Republic of Iraq
Ministry of Higher Education and Scientific Research
University of Babylon

Drug loading on Ag nanoparticles synthetic by chemical method

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A research project submitted to University of Babylon in Partial fulfillment of the requirements for the degree of), in Pharmacy.

University of Babylon

2023-2024


بسم الله الرحمن الرحيم
رب اشرح لي صدري
ويسر لي أمري

الاهداء

وصلت رحلتنا الجامعية الى نهايتها بعد تعب ومشقة...

وها نحن ذا نختم بحث تخرجنا بكل همة ونشاط،

ونحن ممتنين لكل من كان له فضل في مسيرتنا

وساعدنا ولو باليسير،

الأبوين ،والاهل والأصدقاء والأساتذة المبجلين...

اهديكم بحث تخرجي

ونهدي تعبنا وجهدنا الى سيدي صاحب العصر والزمان عجل الله فرجه الشريف

شكر وتقدير

اشكر الله عز وجل وأحمده على توفقيه لنا لإنجاز هذا البحث كما أتقدم بخالص الشكر الى الاساتذة المشرفين "الدكتورة اسماء هاشم حمادي" و"الدكتورة صبا عبد المنعم حبيب"

على ارشادهم وتوجيههم لنا

الشكر موصول ايضا الى الاساتذة اعضاء لجنة المناقشة الذين تفضلوا بقراءة هذا البحث الأخير اشكر كل من ساهم من قريب أو بعيد في انجاز هذا البحث

Content

Abstract

Many pharmacological and therapeutic applications in the medical field have bright futures thanks to nanotechnology. Nanoelements are a key component of modern technological approaches appropriate for cutting-edge medicinal uses. Antibacterial nanoparticles called silver nanoparticles (AgNPs) have been created in a new way to deal with the problem of drug resistance in the environment. In this study, an easy and safe chemical approach to generate a nano powder of Ag-NPs. The sample was analyzed using X-ray Diffraction (XRD) and scanning electron microscopy (SEM). The XRD study showed that the AgNPs have a crystalline shape particle size very small (18.75 nm) and shaped like spheres. To investigation our aim, the fine powder of AgNPs had been loaded with clindamycin as antibiotic.

Chapter one

Introduction

1.1 Nano material

Nanomaterials mainly refer to some particles with certain physical or chemical properties or biological effects, whose external size or Internal size or surface structure are within the nanoscale range (1 nm-100 nm) [1]. Nanomaterials can be divided Into organic and inorganic nanomaterials, of which organic nanomaterials Include nanofibers, nanotubes, liposomes, and polymer nanoparticles and inorganic nanomaterials include elementary substances, alloys, silica, and quantum dots [2].

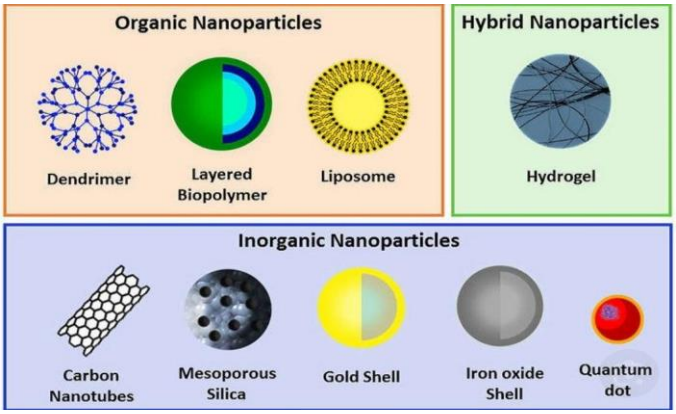


Fig1: Different types of nanomaterials.

Nanomaterials can effectively transport and load drugs since they have the largest specific surface area among all the known materials at present. At the same time, nanomaterials have good biocompatibility and biodegradability, and they can accumulate in human organs with less side effects [3] .

