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Department of Chemistry

Synthesis and Characterization of Nano Graft Copolymer Drugs and study their Ability to Inhibit Liver Cancer

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Written by

Surur Falih Hassan Gomaa

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Supervised by

Prof. Dr. Mohammad Nadhum Al-Baiati

Lect. Dr. Zeyad Tareq Habeeb

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سُورَةُ الإِسْرَاءِ

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

وَيَسْـَٔلُونَكَ عَنِ ٱلرُّوحِ ۖ قُلِ ٱلرُّوحُ مِنْ أَمْرِ رَبِّى وَمَآ أُوتِيتُم مِّنَ ٱلْعِلْمِ إِلَّا قَلِيلًا ﴿٨٥﴾

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We certify that this thesis (**Synthesis and characterization of Nano Graft copolymer Drugs and study their Ability to Inhibit Liver Cancer**) was papered under our supervision in the chemistry department-College of Education for Pure Sciences- University of Karbala, in partial Fulfillment of the requirements for the degree of Master in Chemistry Sciences by the student (**Surur Falih Hassan Gomaa**).

Signature: Signature:

Prof. Dr. **Mohammad N. Al-Baiati** Lect. Dr. **Zeyad Tareq Habeeb**

Supervisor Supervisor

Date: / /2024 Date: / /2024

In view of the available recommendations, I forward this thesis for debate by the examining committee.

Signature:

Name: Prof. Dr. **Mohammad Nadhum Bahjat**
Date: / /2024
Head of Chemistry Department

Committee Certification

We certify that, we read this thesis **(Synthesis and characterization of Nano Graft copolymer Drugs and study their Ability to Inhibit Liver Cancer)** and as examining committee examined the student **(Surur Falih Hassan Gomaa)** in its content, and that in our opinion it is adequate (***Excellent***) with standing as a thesis for degree of master in chemistry sciences.

Chairman

Signature:

Name: **Dr. Sawsan Khudhair Abbas**
Sci. Title: Asst. Profe
Address: Department of Chemistry/ College of Education for Pure Sciences
Date: / /2024

Member

Signature:
Name: **Dr. Ehab Kareem Obaid**
Sci. Title: Asst. Prof
Address College of Agriculture/ University of Al-Qassim Green
Date: / /2024

Member

Signature:
Name: **Dr. Jalal Mohammad Hassan**
Sci. Title: Asst. Professor
Address: College of Pharmacy/ University of Kerbala

Supervisor & Member

Signature:

Name: **Dr. Mohammad N. AL- Baiati**
Sci. Title: Professor
Address: Department of Chemistry/ College of Education for Pure Sciences

Date / /2024

Supervisor & Member

Signature:

Name: **Dr. Zeyad Tareq Habeeb**
Sci. Title: Lecturer
Address: Department of Chemistry/ College of Education for Pure Sciences

Date: / /2024

Approved for the College Council.....

Signature:

Name: **Prof. Dr. Hamieda Idan Salman**
Dean of the College of Education for Pure Sciences
Date: 15/12/ 2024

First Scientific Evaluation Report

This is to certify that I have read the thesis entitled **(Synthesis and characterization of Nano Graft copolymer Drugs and study their Ability to Inhibit Liver Cancer**) and corrected the scientific mistakes I found. The thesis is, therefore, qualified for debate

Signature:

Name: ***Zaid Mohammad Abbas***
Sci. Title: Asst. Proof
Address: University of Wasit/ College of Sciences

Date: / /2024

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This is to certify that I have read the thesis entitled **(Synthesis and characterization of Nano Graft copolymer Drugs and study their Ability to Inhibit Liver Cancer**) and corrected the scientific mistakes I found. The thesis is, therefore, qualified for debate

Signature:

Name: ***Ahmed Hasson Majeed***
Sci. Title: Asst. Proof
Address: University of Kufa/ College of Sciences

Date: / /2024

Amendment Report

This is to certify that the thesis entitled **(Synthesis and characterization of Nano Graft copolymer Drugs and study their Ability to Inhibit Liver Cancer**) and corrected the grammatical mistakes I found. The thesis is, therefore, qualified for debate .

Signature:

Name: Muayad Omran Chyad
Sci. Title: University of Kerbala/ College of Education for Humanities Sciences
Address: Proof

Date: / /2024

Dedication

To my father, who has taught me to help others without expecting anything back, and whom I am always proud of

To my mother, who has taught me to meaning of love, compassion and dedication and the one whose paradise is under her feet

To my loving husband, the love of my life, who has spared no efforts in assisting me

To my dear sisters, my better half

To my brothers, who have been always a support in my life

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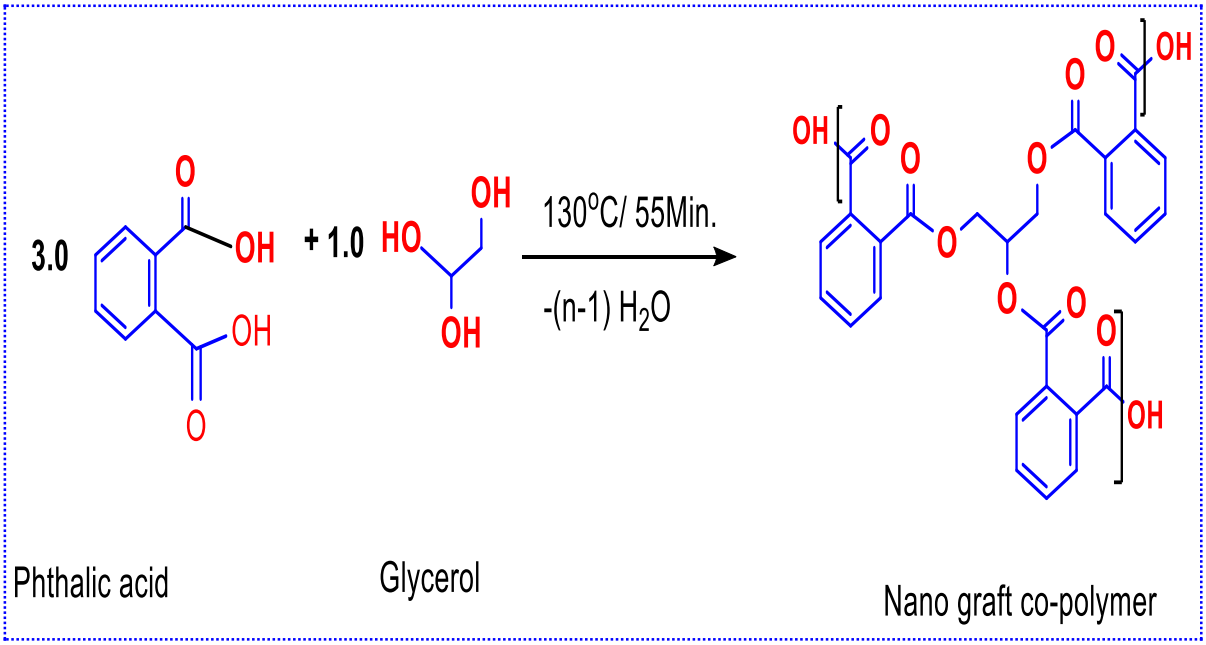
Summary

