protein or RNA molecules. This property is related both to the harmful effects of nanoparticles on the living

kingdom and the pharmaceutical or biochemical studies conducted voluntarily, to the level of peptide molecules.

- Quantum confinement. Changes in size-dependent properties also include quantum confinement, a phenomenon which causes spontaneous properties of semiconductivity, conductivity or electric insulation for neighboring particles less than 10 nm in diameter [10,15,16]

3.3.1 Classification of NPs:

Nanoparticles are broadly classified in to three:-

i. One dimension NPs:

One dimensional system (thin fi lm or manufactured surfaces) has been used for decades. Thin films (sizes 1–100 nm) or monolayer is now common place in the field of solar cells offering, different technological applications, such as chemical and biological sensors, information storage systems, magneto-optic and optical device, fiber-optic systems.

ii. Two dimension NPs:

The carbon nanotubes.

iii. Three dimension NPs:

Dendrimers, Quantum Dots, Fullerenes (Carbon 60).

3.3.2 Characterization of NPs:

Characterization of nanoparticles is based on the size, morphology and surface charge, using such advanced microscopic techniques as atomic force microscopy (AFM), scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Properties such as the size distribution, average particle diameter, charge affect the physical stability and the in vivo distribution of the nanoparticles. Properties like surface morphology, size and overall shape are determined by electron microscopy techniques. Features like physical stability and

redispersibility of the polymer dispersion as well as their in vivo performance are affected by the surface charge of the nanoparticles. Different characterization tools and methods for nanoparticles are mentioned in table (3.2). Therefore it's very important to evaluate the surface charge during characterization of nanoparticles [17].

Table 3.2 various characterization tools and methods for nanoparticles

Parameter	**Characterization method**
Carrier-drug interaction	Differentials scanning calorimeters
Charge determination	Laser Doppler Anemometry Zeta potentiometer
Chemical analysis of surface	Static secondary ion mass spectrometry Sorptometer
Drug stability	Bioassay of drug exacted from Nanoparticles Chemical analysis of drug
Nanoparticle dispersion stability	Critical flocculation temperature (CFT)
Particle size and distribution	Atomic force microscopy Laser defractometry Photon correlation spectroscopy (PCS) Scanning electron microscopy Transmission electron microscopy
Release profile	In vitro release characteristics under physiologic and sink
Surface hydrophobicity	Rose Bengal(dye) binding Water contact angle measurement X-ray photoelectron spectroscopy

3.3.3 Gold NPs (GNPs, AuNPs):

Gold nanoparticles are widely used in many fields as preferred materials for their unique optical and physical properties, such as surface plasmon oscillations

for labeling, imaging, and sensing. Recently, much advancement was made in biomedical applications with better biocompatibility in disease diagnosis and therapeutics. AuNPs could be prepared and conjugated with many functionalizing agents, such as polymers, surfactants, ligands, dendrimers, drugs, DNA, RNA, proteins, peptides and oligonucleotides [3].

3.3.3.1 Types of AuNPs:

- **Au Nanospheres:-**

  The other name of Au colloid is "Au nanospheres". The diameters could vary from 2 nm to100 nm, which could be synthesized by reducing aqueous $HAuCl_4$ solution with addition of various reducing agents under different parameters and conditions. The size of nanospheres could also be controlled by changing the ratio of citrate and Au.

- **Au Nanorods:-**

  Several strategies were tested for synthesizing Au nanorods. Synthesis of Au nanorods was performed using the template method, based on the electrochemical deposition of Au within the pores of nanoporous polycarbonate or alumina template membranes. The diameter of Au nanorod could be pre-determined by the diameter of the pores of the template membrane. The length of Au nanorod could be controlled by the amount of deposited Au within the pores of the membrane.

- **Au Nanoshells:-**

  Nanoshell referred as a type of spherical nanoparticle with a dielectric core, which was covered by a thin metallic shell (usually Au). These nanoshells involved a quasi-particle, called Plasmon, produced from collective excitation or quantum plasma oscillation, where the electrons could simultaneously oscillate with respect to all ions.

- **Au Nanocages:-**

In 2006, Au nanocages, consisted controllable pores on the surface, were synthesized by the galvanic replacement reaction of truncated silver nanocubes and aqueous $HAuCl_4$. Furthermore, it was observed that the generated morphologies of the Silver nanostructures could be controlled through Pylol reduction. Here, ethylene glycol reduced $AgNO_3$ to generate silver atoms, and further reduction yielded nanocrystals or seeds. [3]

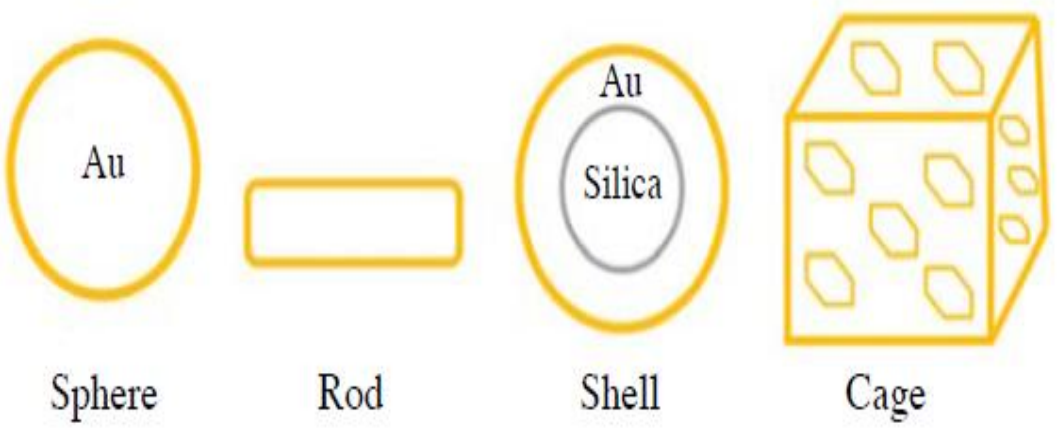

Figure 3.2 schematic representations of various types Au nanomaterials

3.3.3.2 Synthesis of GNPs:

There are a lot of methods uses to synthesis of GNPs:-

1. **Chemical method:**

The preparation of AuNPs by the chemical reduction method includes two main parts:

- **Reduction by agents:** for instance borohydrides, aminoboranes, formaldehyde, hydrazine, hydroxylamine, polyols, citric and oxalic acids, sugars, hydrogen peroxide, carbon monoxide, sulfi tes, hydrogen, acetylene, and on electronic reducing agents including electron-rich transition-metal sandwich complexes.
- **Stabilization using agents:** for instance trisodium citrate dihydrate, sulfur ligands (in particular thiolates), phosphorus ligands, oxygen-based ligands,

nitrogen-based ligands (including heterocyclic compounds), dendrimers, polymers and surfactants (in particular, cetyltrimethylammonium bromide (CTAB))

2. Turkevich method:

One of the most well-known techniques for the synthesis of AuNPs is based on the reduction of HAuCl4 by citrate in water, which was first designed by Turkevich in 1951. In this method, the HAuCl4 solution is boiled, and the trisodium citrate dihydrate is then rapidly added into the boiling solution under vigorous stirring. After a few minutes, the color of the solution changes from light yellow to wine red. This method results in AuNPs measuring about 20 nm in diameter. In this technique, citrate ions play a double role, as both stabilizing and reducing agents. The schematic route for synthesis of AuNPs by the Turkevich method is shown in Figure (3.3).

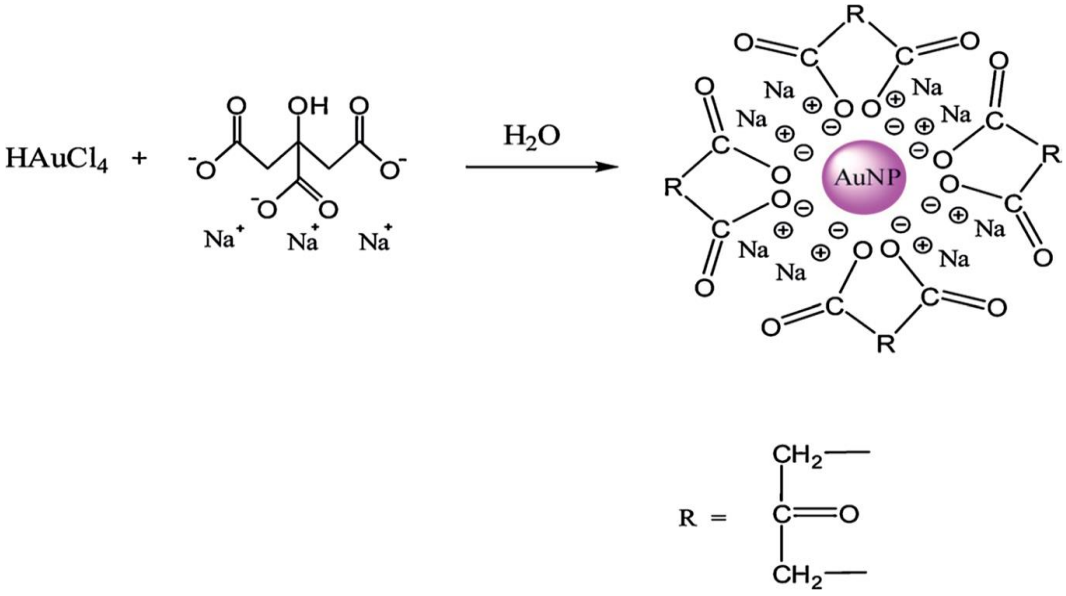

Figure 3.3 AuNPs syntheses using the Turkevich method.

3. The Brust-Schiffrin method:

The Brust-Schiffrin method was discovered by Brust and Schiffrin in 1994. This method allowed an easy approach to the synthesis of thermally stable and air-stable AuNPs of controlled size and low dispersity. In this technique, AuCl4- was transferred to a toluene phase from an aqueous solution using

tetraoctylammonium bromide (TOAB) as the phase-transfer agent, and reduced by NaBH4, in the presence of dodecanethiol. Addition of the reducing agent causes a color change of the organic phase, from orange to deep brown. This clearly indicates the formation of AuNPs.

4. Electrochemical method:

On this method the gold nanoparticles were prepared electrochemically using a simple two-electrode cell, with oxidation of the anode and reduction of the cathode. Figure 3.4 schematically depicts the electrochemical apparatus. The electrochemical process has been verified to be superior to other methods of nanoparticle production, due to its modest equipment, low cost, lower processing temperature, high quality, and ease of controlling the yield.

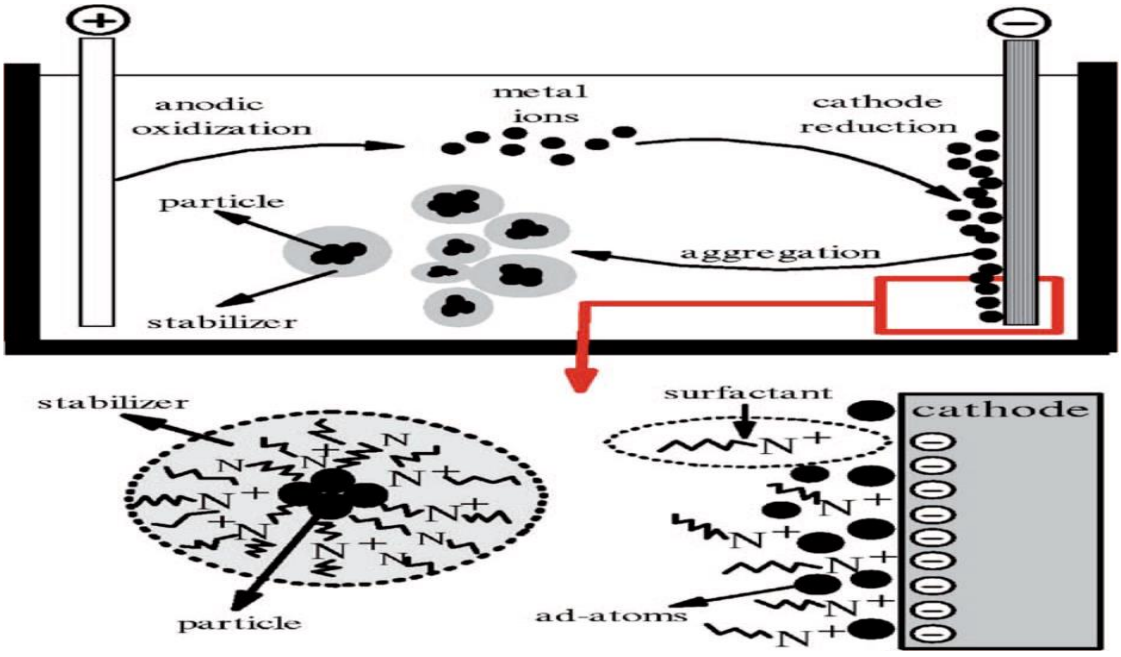

Figure 3.4 Scheme of the electrochemical system for synthesizing GNPS

5. Seeding growth method:

Method that has also been reported for the synthesis of gold nanoparticles is the seeding growth method. According to the seeding growth process, gold nanoparticles of diameters 5-40 nm and a narrow size distribution were synthesized. Particle size can be controlled by the changeable ratio of seed to metal salt, and therefore every size in the range 5-40 nm can be prepared. This