In addition, nanomaterials have the properties of slow release, which can reduce drug concentration and toxic side effects [4]. Compared to traditional drugs which are with defects such as being ubiquitous in poor stability, apt to deform and inactivate, short biological half-life, and low bio-availability, and unable to easily go through the physiological barrier, biological nanomaterials play a role that cannot be ignored in the field of biological medicine, such as in diagnosis, treatment, repair, or replacement of the damaged organization. For example, the nanoparticles with small size are easy to be swallowed up by cells; nanodrugs of large specific surface area and more functional groups or active centers can realize a large load of specific drugs; nanomaterials with the characteristics of porous, hollow, multilayer structures. are easy for control and release of drugs, so as to change the half-life period of drugs in the body and prolong the action time of drugs. With the deepening of research on nanomaterials, nanomaterials have been developed from being only the delivery carrier of drugs to a new type of materials which are with certain biological effects and can participate in the treatment of diseases [5]. With the continuous innovation of nanomaterials, the physicochemical properties and structural characteristics of nanodrugs are enriched and the multifunctional nanomaterials have great application potential in the field of biomedicine.

In the recent past, metal and metal oxide nanomaterials have received a great deal of attention and have mobilized various synthetic routes [6-7]. The wide range of efficiency and versatility of these nanomaterials have further promoted their designing and has also initiated the tailoring of suitable size and morphology of metal and metal oxide NPs. Synthesis of nanoscale transition metal oxides (8), such as tin oxide, iron oxide titanium oxide, copper oxide, etc., are of significant. Interest owing to thermal conductivity, their enhanced excellent catalytic activity, high antibacterial/antimicrobial easy availability of economical & up-scalable synthetic routes and non-toxicity. Activity,

The advantages of nanomaterials are their large surface area and small particle size, making them excellent for synthesizing pharmaceutical formulations [9]. Metal oxide nanoparticles have recently come up as a promising research area due to their vast range of applications [10].

1.2 Nanotechnology

Nanotechnology is currently playing a critical role in electronics, biology, and medicine. Its utility can be assessed since it includes materials that must be developed at the atomic and molecular level. Nanospheres have been found to be reliable drug delivery systems due to their small size, and they may be beneficial for encapsulating pharmaceuticals and permitting more accurate targeting with controlled release. In this study, we focus on current advances in this technology for drugs and drug delivery systems(11).In recent decade drug development and delivery becomes one of the high growing, demanding and manufacturing sector with high capital investment. This process a time consuming and expensive process, facing the problem of low bioavailability, toxicity, low efficacy, biocompatibility, side effects, fast excretion and degradability. Biocompatible nanomaterials having exceptional properties of high invasion rate, slow, controlled and targeted drug release, easily accessible to receptors overcome all these problems and are advantageous over traditional form of drug. Inspite of all the significance, toxicity of various nanoparticles used as drug delivery system is one of the major concem associated with it.

Recently particulate systems like nanoparticles have been used as a physical approach to alter and improve the quality of human life. The potential use of polymeric nanoparticles as carriers for a wide range of drugs for therapeutic applications has been increased due to their versatility and wide range of properties. Nanomaterials are not simply another step in the miniaturization of materials. They often require very different production. Approaches. The large surface area provided by nanoparticles, together with their ability to self-assemble on support surface, could be of use in all of these applications. Nanoparticles have unique properties as compared to micro and macro particles.

A nanoparticle Is the most fundamental component in the fabrication of a nanostructure, and is far smaller than the world of everyday objects that are described by Newton's laws of motion, but bigger than an atom or a simple molecule that are governed by quantum mechanics.

Are materials with overall dimensions in the nanoscale, ie, under 100 nm. In recent years, these materials have emerged as important players in modern medicine, with clinical applications ranging from contrast agents in imaging to carriers for drug and gene delivery into tumors. Indeed, there are some instances where nanoparticles enable analyses and therapies that simply cannot be performed otherwise. However, nanoparticles also bring with them unique environmental and societal challenges, particularly in regard to toxicity. This review aims to highlight the major contributions of nanoparticles to modern medicine and also discuss environmental and societal aspects of their use(12).