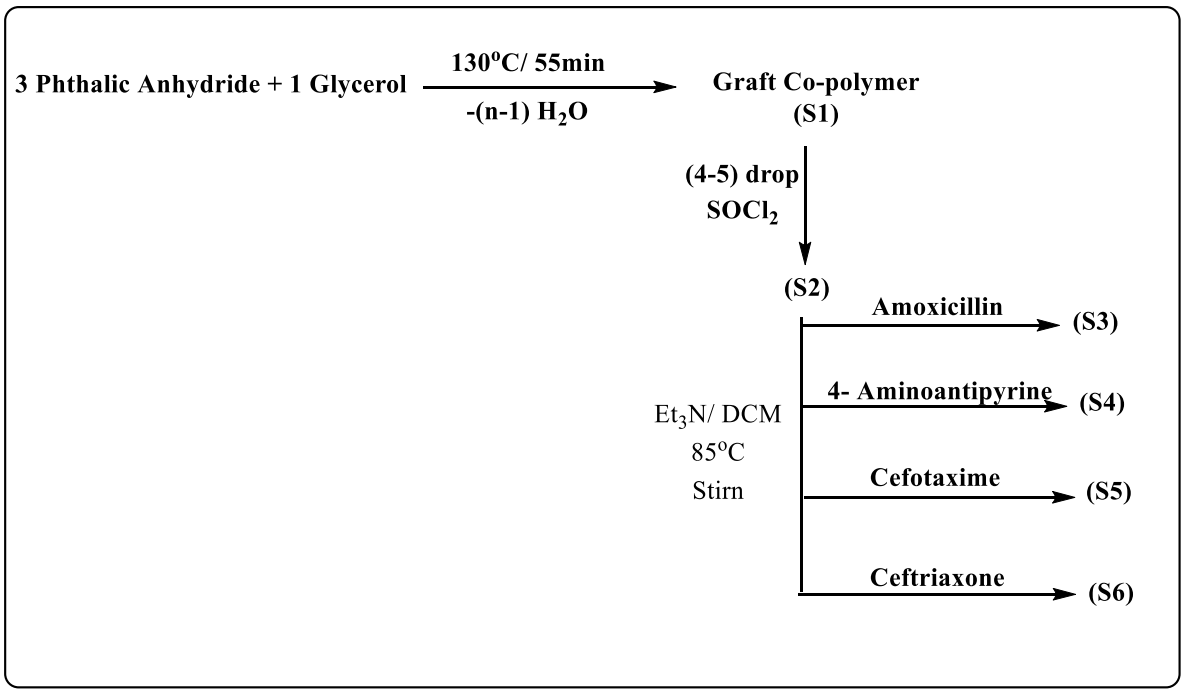
In current study the synthesized of a new Nano graft Co-polymer, one mole of glycerol was reacted with three moles of phthalic acid at 130 °C in 55 min, as shown in the equation below nano graft go-polymer was then characterized using (FT-IR, ^{1}H-NMR, AFM, and XRD) techniques.



Nano Graft Co-polymer was linked with some common drugs are (Amoxicillin, 4-aminoantipyrane, Cefotaxime, and Ceftriaxone) respectively as shown equation, The Nano Graft Co-polymer- Drugs was characterization by (FT-IR, ^{1}H-NMR, ^{13}C-NMR) techniques

The solubility properties of Nano Graft Co-polymer bonded with some drugs in different solvents were studied (H_2O, Ethanol, Methanol, Hexane, DMSO, and Acetone).

Using a UV-Vis spectrophotometer, the release of Drug (Abs.) was monitored as a function of time (hours and days) at various pH values (2.2, 6.0, 7.2, and 8.0) at a constant 37 °C.



The most efficient binding energy of nano Graft Co-polymer drugs, the kind and length of Nano Graft Drug Composites, the prediction of protein-bonding interactions, and the preparation of the target protein's active site were all studied in relation to the binding of medications to the proteins of liver cancer cells.