method has the advantage of being a simple, quick, and low cost process; while trisodium citrate was used as a source of OH^- ions in the seeding step, sodium borohydrate (NaBH 4) was used as a reducing agent. Figure 3.5 presented this method.

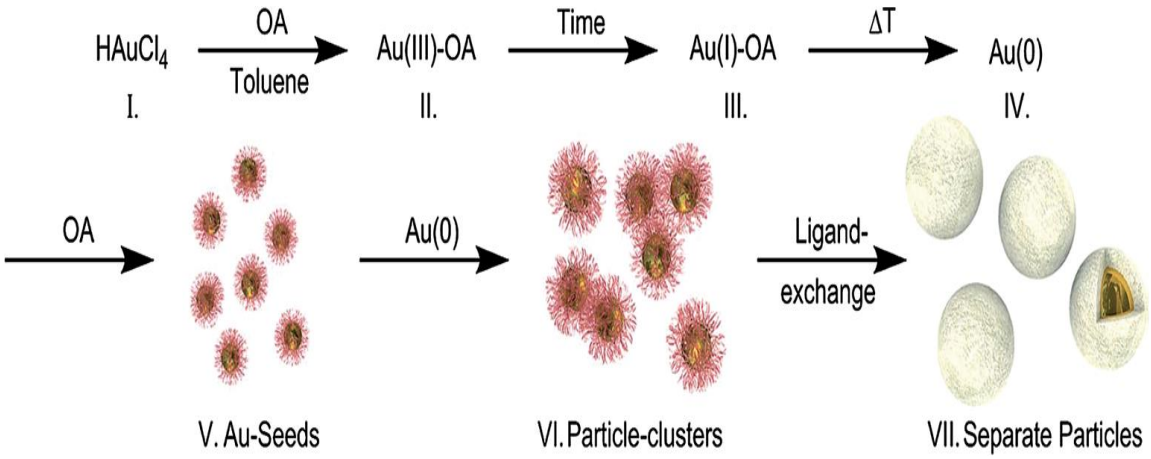

Figure 3.5 Growth mechanisms of GNPs

6. Biological method:

In this method nanoparticles are synthesized by microorganisms, enzymes, and plants or plant extracts. Recently, the use of plants for the synthesis of nanoparticles is gaining importance, because of their availability, low cost, eco-friendliness and non-toxic nature [18].

3.3.3.3 Advantages of GNPs:

1. Gold nanoparticles have unique optical, physical and chemical properties due to their size and shape.
2. Gold nanoparticles have high surface area which provide dense drug loading.
3. These particles are biocompatible and are readily available for conjugation with small biomolecules such as proteins, enzymes, carboxylic acid, DNA, and amino acids.
4. Gold nanoparticles have controlled dispersity.

5. Due to small size and uniform dispersion they can easily reach to the targeted site with blood flow.
6. They are non-cytotoxic to the normal cells.
7. Gold nanoparticles are easily synthesized by various methods.
8. Ease of preparation in a range of sizes.
9. Good biocompatibility.
10. Easily functionalized.
11. Their ability to conjugate with other biomolecules without altering their biological properties [19, 20].

3.4 Drug Delivery Systems (DDSs):

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals [21]. Drug delivery system (DDS) is defined by national institute of health in USA as, "Formulation of a device that enables the introduction of therapeutic substances in to the body and improves efficiency and safety by the control the rate, time and place of release of drug in the body". The process of drug delivery can be mainly divided into:

1. The administration of the drug or therapeutic product can be divided as non-invasive and invasive administration. Non-invasive administration such as oral, topical (skin), nasal, and inhalation routes. Invasion administration is injection or nanoneedle array.
2. The release of the active part of the drug by the product.
3. Transport active ingredients across the biological membrane to the target site to perform action.

New DDS has the ability to deliver drugs to specific target cells in various areas of the body without degradation in the gastrointestinal track. It includes delivery and targeting of pharmaceutical, therapeutic and diagnostic agents by the help of NPs to the cells such as cancer cells. The ultimate goal of NP drug delivery is to improve the proper treatment diagnostics and prevention of disease [22].

3.4.1 Nanotechnology-based drug delivery systems:

Nanotechnology based delivery system would allow faster drug absorption, controlled dosage release into the human body and would have other unique properties of minimizing side-effects by eliminating requirement of co-solvent as used in conventional dosage form. Further, drugs that have side-effects due to triggering an immune system response can be wrapped in nanoparticle coating and prevent immune system from recognizing and reacting to a foreign substance. It is an ideal targeting system should have long circulating time, it should be present at appropriate concentrations at the target site, and it should not lose its activity or therapeutic efficacy while in circulation [10].

3.4.1.1 Smart drug delivery systems (SDDSs) or Target Drug Delivery:

Targeted drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. This improves efficacy of the while reducing side effects. It is very difficult for a drug molecule to reach its destination in the complex cellular network of an organism. Targeted delivery of drugs, as the name suggests, is to assist the drug molecule to reach preferably to the desired site. The inherent advantage of this technique has been the reduction in dose & side effect of the drug [22].