1.3 Synthesis of Nanoparticles

Nanoparticle synthesis refers to methods for creating nanoparticles. Nanoparticles can be derived from larger molecules, or synthesized by “bottom–up” methods that, for example, nucleate and grow particles from fine molecular distributions in liquid or vapor phase. Synthesis can also include functionalization by conjugation to bioactive molecules. Synthesis of nanomaterials in high yield and low cost has been a great challenge since the very early development of nanoscience. Application of the nanoparticles in medicine depends on the ability to synthesize particles with different shape, monodispersity, chemical composition, and size.(13)

1.4 Application of nanoparticles

Nanoparticles currently exist in a wide variety of consumer products. They can be applied as fillers or coatings for UV protection, which are important in windows, lenses, and sunscreens (14). The known antimicrobial properties of materials such as silver and copper can be incorporated as nanoparticles to keep packaged foods fresh or to reduce odor in socks. In medicine, gold nanoparticles have been widely studied as a potential agent for targeted drug delivery and cancer detection (15). For reaction catalysis, nanoparticle effectiveness compared to bulk materials is primarily driven by the huge increase in surface area when particle size decreases. This leads to much more efficient application of the catalyst material (16). In the field of plasmonics, nanoparticles are routinely exploited for their unique optical properties called surface plasmons that can be used for enhanced detection in Raman spectroscopy commonly called Surface-Enhanced Raman Spectroscopy (SERS)

1.5 CLASSIFICATION OF NANOMATERIALS

nanomaterials can be divided into five categories depending on their size, place of origin, structural configuration, pore size, and potential toxicity.

1.5.1 Classification of nanomaterials based on origin

Natural and artificial nanoparticles are the two groups into which nanomaterials are divided based on origin.[17, 18]

* Natural nanomaterials

Natural nanomaterials can be found in a variety of forms in nature, including viruses, protein molecules, minerals like clay, natural colloids like milk and blood (liquid colloids), fog (aerosol type), gelatin (gel type), mineralized natural materials like shells, corals, and bones, insect wings and opals, spider silk, lotus leaves, gecko feet, volcanic ash, and ocean spray.

* Artificial nanomaterials

Carbon nanotubes and semiconductor nanoparticles like quantum dots (QDs) are examples of artificial nanomaterials that are made consciously using precise mechanical and manufacturing procedures. Nanomaterials are categorized as metal-based materials, dendrimers, or composites depending on their structural makeup.[17, 18]

1.5.2 Classification of nanomaterials based on the structural configuration/composition

According to their structural makeup, nanoparticles can be broadly divided into four groups: organic/dendrimers, inorganic, carbon-based, and composite.

* Organic nanomaterials

On the nanoscale, organic compounds are converted into organic nanomaterials. As shown in Figure 2,[19, 20] some examples of organic nanoparticles or polymers are liposomes, dendrimers, micelles, and ferritin. Non-toxic biodegradable nanoparticles known as nanocapsule micelles and liposomes have hollow interiors and are sensitive to heat, electromagnetic radiation, and light.[21] The surface of a dendrimers is coated with numerous chain ends that can perform specific chemical reactions. Dendrimers are used in molecular recognition, nano sensing, light harvesting, and optoelectrochemical systems. Furthermore, because three-dimensional (3D) dendrimers feature internal holes that can hold additional molecules, they may be useful for drug administration, [22, 23]