The effects of the composite drugs listed above on the liver cancer cell line were investigated. Results from our data showed promising outcomes when a number of well-known drugs and nano graft composites were combined. The rationale behind this is that the medication needs to keep working for a substantial period of time until it more effectively targets particular body parts while avoiding negative effects on other body parts. Indicating that the drug-infused synthetic nano graft composites were highly biologically successful in preventing liver cancer from rapidly spreading throughout the cells, the percentage of these cells dramatically dropped. Additionally, this sequence illustrates how well the manufactured nano graft co-polymer-drugs work to stop the spread of liver cancer:

$$S3 > S4 > S6 > S5$$

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List of Abbreviations

Symbol	Description
Et_3N	Triethyl ammine
EtOH	Ethanol absolute
THF	Tetrahydrofuran
DMSO	Dimethyl Sulfoxide
FT-IR	Fourier Transform Infra red
^{1}HNMR	Proton nuclear magnetic resonance
^{13}C-NMR	Carbon nuclear magnetic resonance
AFM	Atomic Force Microscope
XRD	X-Ray Diffraction
TEM	Transmission Electron Microscopy
DNA	Deoxyribose Nucleic acid
T	Temperature
pH	potential of hydrogen
UV-Vis	Ultraviolet-visible
PDB	Protein Data Bank
SDI	The General Company for the manufacture of medicines and medical supplies / Samarra
O.D.	Optical Density
$SOCl_2$	Thionyl Chloride
DDS	Drug Delivery System
RPMI 1640	Roswell Park Memorial Institute
IC50	medium inhibition concentration
EDTA	Ethylene Diamine Tetra Acetate
λ_{max}	Wave Length
MTT dye	Tetrazolium dye
DCM	Dichloromethan

Chapter One
Introduction

1. INTRODUCTION

1.1. Polymer

Polymers is compound has a high molecular weight and is made up of small molecules called monomers that repeat themselves and are joined by chemical bonds to form extended, branching, or ring sequences. Repetitive molecular units make up these chains [1, 2]. Many biomaterial applications, including orthopedic and dental surgery, hard and soft tissue replacement, and cardiovascular devices, can benefit from the unique features of polymer materials. The majority of materials utilized in medicine are actually polymers [3].

Since polymers are naturally occurring substances that appear in wood and plants as cellulose or starch, they can be either naturally occurring or artificially produced. The majority of polymeric materials that we encounter are industrial polymers since they are made from natural gas and petroleum, however examples of polymeric components originating from living beings include collagen, DNA, RNA, and protein [4].

Polymers are characterized by a wide range of properties and attributes, including resistance to environmental factors, low weight, insulating or occasionally conducting electricity, hard, soft, or rubbery, transparent, or opaque. Because its molecules are constructed in the shape of chains that can be joined in a variety of ways to produce goods with unique specifications, its structure plays a significant role in the diversity of its products [5].

The term "linear polymer" refers to a polymer where the molecules are joined in a straight line such as **Poly vinyl chloride**; conversely, the term "branched polymer" refers to a polymer where the molecules are branched such as Poly Ethylene. The branches inside the polymer chain can have a variety of shapes and lengths, including comb, ladder, and cruciform structures. Four varieties of polymers are depicted in Figure (1-1): [6, 7]

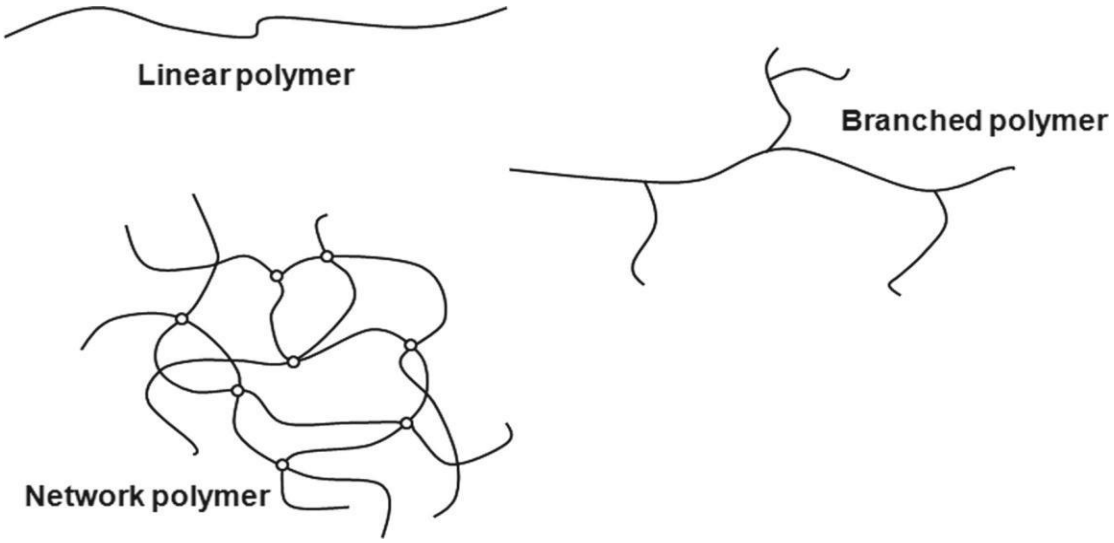


Figure (1-1). Different the types of polymers

Due to their special qualities, polymers play a fundamental and integral part in everyday life. Paints, packing boxes, tires, textile fibers, medical and surgical supplies, public health materials, automobile spare parts, electrical and electronic equipment, and many other applications are just a few examples of the many uses for polymers [8, 9].

1.2. Polymer Drugs

Polymer drugs are defined as polymers that are active pharmaceutical ingredients, i.e., they are neither drug carriers nor prodrugs[10].

Over the previous twenty years, there has been a noticeable increase in the usage of functional polymers in medicine. Biomaterials made of polymers have been used in dental, medical device, tissue engineering, and artificial organ applications. The macromolecules that cause biological action are the polymeric medicines. Numerous man-made polymers lack biological activity. On the other hand, some show toxicity and others show a variety of therapeutic activity [11, 12]. Since polymers offer an almost limitless range of topological and chemical diversity, they make up a significant fraction of materials employed in drug-

targeting systems and controlled release formulations. This gives this class of materials a significant advantage over others in meeting the ever-increasing needs of novel drug delivery formulation designs. A single polymer molecule's shape is described by its topology, or polymer architecture. Each type of polymer natural, seminatural, and synthetic—fits into one of the following architecture categories: block, star-shaped, branching, linear, graft, cross-linked, and grafted [13]. Researchers focused on the synthesis of bioactive polymeric materials by covalently binding the drug to a polymer. For example, chloramphenicol was copolymerized with 2-hydroxyl methacrylate after being first connected to a methacrylic to provide an acetal function [14].