3.4.1.1.1 Strategies of Drug Targeting:

Drug targeting to an area of interest within the body increases the therapeutic effectiveness as well as it reduces the toxicity that may arise otherwise. Two strategies are widely used for drug targeting to the desired organ/tissue:

i. **Passive targeting:** This is based on the accumulation of drug at areas around the site of interest, such as in case of tumor tissues. This is called

Enhanced Permeability Retention (EPR) effect. Such types of targeting occur with almost all types of drug delivery carriers. Passive targeting is actually a misnomer because it cannot really be described as a form of selective targeting. Although the EPR effect applies for nanoparticle administered, the majority (>95%) of these nanoparticles tend to accumulate in organs other than those of interest such as liver, lungs and spleen. Thus, it is the distribution of drug by blood circulation. Examples include the use of antimalarial drugs being targeted for the treatment of microbial infections such as leishmaniasis, candidiasis and brucellosis.

ii. **Active targeting:** Through the use of ligand-receptor interactions, active targeting describes the drug targeting interactions. However, interactions between a ligand and a receptor are possible only when the two are in close propinquity, (i.e. less than about 0.5mm). The currently available drug delivery systems are able to reach the target by the virtue of blood circulation and extravasation. Therefore, we can conclude that active receptor targeting actually means ligand-receptor interaction but that takes place only after blood circulation and extravasation. Active targeting can further be divided into three different targeting levels. As shown in figure 3.6 [23].

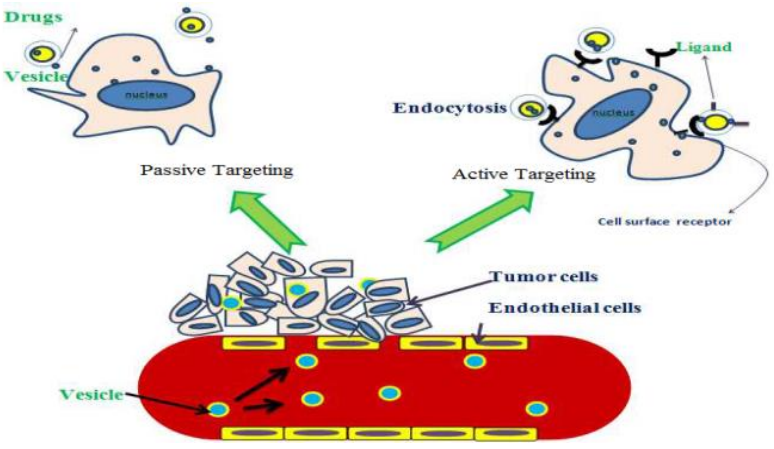

Figure 3.6 Active and Passive targeting

3.4.1.2 Polymer–drug conjugates:

Polymer–drug conjugates are a class of polymer therapeutics that consists of a water-soluble polymer that is chemically conjugated to a drug through a biodegradable linker. The idea started in 1975 when Ringsdorf proposed the use of polymer–drug conjugates to deliver hydrophobic small molecules. The reasoning was that, small molecule drugs, especially hydrophobic compounds, have a low aqueous solubility and a broad tissue distribution profile such that, administration of the free drug may result in serious side effects. Therefore, conjugation of these compounds to hydrophilic, biocompatible polymers would significantly increase their aqueous solubility, modify their tissue distribution profile and enhance their plasma circulation half-life. An important attribute of colloidal systems is their hydrodynamic diameter, which are typically about 3–20 nm for polymer–drug conjugates and between 10 and 200 nm for colloidal particles such as micelles or liposomes. The colloidal nature or size of these vehicles can facilitate their retention within the circulation for prolonged periods, in comparison to low molecular weight small molecules. One major difference between polymer–drug conjugates and delivery systems that contain physically entrapped drug (e.g., micelles and liposomes) is that the drug is chemically conjugated to the polymer and therefore these systems qualify as new chemical entities (NCE). Classification as an NCE is often accompanied by additional development and regulatory hurdles that must be met in order to receive approval

3.4.1.3 Multifunctional drug carriers:

A multifunctional drug delivery system (MDDS) refers to drug carrier that has multiple properties of prolonged blood circulation, passive or active localization at specific disease site, stimuli-sensitivity, ability to deliver drug into intracellular target organelles, and/or imaging ability. Technically therefore, it has two or more functions, in fact, SDDS and polymer–drug conjugates discussed above can be considered MDDS. In addition to delivering drugs, MDDS can carry out the

second function, such as stimuli-responsiveness or hydrolysis inside cells. Some reported MDDS include the biotin-tagged pH-sensitive polymeric micelles based on a mixture of PLA-b-PEG-b-PHis-biotin (PLA=poly (L-lactic acid)) and PEG-b-PHis block copolymers in which the targeting moiety, biotin, was masked until the carrier was exposed to an expected environment of pH 7.0. Once the nanocarrier was internalized to cancer cells by ligand– receptor interactions, lowered pH (< 6.5) destabilized the carrier resulting in a burst release of the loaded drug, where a pH-degradable PEG-b-phosphatidylethanolamine (PE) liposome had anti-myosin monoclonal antibody as well as TAT or biotin attached on its surface.

3.4.1.4 Organic/inorganic composites:

An inorganic-organic composite usually comprises an inorganic phase and a film forming organic phase. A typical green approach to developing an inorganic organic composite involves the selection of film forming organic phase from starches having a degree of polymerization; degree of substitution and viscosity such that the substituted starches are insoluble in water during mixing but dissolve at a higher processing temperature during forming, setting or drying of the composite. Thus, excessive migration of the starch is prevented and the composite is substantially strengthened. There have also been reports on the lab-on-a-chip approach, which embodies micron- or nano-sized machines composed of sophisticated circuits. Small devices have many advantages including portability/disposability, low cost, high reproducibility, high-throughput screening, and multiple functionalities in a single device. Recently, combined with other technologies such as optics, single molecular imaging, or cell/protein-based assay systems, biomedical lab-on-a chip devices have become an important part of drug discovery and diagnosis, but its application in drug delivery systems based on are just beginning to appear [24].