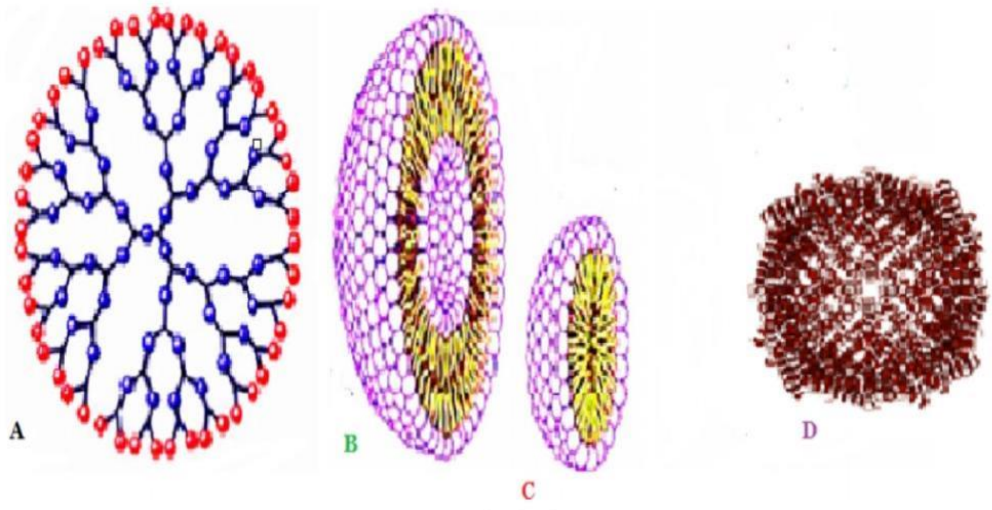


FIGURE 2 The examples that follow consist of organic nanomaterials: A, dendrimers; B, liposomes; C, micelles; D, ferritin.[28,31]

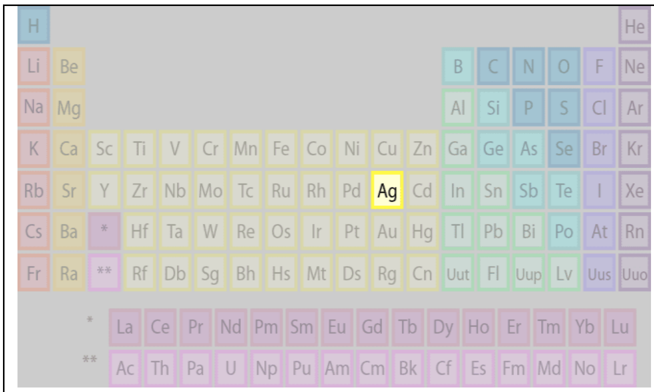
* Inorganic nano materials

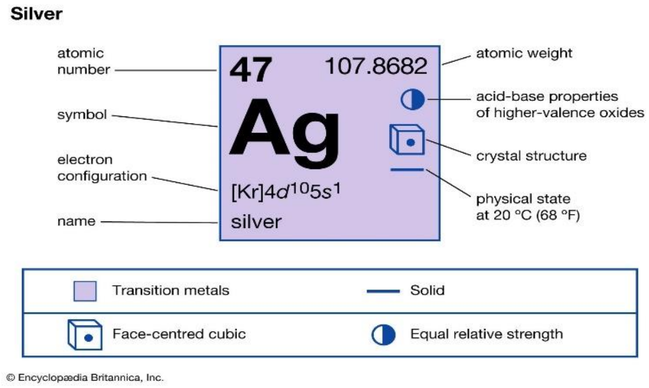
Inorganic nanoparticles are nanoparticles that lack carbon atoms and are known as inorganic nanoparticles. Inorganic nanoparticles are typically classified as those composed of metal-based or metal oxide-based nanomaterials.

1.6 Ag nanoparticles

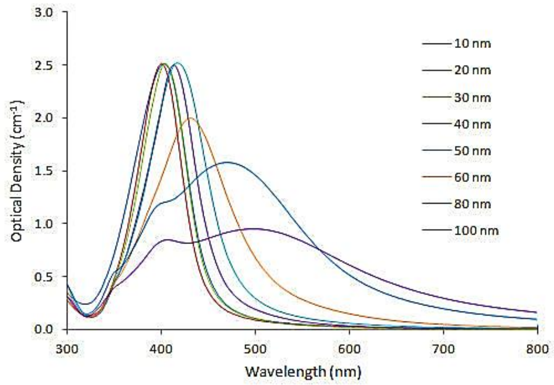
Silver nanomaterials (NMs) (nanosilvers) are clusters of silver atoms of 1-100 nm in at least one dimension. Due to their unique physical and chemical properties, nano-silvers are widely used in various areas with exponentially increasing production [24]. Silver is the noblest metal in the fabrication of nanoparticles due to its wide spectrum of bactericidal and fungicidal activities. Silver nanoparticles can coordinate with various ligands and macromolecules in the microbial cell. Silver has been widely used in the control of microbial proliferation as well as curing wound healing due to its anti-inflammatory effect. Silver has many modern industrial uses and it is considered a store of wealth. This review targets about the synthetic methods of preparation of silver nanoparticles and their applications in various fields (25).