Polymers are typically employed as implants in the biomedical field, where they are supposed to provide long-term functionality. For this to be possible, the polymers must possess certain qualities that those meant for wider use do not provide. Film-forming (coating), thickening (rheology modification), gelling, adhesion, pH-dependent solubility, and barrier qualities (packing and protection) are often the preferred polymer features in pharmaceutical applications [15, 16]. Gene therapy has made use of polymers as non-viral vectors for the transfer of genetic material [17]. Significant progress has been made in the field of polymeric drug delivery systems. The crucial aspect of conventional drug administration is maintaining the agent's blood level between a minimum value, below which the medicine loses its effectiveness, and a maximum value, which may indicate a toxic amount [18].

1.3. Nanotechnology

Norio Taniguchi was the first scientist to define the term nanotechnology. He defined “nanotechnology” as the process of separating and combining materials by manipulating a single atom or molecule [19]. Nanotechnology is involved in many fields such as science, engineering, medicine and technology [20]. The term

"nano" is a Greek word meaning dwarf [21], and the sizes of nanomaterials range from nm (1-100) [22, 23].

Nanotechnology provides a path to entirely new classes of nanocarriers with effective engineering, biosensors and systems that have dramatically changed modern drug delivery methods [24]. Researchers are currently trying to reach unexplored biological sites by reducing the sizes of the carrier without affecting the drug loading to provide better and faster treatment, such as the central nervous system, so a variety of organic and inorganic materials have been developed, in order to enhance drug delivery systems [25]. Nanoparticles include atomic or molecular materials in the form of small nano-sized spheres [23, 26], which can be more easily transported inside the human body when compared to materials of larger sizes, and the fabrication and engineering of materials at a molecular size helps in reaching biological sites such as the blood-brain barrier [25]. Nanomedicines have become important due to the use of nanostructures by encapsulating drugs as delivery agents, or binding therapeutic drugs and delivering them to the target tissues [22, 27].

In addition, there are two main strategies that are used to assemble the processes of nanomaterials (Nano polymers) from the top down and the bottom up [28]. In the top-down strategy, nanomaterials can be manufactured using several processes to disassemble large structures into smaller things that are within the nano scale while maintaining their original properties, in the bottom-up strategy, nanomaterials are assembled by several engineering processes such as disassembling the structure of atoms together to produce nanocomposites within the nano scale [29].

1.4. Nanoparticles

The term nanoparticles include Nano capsules and Nano shells, which differ in many key factors regarding their size and method of formation, and by some microscopic techniques such as (AFM) Atomic Force Microscope – Transmission Electron Microscopy (TEM) and (Scanning Electron Microscopy) SEM, can be measured depending on the method of preparation and composition of the organic phase [30], Nano shells or Nano capsules can be produced [31]. The Nano capsule particle contains a core shell with an oily or water cavity, and on the other hand the active compounds are surrounded by a nano-polymer shell, this Nano shell is in the form of a polymer matrix in which the active compounds and the polymer are separated, where these compounds and the polymer are separated equally so that the drug is retained inside the polymer or absorbed on its surface [32]. The reservoir system is called a Nano capsule, while the matrix system is called a nanoball, as shown in Figure (1-2) [28].

Different methods can be used to prepare polymeric nanoparticles depending on the type of drug loaded into the polymeric nanoparticles, because the drug needs a suitable dosage route according to the physical and chemical properties of the drug [33]. Organic solvents are often used in the initial steps to dissolve the polymer, and these solvents may cause toxicity problems and environmental hazards, in addition to the solvent residues present in the final product must be disposed of. Most of the preparation methods used in drug production are in the form of an aqueous colloidal suspension [28].