3.5 COMSOL Multiphysics:

3.5.1 Introduction:

A computer simulation environment is simply a translation of real-world physical laws into their virtual form. How much simplification takes place in the translation process helps to determine the accuracy of the resulting model. It would be ideal, then, to have a simulation environment that included the possibility to add any physical effect to your model. That is what COMSOL is all about. It's a flexible platform that allows even novice users to model all relevant physical aspects of their designs. Advanced users can go deeper and use their knowledge to develop customized solutions, applicable to their unique circumstances. With this kind of all-inclusive modeling environment, COMSOL gives you the confidence to build the model you want with real-world precision. Certain characteristics of COMSOL become apparent with use. Compatibility stands out among these. COMSOL requires that every type of simulation included in the package has the ability to be combined with any other. This strict requirement actually mirrors what happens in the real world. For instance in nature, electricity is always accompanied by some thermal effect; the two are fully compatible. Enforcing compatibility guarantees consistent Multiphysics models, and the knowledge that, even as the COMSOL family of products expands, you never have to worry about creating a disconnected model again. Another noticeable trait of the COMSOL platform is adaptability. As your modeling needs change, so does the software. If you find yourself in need of including another physical effect, you can just add it. If one of the inputs to your model requires a formula, you can just enter it. Using tools like parameterized geometry, interactive meshing, and custom solver sequences, you can quickly adapt to the ebbs and flows of your requirements [25].

3.5.2 COMSOL Features:

- Material library.
- Multiphysics in single simulation process.
- Practical physics extending various features from that treatment to optics.
- Model library.
- Link to various software such as AUTOCAD, Solidwork, MS Excel, MATLAB and many others.
- Online webinar.
- Multi-plot features.
- Curves and geometries [26].

Chapter four

Methodology and design model

4.1 Introduction:

To fulfill the aims of these research specific steps were done; the model was designed in COMSOL Multiphysics. Then mathematical calculation (mathematical model) were done to design the model; and finally the model was simulated to sure that is work.

4.2 Methodology:

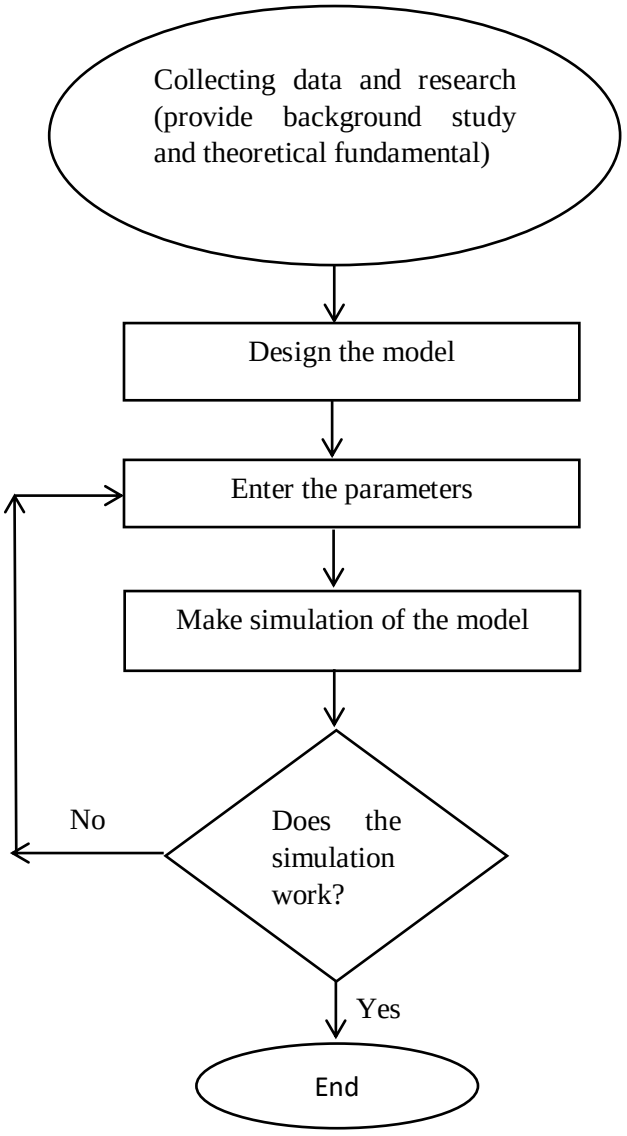

Figure 4.1 The block diagram of the method

4.3 Design Model:

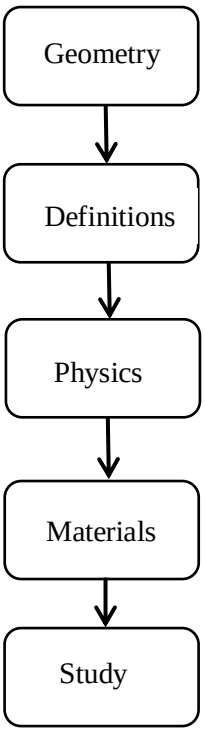

Figure 4.2 The flow diagram present the steps used to design the model

4.3.1 Geometry:

The type and the dimension of the model were selected in this step. The model type is fluid flow exactly use Laminar Two-Phase Flow, Moving Mesh; and the dimensions is 2D axisymmetric. Figure 4.3 shows the geometry.

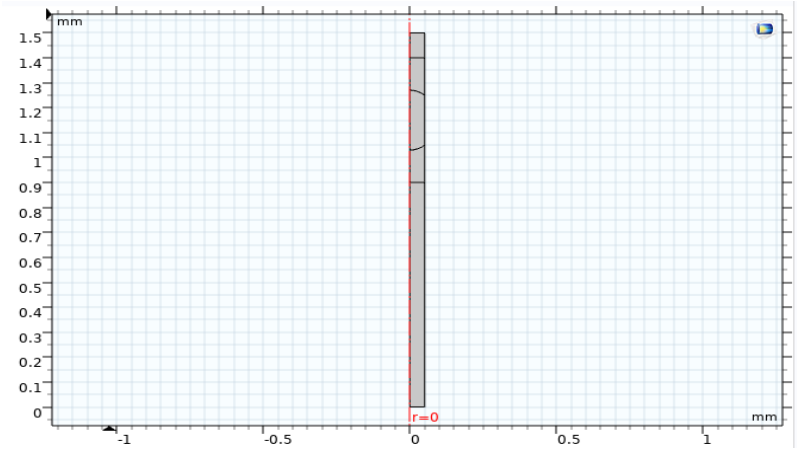

Figure 4.3 Axisymmetric model geometry

4.3.2 Definition:

1. **Global definition:** the parameters were inserted and the value of each parameter also was been selected**.**

$$\mathbf{u0 = 0.004\ m/s} \quad \textbf{(4.1)}$$

u0= droplet velocity.