Chemical symbol of Ag element





Ag Nano-power



Ag-NPs exhibit a specific absorbance peak **between 400 and 450 nm**

Fig. (3): main prperties for Ag element

1.7 Antibacterial

Antibacterial activity is the most important characteristic of medical textiles, to provide adequate protection against microorganisms, biological fluids, and aerosols, as well as disease transmission.

The antibacterial activity is calculated dividing the number of bacteria present after 24 hours of cultivation onto a testing treated article/product (C) into the number of bacteria present after 24 hours of cultivation onto the corresponding untreated (without antimicrobial agent)

article/product. Antibacterial technologies are effective against a broad spectrum of harmful bacteria and they

will typically incorporate several active ingredients, allowing for successful application in a wide variety of product types. Antimicrobial technologies actually minimize the presence of bacteria, mold, and fungi [26].

The features of an ideal antibacterial drug are as follows:

Selective target-target unique.

- Bactericidal--kilis the bacteria.
- Narrow spectrum-does not kill normal flora.
- High therapeutic index---ratio of toxic level to therapeutic level.
- Few adverse reactions-toxicity, allergy.
- Various routes of administration.

1.8 Clindamycin

Drug Class: Antibiotics, Lincosamide

Clindamycin is an antibiotic that fights bacteria in the body.Clindamycin is used to treat serious infections caused by bacteria.

Clindamycin is usually available as one of three salts: clindamycin phosphate, clindamycin hydrochloride, or clindamycin nicotinamide. These salt forms are all prodrugs of clindamycin but once inside the body or applied to the skin, they are rapidly converted to active clindamycin by hydrolysis. All three salt forms of clindamycin: clindamycin phosphate, clindamycin hydrochloride, and clindamycin nicotinamide have the same antimicrobial spectrum and effectiveness.

Clindamycin phosphate salts are usually used for intravenous, intramuscular, and topical formulations of clindamycin. Clindamycin hydrochloride salts are usually used for oral forms of clindamycin, and clindamycin nicotinamide is another topical form of clindamycin. (27)

Fig. (4): types drug of clindamycin

Side effects

- Fungal overgrowth,
- Pseudomembranous colitis,
- Hypersensitivity,
- Stevens-Johnson syndrome,
- Hives,
- Low blood pressure (hypotension),
- Nausea,
- Blood clot,
- Granulocytopenia,
- Low white blood cell count (neutropenia),
- Low platelet count (thrombocytopenia),
- Polyarthritis,
- Kidney dysfunction,
- Vomiting,
- Diarrhea,
- Stomach pain,
- Joint pain,
- Vaginal itching or discharge,
- Skin rash or itching,
- Heartburn,
- Sore throat

Clindamycin can cause watery or bloody diarrhea, which may be severe or lead to serious, life-threatening intestinal problems.

Mechanism of action of Clindamycin

Clindamycin acts by inhibiting bacterial protein synthesis at the level of the 50S ribosome. As a result, it exerts a prolonged postantibiotic effect. It may decrease toxin production and increase microbial opsonization and phagocytosis even at subinhibitory concentrations

The chemical name for clindamycin hydrochloride is

"Methyl 7-chloro-6,7,8-trideoxy-6Â(1-methyl-trans-4-propyl-L-2 pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galactoÂoctopyranoside monohydrochloride" as seen in figure 5.