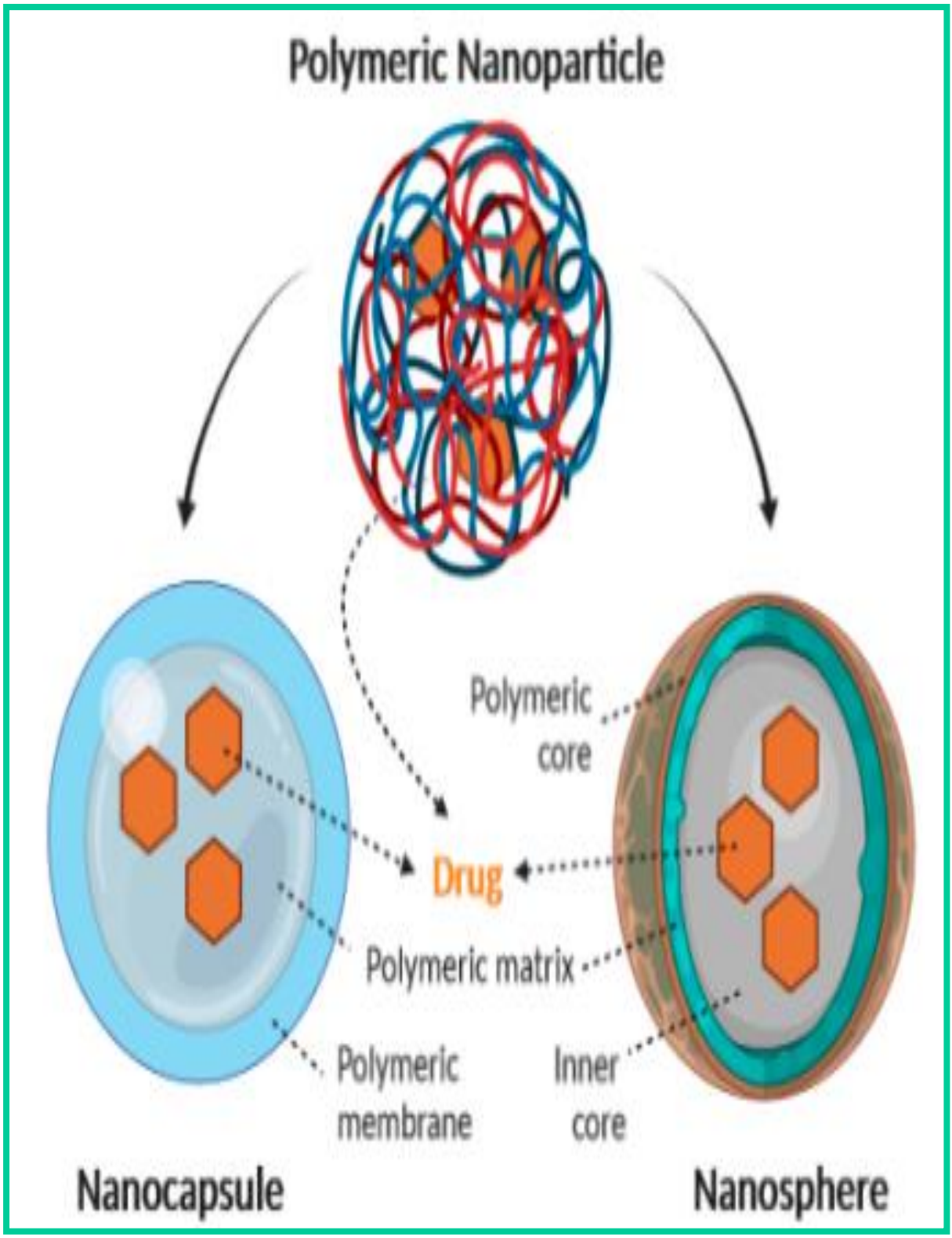


Figure (1-2). Schematic diagram of the structure of Nano capsules and nanospheres (arrow indicates the presence of a biologically active drug inside the nanoparticles)

1.5. Drug Delivery System

The treatment is administered to humans in different ways in order to reach the tissue that is supposed to achieve the therapeutic effect [34, 35]. To achieve high pharmaceutical efficiency and accuracy in delivering the drug, it is necessary to overcome the obstacles that accompany the method of delivering the drug [36, 37]. There are several ways to administer the drug, including: oral, intravenous, intramuscular, cutaneous, and nasal inhalation [38, 39]. Oral administration is the most common, representing 52% of the drugs available in pharmacies [38], and is the method preferred by the majority of society. The most important reasons for this preference are simplicity, ease, and comfort when using, and flexibility in terms of manufacturing in designing the drug dose with low cost, but this method is not without some limitations, some of which depend largely on the patient in terms of adhering to the drug taking times, and the drug may be metabolized and enzymatically destroyed when crossing the digestive tract [40].

Researchers in the field of pharmaceutical sciences and drug development have faced several problems, especially in drugs given orally, and thus the idea of a controlled-release drug delivery system began, and at the present time this method is used with anti-cancer drugs in order to reduce toxicity to other parts of the body and target cancer cells only, and also reduce the damage caused by these drugs to healthy cells [41]. What distinguishes the controlled-release drug delivery system from the traditional system is the release of the drug dose in the place to be treated and the treatment remains For the longest period of time when taken and passing through the body parts and not having an effect until reaching the place to be treated in the patient, and thus the frequency of drug doses is reduced and as a result drug toxicity is reduced, and changes in drug concentrations in plasma levels are reduced, as their increase leads to other side effects that are sometimes harmful or undesirable, but if the drug concentrations are lower, they do not give sufficient therapeutic efficacy, and protect the drug

substance from secretions and effects of the intestinal tract and determine the effect of the dose significantly, and this leads to giving high therapeutic efficiency [42].

1.6. Drug Loaded

Nanoparticle (NP) formulation has been the focus of much research over the last few decades. Drug physicochemical characteristics, such as solubility and chemical stability, influence the choice of an appropriate NP formulation method. Drug loading, drug entrapment efficiency, and release kinetics are all impacted by the various NP production processes, which also allow for manipulation of the physicochemical properties such size, structure, morphology, and surface texture [43]. An update on the state of the art in the production of polymeric nanoparticles from premade polymers is provided in this paper. New developments in NP technology as well as traditional techniques for NP preparation, such as emulsification-based and spontaneous formation, are discussed. The nature of the polymer, drug, and solvent, as well as their toxicity, purification, drug stability, and method's scalability, are compared. The data gathered enables the establishment of selection criteria for NP preparation methods based on their benefits and drawbacks. The structure of an intravascular stent can be coated with a drug-loaded polymeric substance that contains a therapeutic medication. To prevent interfering with the stent's functionality, a therapeutically effective dose of a medication is added into such a layer of polymeric material without appreciably thickening the stent[44].

The stent drug-loaded polymer coating has the ability to form pores, be multi-layered to allow multiple drug-containing materials to be combined into a single stent, and have a rate-controlling membrane to enable the controlled delivery and retention of specific drugs within the impacted blood vessel after implantation[45]. Through a heat-processed method called coextrusion, the therapeutic drug and the polymeric material are combined with a relatively high

loading to create the layer of polymeric material. Little particles of the therapeutic medicine are disseminated and incorporated into the polymer, ideally with a maximum cross-sectional dimension of 10 microns [46].

1.7. Drug Release

The rate and volume of drug that reaches its designated target (site) is known as drug release. The outcome Release is the initial phase of a drug's absorption process, during which the supplied active component is released into the body. After that, the medication passes through a number of phases, including distribution, metabolic conversion, excretion, and absorption [47, 48].

The drug's solubility and dispersion are affected by the release mechanism, which also has an impact on its effectiveness. Smaller particle sizes have a high surface area to volume ratio, which promotes quicker drug release. Conversely, bigger particles have bigger nuclei that encapsulate the medication and cause a delayed release. Consequently, the rate is controllable. For a medicine to have a therapeutic impact, it must first be liberated from the pharmaceutical form; this can be achieved to some extent by regulating the particle size distribution [49]. Drug release comes in various forms [50]:

Immediate-release: The most popular type of oral dosage is immediate-release, which is a fast-release medication with precise liberation. There are other categories within modified release, such as sustained or extended release: The medication is continually delivered over the course of 12 or 24 hours; some is released right away, and the remainder is released in accordance with the release schedule.