2. **Definition:** Set up model variables to track drug dose and drop location. Define a function to represent the permeable part of the capillary wall. The function used is integration after select the point and domain from the shape (domain 3 and pint 4 only). The variables are the number of moles delivered and position of top of droplet (m). Create a rectangle function that is zero everywhere except at heights corresponding to the permeable membrane [27].

$$\mathbf{n\_abs = intop1(2 * pi * r * c)} \quad \textbf{(4.2)}$$

n-abs = numbers of moles delivered

intop1= integration 1

pi = 3.14

r = radius (distance from the center of circle to the circumference).

c = circumference (in geometry the circumference of circle is the (linear) distance around it. That is, the circumference would be the length of the circle if it were opened up and straightened out to a line segment. Since a circle is the edge (boundary) of a disk, circumference is a special case of perimeter. The perimeter is the length around any closed figure and is the term used for must figures excepting the circle and some circular-like figures such as ellipses. Informally, circumference may also refer to the edge itself rather than to the length of the edge) [28].

$$\mathbf{z\_pnt = intop2(z)} \quad \textbf{(4.3)}$$

z_pnt = position of top of droplet

intop2 = integration 2

4.3.3 Physics:

4.3.3.1 Introduction:

The type of flow were been selected in this step and the equations represent this type of flow were been explained. Laminar flow can be defined as the flow separates into "layers" that slide relative to one another without mixing. Laminar flow can be represented by a set of lines known as streamlines (flow lines).

4.3.3.2 The Equations:

4.3.3.2.1 Wall:

The Navier Slip boundary condition must be used on the walls along which the contact line moves.

$$\mathbf{u}.\mathbf{n} = \mathbf{0} \tag{4.4}$$

$$\mathbf{k_n} - (\mathbf{k_n}.\mathbf{n})\mathbf{n} = -\frac{\mu}{\beta}[\mathbf{u}-(\mathbf{u}.\mathbf{n})\mathbf{n}] \tag{4.5}$$

$$\mathbf{k_n} = \mathbf{kn} \tag{4.6}$$

$$\beta = \mathbf{f_h}.\mathbf{h_{min}} \tag{4.7}$$

u = velocity.

n = numbers of moles.

k_n = total numbers.

μ = dynamic viscosity.

β = constant.

f_h = density bandwidth.

h_{min} = minimum bandwidth.

4.3.3.2.2 Inlet:

Set the inlet boundary condition to accelerate the droplet rapidly to a constant velocity.

$$\mathbf{u}.\mathbf{t} = \mathbf{0} \tag{4.8}$$

$$[-\mathbf{pl}+\mathbf{k}]\mathbf{n} = -\mathbf{p_{grad}}\mathbf{n} \tag{4.9}$$

t = time.

p = pressure.

l = length.

$$\mathbf{U_{av} = u0*step1(t/1[s])} \quad \mathbf{(4.10)}$$

U_{av} = velocity average.

4.3.3.2.3 Outlet:

Apply a Pressure constraint at the Outlet.

$$\mathbf{[-pl+k]n=-\widehat{p0}n} \quad \mathbf{(4.11)}$$

$$\mathbf{\widehat{p0} \leq p0} \quad \mathbf{(4.12)}$$

p0 = initial pressure and it is equal 0.

4.3.3.2.4 Fluid-fluid interface:

Set up the boundary conditions for the droplet surface and the contact point.

$$\mathbf{n_{1.}\,[T_1\text{-}T_2]=\sigma(\nabla_t .\, n_1)\, n_{1\text{-}}\, \nabla_t \sigma} \quad \mathbf{(4.13)}$$

$$\mathbf{T = -pl+k} \quad \mathbf{(4.14)}$$

$$\mathbf{u_1=u_2+M_f\,[\frac{1}{\rho 1} - \frac{1}{\rho 2}]\, n_1} \quad \mathbf{(4.15)}$$

$$\mathbf{u_{mesh}\,.\, n_1=[\, u-\frac{Mf}{\rho 1}\, n_1\,].\, n_1} \quad \mathbf{(4.16)}$$

u_{mesh} = mesh velocity

ρ_1 = density of the first material

ρ_2 = density of the second material

4.3.3.2.5 Wall fluid interface:

Using the rectangle function in this manner makes the contact angle vary on the permeable part of the wall.

$$\mathbf{\Theta_c = \Theta_w} \quad \mathbf{(4.17)}$$

$$\mathbf{\Theta_w = 3*pi*(1\text{-}rect1(z/1[m]))/4+7*pi*rect1(z/1[m])/8} \quad \mathbf{(4.18)}$$

Θ_c = contact angle.

Θ_w = wall angle.

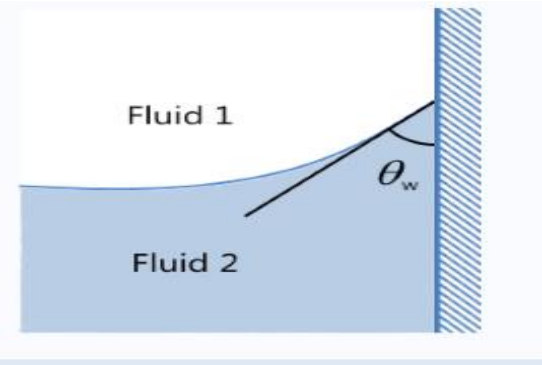

Figure 4.4 contact angle

4.3.3.2.6 Transport of diluted species and Transport properties:

Add the diluted species interface to model the solute transport in the droplet. Ensure the drug transport occurs only in the liquid domain. Set up convection and diffusion for the drug.

$$\frac{\partial ci}{\partial t} + \nabla . J_i + u . \nabla c_i = R_i \quad (4.19)$$

$$J_i = -D_i \nabla c_i \quad (4.20)$$

J_i = flux.

c_i = concentration.

R_i = Transport of diluted species.

D_i = diffusion.

D_c = diffusion coefficient and it is equal 5E-9.

4.3.3.2.7 Flux:

Add a boundary condition for the drug flux into droplet. This expression ensures flux only enters the droplet as it passes the permeable membrane.

$$-n . J_i = J_{0,i} \quad (4.21)$$

$$J_{0,c} = \text{rect1}(z/1[m])*0.001[mol/(m^2*s)] \quad (4.22)$$

4.3.4 Materials:

Add the materials properties that were used to design this model. The selected materials are blood and GNPs as drug carrier. The properties of materials that were worked on it are density (ρ) and dynamic viscosity (μ).