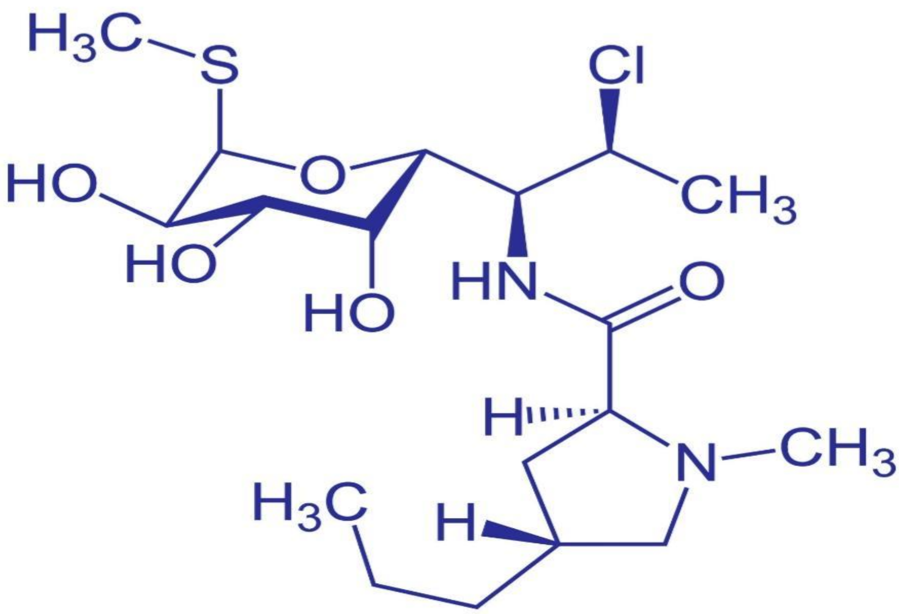


Figure (5) Clindamycin

Chapter two

Literature review and Methods

2.1. Synthesis methods AgNPs nanoparticles

In recent years, researchers have been interested in Ag prepared with nanotechnology and applying them in various fields, especially medicines, and their effect has been proven in improving the effectiveness of drugs against diseases. The following table shows a summary of the efforts of some researchers in the manufacture of sliver element nanoparticles and their medical and pharmaceutical applications.

Preparation methods of silver nanoparticle		Characterization method	Application	
Green sedimentation	1)Silver nitrate was used as metallic precursor and the extract of Moringa oleifera leaves with different concentrations was used as reducing as well capping agent	XRD SEM	Used as antibacterial agent	
	2)Synthesize silver nanoparticles using aqueous extract of fresh garlic as reducing and as a stabilizing agent silver nitrate solution	XRD SEM AFM TEM DLS	Reducing the damage to sperm parameters. In diabetic compared to metformin	
	3)Silver nitrate with extract of fresh leaves of pedalium murex	UV_vis FTIR XRD TEM	Antibacterial activity	
Physical methods	Evaporation condensation	XRD	Antibacterial	[36]
	Preparation of silver nanoparticles in virgin coconut oil using laser ablation	TEM	Antibacterial	[37]
	Phase separation ((Continuous Synthesis and Separation of Silver Nanoparticles Using an Aqueous Two-Phase System)	TEM	Wound healing	[38]
Chemical methods	Irradiation method	XRD	Antibacterial	[39]
	Microwave assisted	TEM XRD	Antibacterial	[40]
	Atomic molecular condensation	TEM XRD	Antibacterial	[41]

2.2. AgNPs preparation

The AgNPs were made using chemical reduction method. Glucose was used as a reducing agent, and PVP was used to spread the particles out. To make a reducing solution, 3.6 g of glucose, 0.56 g of NaOH, and 2.4 g of PVP were mixed together in 20 ml of Di water. The reduction solution was put into a beaker, which was then put in a water bath that was 70 °C.