Delayed release: These medications are also known as enterally coated medications because they are coated in a material that keeps the stomach's acidity from dissolving them. When a dose is taken, its release is timed to correspond with how long it stays in the stomach. This approach may be used to shield the

medication from the stomach or to shield the medication from the stomach's acidic environment.

Controlled release: Depending on the degree of (pH), the medicine is released in a certain location of the gut. This category includes medications that act locally in the gastrointestinal tract [51].

1.8. Oral Absorption

The reason for poor absorption is the natural and polar factors that are poor metabolism and affinity in the absorption process. Many pharmaceuticals, including their synthetic analogues of pyridine nucleoside, natural purines, and antibiotics like ampicillin and carbicillin, can dissolve in water. A secondary medication that improves the drug solubility and absorption in water can be used to mitigate the adverse effects of the biological effect through the mouth, which results in restricted water solubility [52]

1.9. Solubility of Drug

Based on the way the medicine is being taken, the adjuvant might either make it less or more soluble. When a drug's chemical stability is altered, either by changing the drug's physical properties or by modifying the effective group that is causing the instability, the therapeutic agent can be stimulated to produce drug activity for a longer duration. Appropriate combinations necessitate the creation of a new auxiliary drug, which can then be adjusted. The way that the beta-lactam ring is attached to a second Ampicillin molecule creates various forms of Ampicillin, just as the treatment and transport methods do in the Ampicillin NH_2 series [53, 54].

1.10. Drug Carriers

The increase in the number of active drug groups of the drug compound will face several problems when entering the body, which may cause them to react chemically as a result of acidic and enzymatic changes inside the human body, so these drugs are required to break down enzymatically and have effects on the intestinal tract. Specialists have found a specific way to ensure drug delivery, which is to manufacture a drug delivery system. The drug carrier is known as a system used to transport the drug to specific areas. It consists of several special molecules that either encapsulate the drug or are loaded on the surface. It is thus characterized by its high ability to protect drugs from enzymatic effects and increase their biological availability and deliver them safely to the desired location. Thus, drug carriers work to encapsulate the drug, or adsorb on the surface of the carrier and bring the drug to the desired location in the human body and absorb or pass through the cell membrane into it, then the drug is released or released from the carrier [47, 48]. Drug carriers used in delivering treatments have been designed from natural and synthetic materials, and are of various types, including: lipid carriers, porous materials [55], polymer carriers [56], gold particles [57], and carbon tubes [58]. As shown in **Figure (1-3)**.

The most important reasons that led to the development of drug carriers are:

1. Targeting specific organs in the body without others to avoid affecting their health by using drug carriers.

2. Extending the effective biological half-life of the drug and thus increasing the pharmaceutical efficiency.

3. The small size of drug carriers that reach the micro and nano gives them the ability to cross cell membranes and target damaged tissues [49, 51].

4. Using liposome carriers to transport hydrophobic drugs [59, 60].

5. Through the development of drug carriers, the pharmacokinetic properties have increased, including absorption, distribution, metabolism, extraction, and pharmacodynamic properties [50].