ρ_{blood} = 1063 Kg/m^3

μ_{blood} = 0.003 Pa.s

ρ_{gold} = 19300 Kg/m^3

μ_{gold} = 1e-3 Pa.s

4.3.5 Study:

The simulate model was done in this step and the result must be taken to sure that the model is work.

4.4 Summary:

In this study there are seven properties of physics were concentered on it because it are effect directly on the deliver the drug and the interaction between the droplet of drug and the cell wall was shown by those properties.

Chapter five

Result and discussion

5.1 Results:

5.1.1 The velocity:

The flow velocity is shown for the drop moving at 0.25 mm/s in Figure5.2. Note the change in contact angle as the droplet passes the edge of the membrane at *z*=8 mm is apparent.

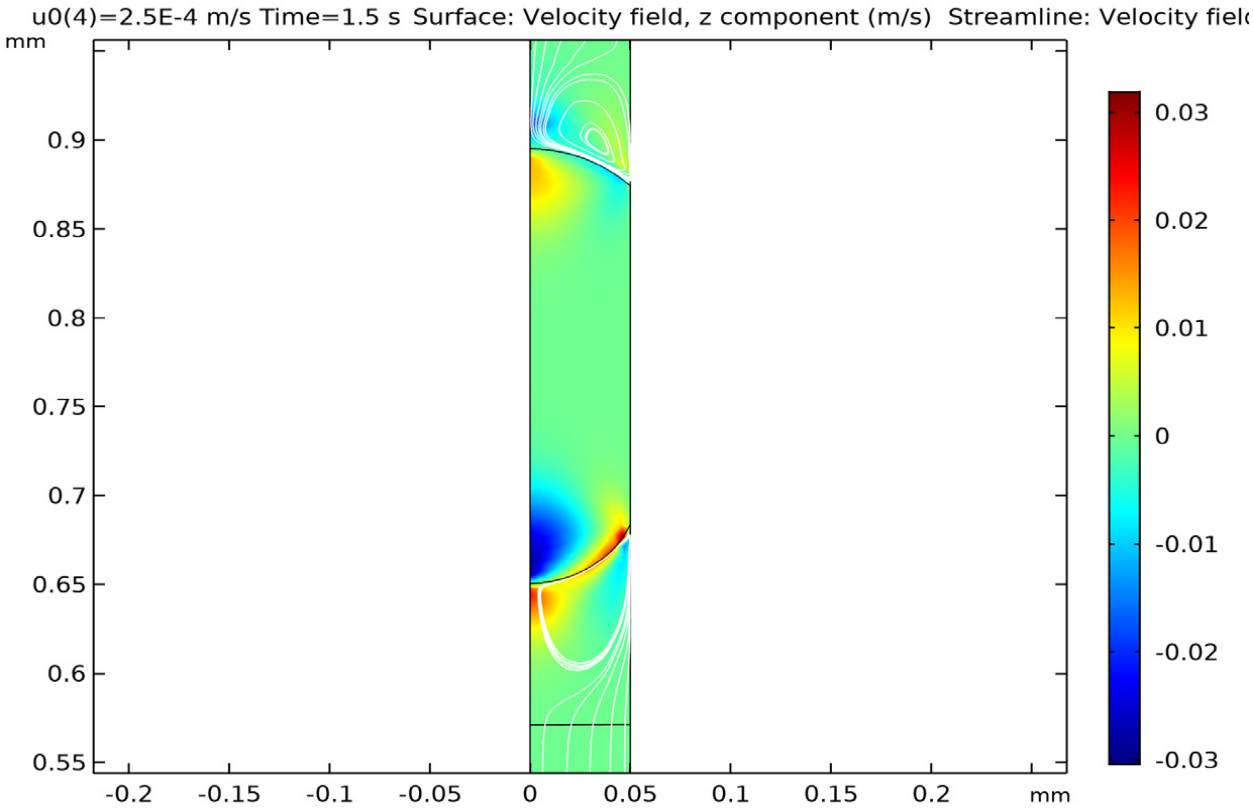

Figure 5.1 Flow velocities around the droplet as it travels past the edge of the permeable membrane.

5.1.2 The concentration:

Figure 5.2 shows the concentration profile for the 0.25 mm/s at the same point in time.

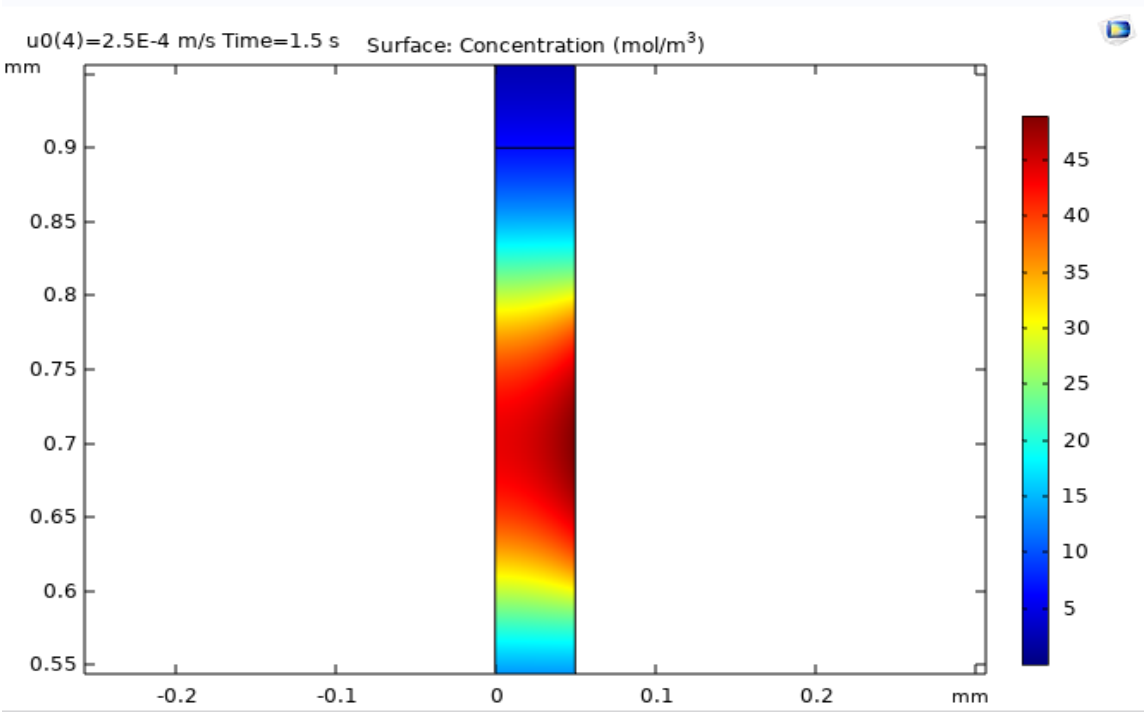

Figure 5.2 Drug concentration in the droplet as it travels past the edge of the permeable membrane.