After that, 10 ml of a 1M silver nitrate solution was slowly added while the mixture was being violently stirred. It took 10 minutes of the reducing reaction to go on before the gray-brown sol of AgNPs was formed. Centrifugation was used to separate the soils, and they were washed three times with pure ethanol and deionized water.[28]

2.3. Ag NPs loaded on clindamycin.

The loaded clindamycin drug on Ag nanoparticles. To prepare the Ag / drug , approximately 60 mg of clindamycin drug were dissolved in 100 mL of a mixture of clindamycin drug and 30 mg Ag NPs. which was used as the drug carrier. The reaction was sonicated for 10 min. After that, it was processed under stirring for 4 h (1,2).

Chapter three
Results and Discussion

3.1. Scanning electron microscope (SEM) analysis

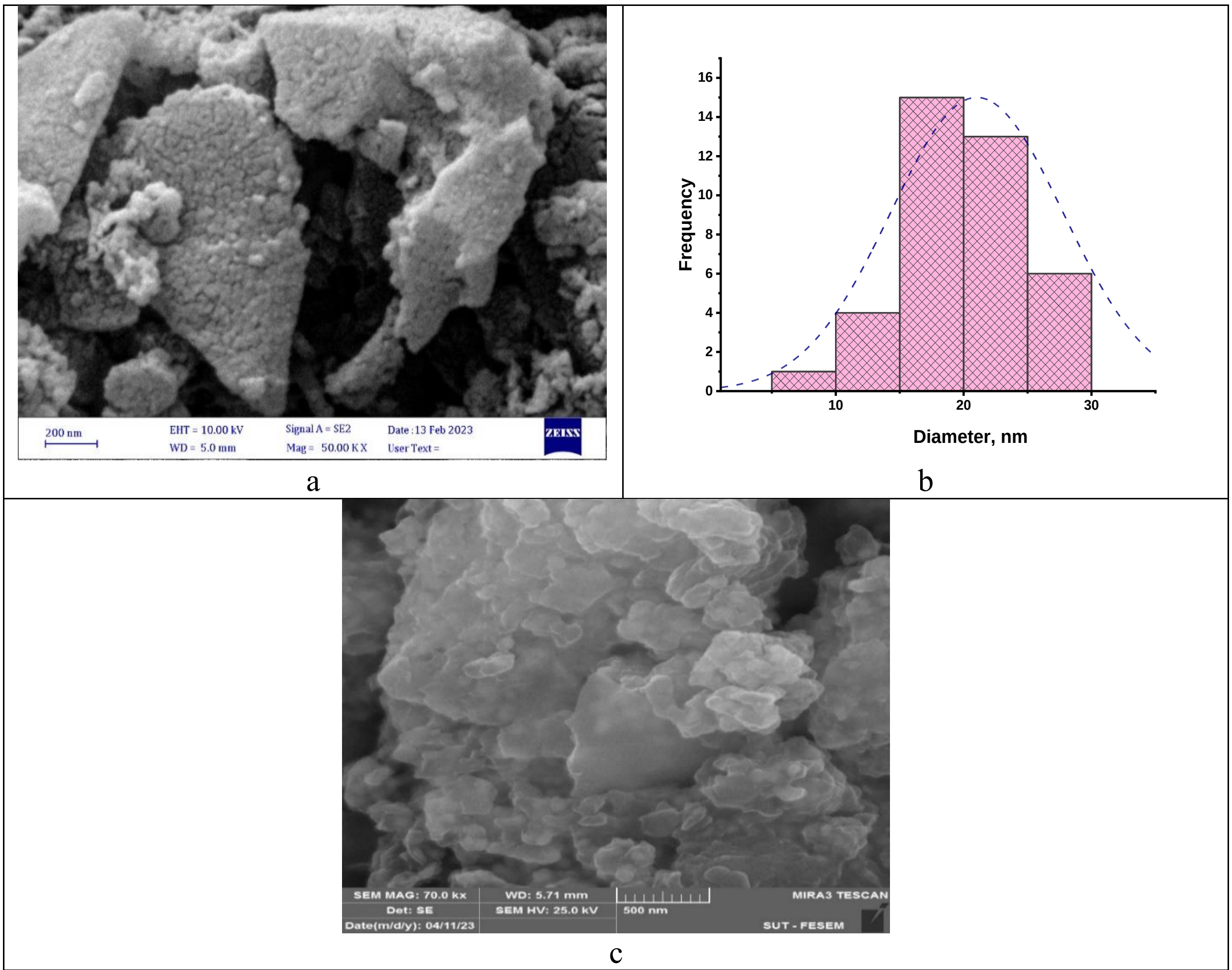


Figure (6): SEM images for a: morphology of Freshly produced Ag element; b. histogram distribution for Ag particles; c. morphology of Ag with clindamycin