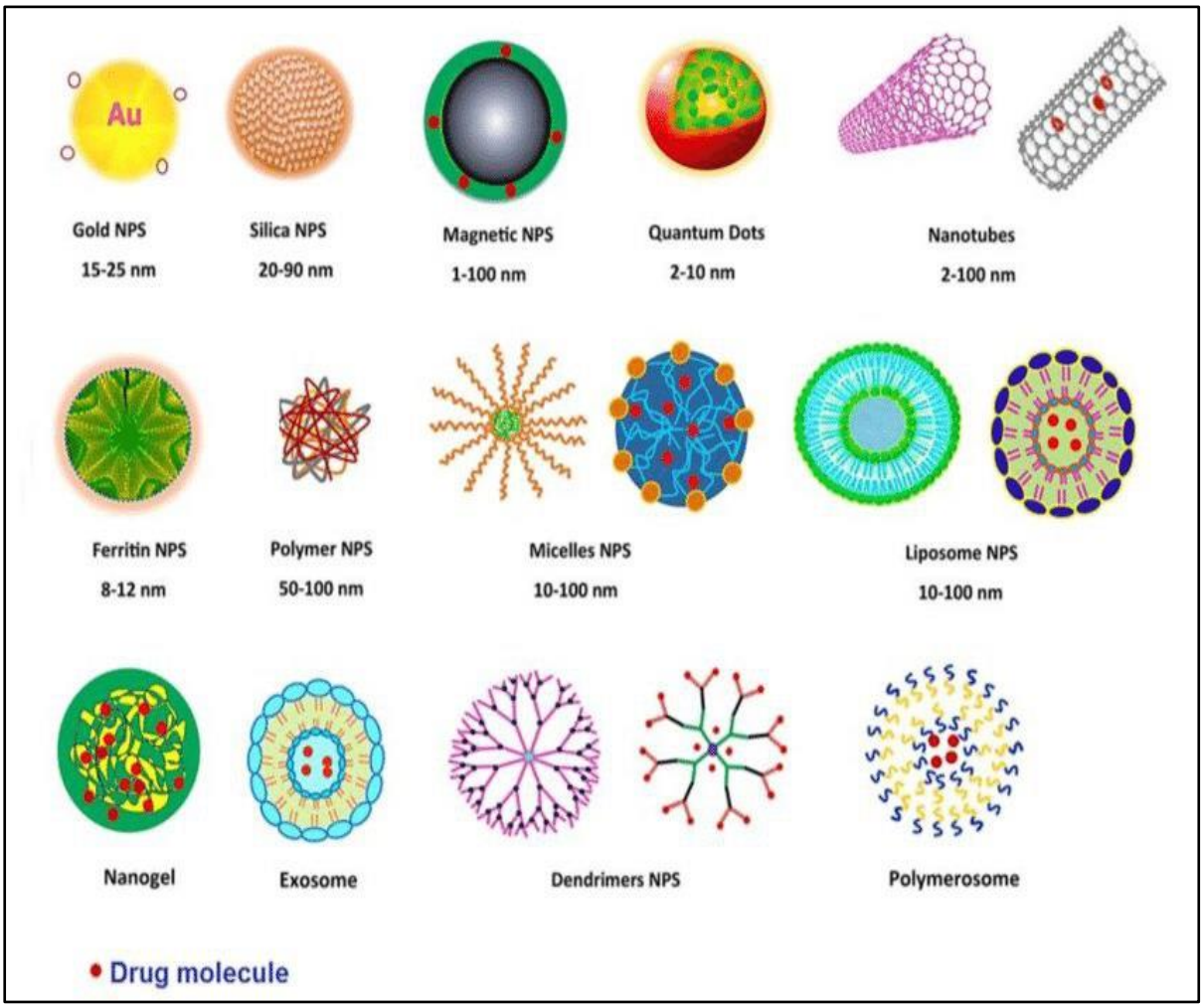


Figure (1-3). Some example Drug Carriers

Improving drug loading efficiency for drug carriers is crucial for the effectiveness of the drug's action [61]. By extending the time that drug carriers stay at the absorption site, it is possible to increase the biological availability of medications and achieve continuous release [62]. One significant benefit of the drug carrier is that, by raising the molecular weight of the medication, it promotes both drug absorption and accumulation [63]. organs such as the kidney, liver, spleen, or lymph gland that move biopolymers through tissues.

Molecular weight plays a key role in manufacturing and design success by forecasting how well the drug-delivering polymer will function in the body. Since numerous factors, including polymer chain formation, multiple compensation, composition, and solubility, affect the behaviors of the polymeric drug, there are polymeric vectors for pharmaceuticals that perform better than the drug itself [64]. Because the sequential drug polymers have multiple groups that enable the combination of anti-cancer medications with hydrophobic groups on the polymer chain through the enzymatic degradation of the bonds, they are regarded as one of the transporting nanoparticles that dissolve in water and are biologically insoluble [65].

1.11. Antibiotics

The structure and metabolism of bacteria differ greatly from those of human cells, and they are a creature of a separate biological realm [66]. Agents that do not disrupt our cells can both stop them from growing and destroy them [67].

Antibiotics, or antibacterial agents, must preferentially target bacteria in order to be employed in clinical practice. As a result, their management can concentrate on the traits of the bacterium that is causing the infection. The special quality of antibiotics over other pharmacological treatments is their ability to target alien cells and bacteria that infect our tissues rather than our own cells. Because of their selective function, their ability to influence bacteriostatic or bactericidal activity requires them to specifically target physiological and biochemical distinctions between human cells and bacterial cells [68].

The years 1928–1940 were crucial for the discovery and development of antimicrobial medications. Natural antibiotics were the first ones, such as streptomycin, which is derived from bacteria in the species Streptomyces, and penicillin, which is made by fungi in the genus Penicillium. Nowadays, the two main methods used to obtain antibiotics are chemical synthesis (for example,

sulfa medicines like sulfamethoxazole) or chemical modification of naturally occurring molecules. Antibiotics' effects have been demonstrated by [69]:

1. Inhibiting cell wall synthesis
2. Increasing the cytoplasmic membrane permeability
3. Preventing the synthesis of nucleic acid
4. Disrupting middle metabolism
5. Inhibiting protein synthesis in ribosomes of bacteria

1.11.1. Amoxicillin

Amoxicillin is abroad- spectrum β-lactam antibiotic that belongs to the penicillin class and is used in veterinary and human medicine, its chemical formula is $C_{16}H_{19}N_3O_5S$ [70]. The chemical structure of Amoxicillin is schematically shown in figure (1-4) [71].

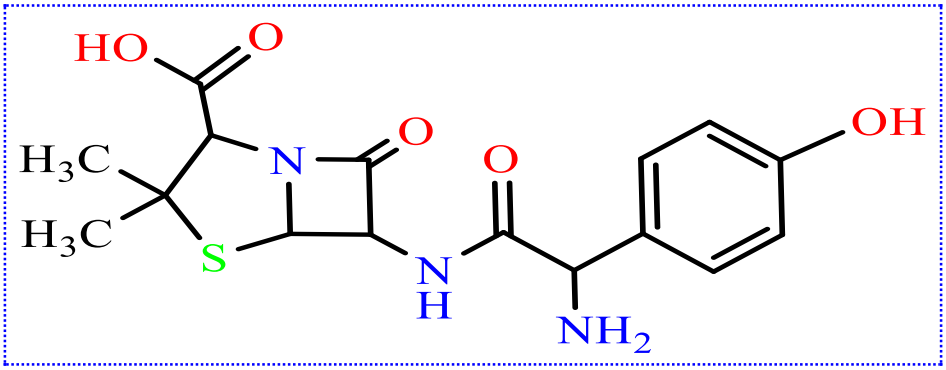


Figure (1-4): Chemical structure of Amoxicillin

Amoxicillin is an antibiotic used to treat a number of bacterial infection. These include middle ear infection, strep throat, pneumonia, skin infection, and urinary tract infection among others. It is taken by mouth, or less commonly by injection [72]. Representing one of the most prescribed antibiotics in Europe and in the United States; it is produced semi-synthetic and is kind of broad spectrum antibiotic in penicillin group. Its color is off- white and it has slightly aromatic

odor. Amoxicillin is generally found in crystalline powder from and has bitter taste. It has molecular weight of 365.4 g/mol and its half-life in the body is 61.3 minutes [73, 74].

1.11.2. 4- Aminoantipyrine

4-aminoantipyrine is a physiologically active substance. According to reports, substances with pyrazole nuclei exhibited strong antibacterial and anthelmintic properties [75, 76]. Analogues of 4-aminoantipyrine, another pyrazole derivative, have demonstrated anti-inflammatory, analgesic, antiviral, and antipyretic effects [77, 78]. It was discovered recently that 4-methylantipyrine are correlated and dipyrone's analgesic action [79].