5.1.3 The total amount of drug:

The total amount of drug in the droplet as a function of time is shown in Figure 5.3, for the drop traveling at 0.1 mm/s.

5.1.4 The total amount of drug delivered against the droplet velocity:

Figure 5.4 shows the total amount of drug delivered against the droplet velocity.

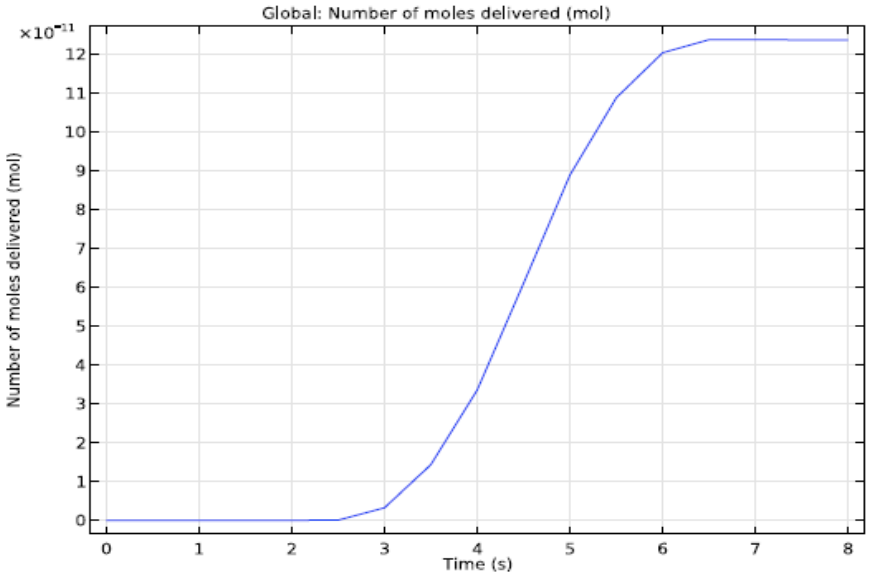

Figure 5.3 Total drug dose contained in the droplet as a function of time for the droplet traveling at 0.1 mm/s.

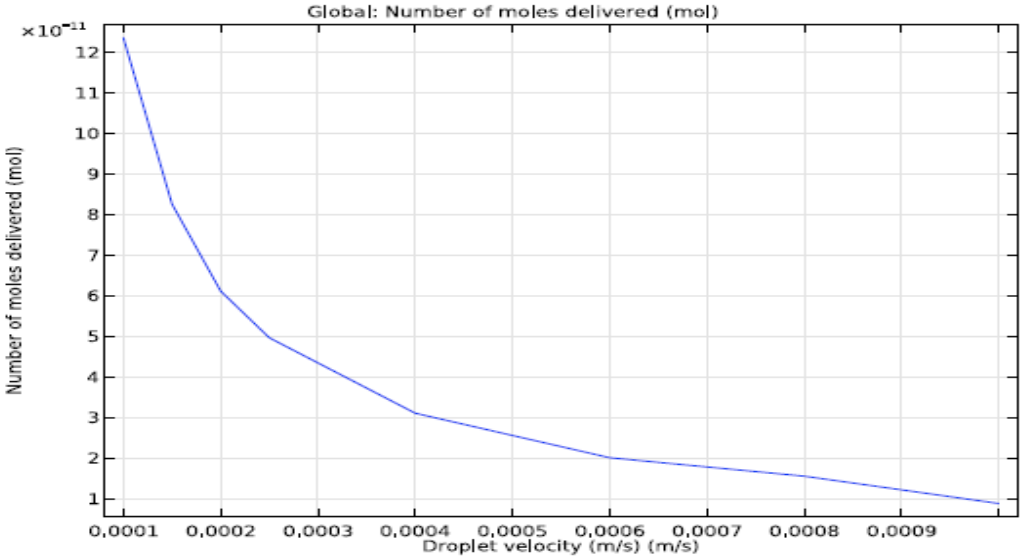

Figure 5.4 Total drug dose delivered shown against the droplet velocity.

5.2 Discussion:

5.2.1 The velocity:

The velocity of the particles within the arteries until they reach the specific cells must be constant or at the same speed as blood flow within the arteries because the number of moles delivered is approximately inversely proportional to the droplet velocity, which is expected as the amount of drug that diffuses into the drop depends on the time the drop takes to traverse the permeable part of the capillary, so as not to lose part of the drug due to high speed, and the results found that the speed is constant.

5.2.2 The concentration:

The problem of drug concentration previously is that; the drug reaching the selected cells does not reach the appropriate concentration and the amount. The results indicated that the concentration of the drug within the particles reaches the appropriate concentration.

5.2.3 The total amount of drug:

The dissolved drug quantity increases with an ‘S’ shaped profile as the drug travels down the capillary, then the drug delivered with suitable amount to the specific cells.

Chapter six

Conclusion and recommendations

6.1 Conclusion:

Nanotechnology based delivery system would allow faster drug absorption, controlled dosage release into the human body and would have other unique properties of minimizing side-effects by eliminating requirement of co-solvent as used in conventional dosage form.

Laboratory experiments uses in the drug delivery system use mice or humans to confirm the accuracy of the results. This - the use of rats or humans - in addition to laboratory devices is considered a very high cost, so COMSOL Multiphysics software used in the research which gives a simple translation of real-world physical laws into their virtual form. This helps to determine the accuracy of the resulting model (concentration, and the amount of drug).

6.2 Recommendations

1. The use of other materials such as titanium or polymer instead of gold to reach the most effective and efficient materials.
2. The use of other flow equations to compare it’s accuracy with the laminar flow equations.

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