SEM images of the nanoparticles prepared via both the routes are shown in Figure (6). Figure 6a , 6b and 6c shows the SEM image of Chemical reduction derived nanoparticles. As seen in figure 6a , the morphology of Ag Nona powder clear nano production consists of highly agglomerated nanoparticles and in figure 6.b can be seen having grain size of rang (5-30 nm) by Image J software employed to calculate particles and average size for SEM zoom 200 nm [29]. Figure 6.c displays the SEM morphology of

Ag-NPs of clindamycin. This suggests that the concentrations of the drug have appropriate viscosity to synthesize NPs. Consequently, constant and regular NPs were formed effectively [30].

3.2 X-ray diffraction pattern (XRD)

(XRD) analytical techniques that give information about the crystalline structure, chemical composition, and physical properties of materials and thin layers of crystalline materials.

One important use of X-ray diffraction is the determination of crystal structure. Ag/AgO NPs were produced by the Chemical reduction synthesis technique showing variations in atomic arrangement, lattice properties, and crystal diameters, as shown in Figure(7) The diffraction angles at 38.2° and 46.3°, 64° and 77.23° corresponding to planes (111), (200), (220), and (311), respectively [31], with previous reports for Ag nanocrystals of face-centered cubic (fcc) Ag nano crystallites, which were consistent. The difference fraction angles at 32° corresponding to planes (111), confirm the behavior of AgO Nps. This pattern also included an unusual peak at 48°, which may have been caused by organic contaminants in the samples [32].

We estimated the Average size of the as-prepared Ag nanocrystals using Scherrer equation by measuring the full width of half maximum (FWHM) of peaks Bragg reflection. The Average size of the Ag nanoparticles was thus determined to be about 18.75nm .

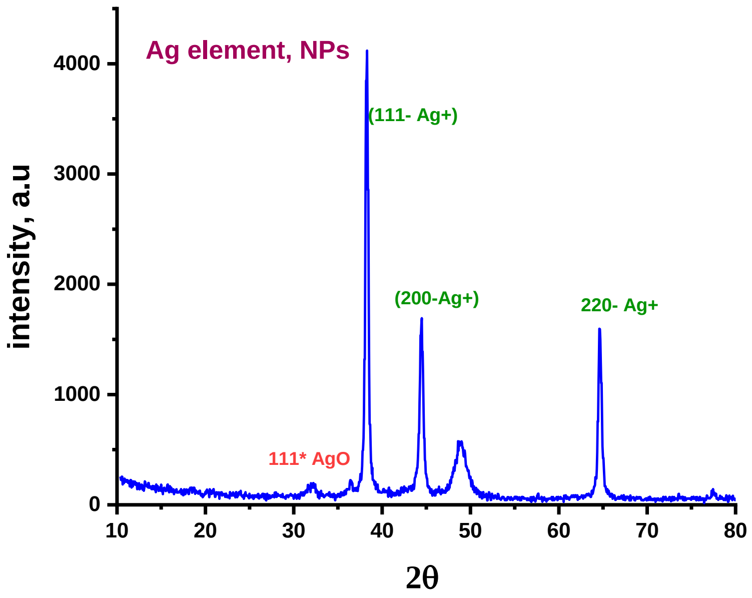


Figure (7): XRD patterns for Ag nonproduction

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وَآخِرُ دَعْوَاهُمْ أَنِ الْحَمْدُ لِلَّـهِ رَبِّ الْعَالَمِينَ ﴿١٠﴾