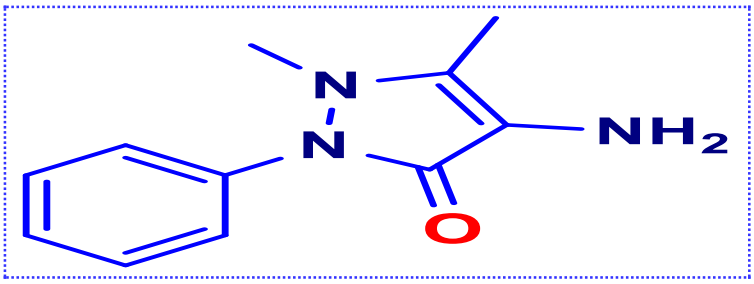


Figure (1-5): Chemical structure of 4- Aminoantipyrine

1.11.3. Cefotaxime

The generation cephalosporin cefotaxime has a wide range of antibacterial action and is delivered parenterally. The chemical structure of Cefotaxime is schematically shown in **figure (1-6)**. Following almost ten years of application, cefotaxime remains a crucial component in the management of patients suffering from severe infections, especially those brought on by Gram-negative bacteria. For hospitalized patients suffering from infections such pneumonia, complex UTIs, and bacteremia, cefotaxime clinical trials have shown bacteriological and/or clinical success rates typically between 75 and 100% [80].

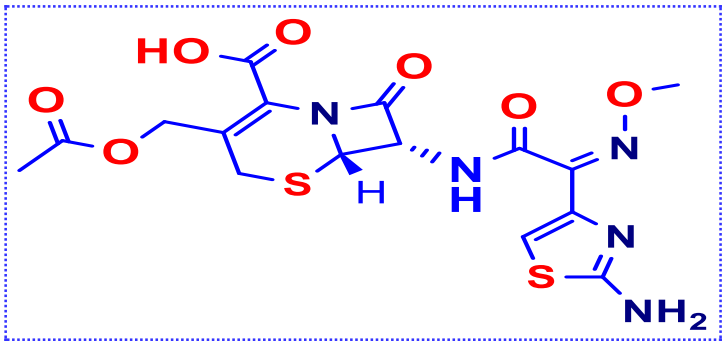


Figure (1-6). The Chemical structure of Cefotaxime

Clinical investigations have generally demonstrated that cefotaxime is equally effective. Reviews of twice-daily regimens have shown that cefotaxime can be used with a longer dosing interval in certain patients, even if it was previously taken at 6- or 8-hourly intervals. Similar to other cephalosporins given intravenously, cefotaxime is well tolerated [81].

1.11.4. Ceftriaxone

The most common side effects of ceftriaxone are rash, nausea, vomiting, diarrhea, and hematopoietic disruption [82]. Ceftriaxone has a favorable tolerance profile. These side effects are typical of beta lactam antibiotics, though. More dosages and/or prolonged administration (more than 2 g/day for more than 28 days) of ceftriaxone may result in biliary pseudolithiasis, though the incidence of pseudolithiasis is less than 0.1% [83].

The chemical structural formula of ceftriaxone in figure (1-7):

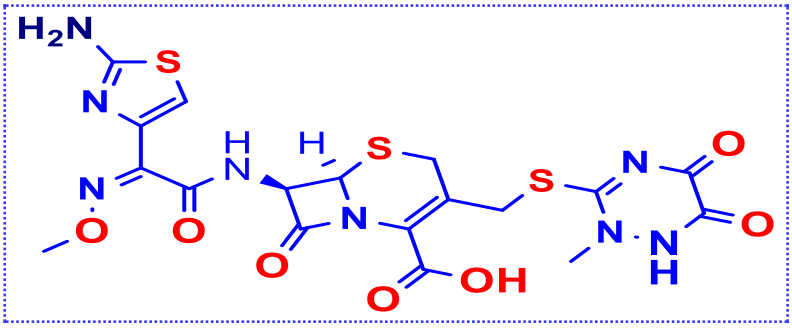


Figure (1-7). The chemical structure of Ceftriaxone

1.12. Cancer

Cancer is defined as uncontrolled cell growth. There are over 100 different types of malignancies, and each is classified by the type of cell that is initially affected. The cancer is one of the leading causes of death in the modem world, with more than 10 million new cases each year, and more than 5 million deaths annually [84]. Cancer can be diagnosed by a number of methods, including the presence of specified signs and symptoms, medical imagine or screening tests such as biopsy or molecular techniques. Cancer is usually treated with chemotherapy, radiation therapy and surgery [85]. Cancer is a multi-factorial disease which means that there are several risk factors that are associated with it including environmental and genetic (family history) factors. Common environmental factors that contribute to cancer death include tobacco (25-30%), diet and obesity (30- 35%), infections (15-20%), radiation (both ionizing and non-ionizing, up to 10%), stress, lack of physical activity, and environmental pollutants [86].

1.12.1.Origins of Cancer

The human body is composed of several sorts of cells, which is where all cancers start. Because the body needs more cells to remain healthy, these cells divide and expand in a controlled way to create new ones. Cells will eventually die and be replaced by new ones when they get old or damaged [87]. However, sometimes this orderly process goes wrong. The genetic material (DNA) of the cell can become damaged or changed, producing mutations that affect the growth and division of cells. When this happens, the cells grow in an uncontrolled manner resulting in the appearance of tumors which can be benign or metastasis. Benign tumors are not cancerous, but often can be removed, and in most cases they do not come back. Malignant tumors are cancerous. Cells in these tumors can invade nearby tissues and spread [88]. To other parts of the body, the spread of cancer from one part of the body to another is called metastases. Some types

of cancers do not form tumors. For example, leukemia is a cancer of the bone marrow and blood [89, 90].

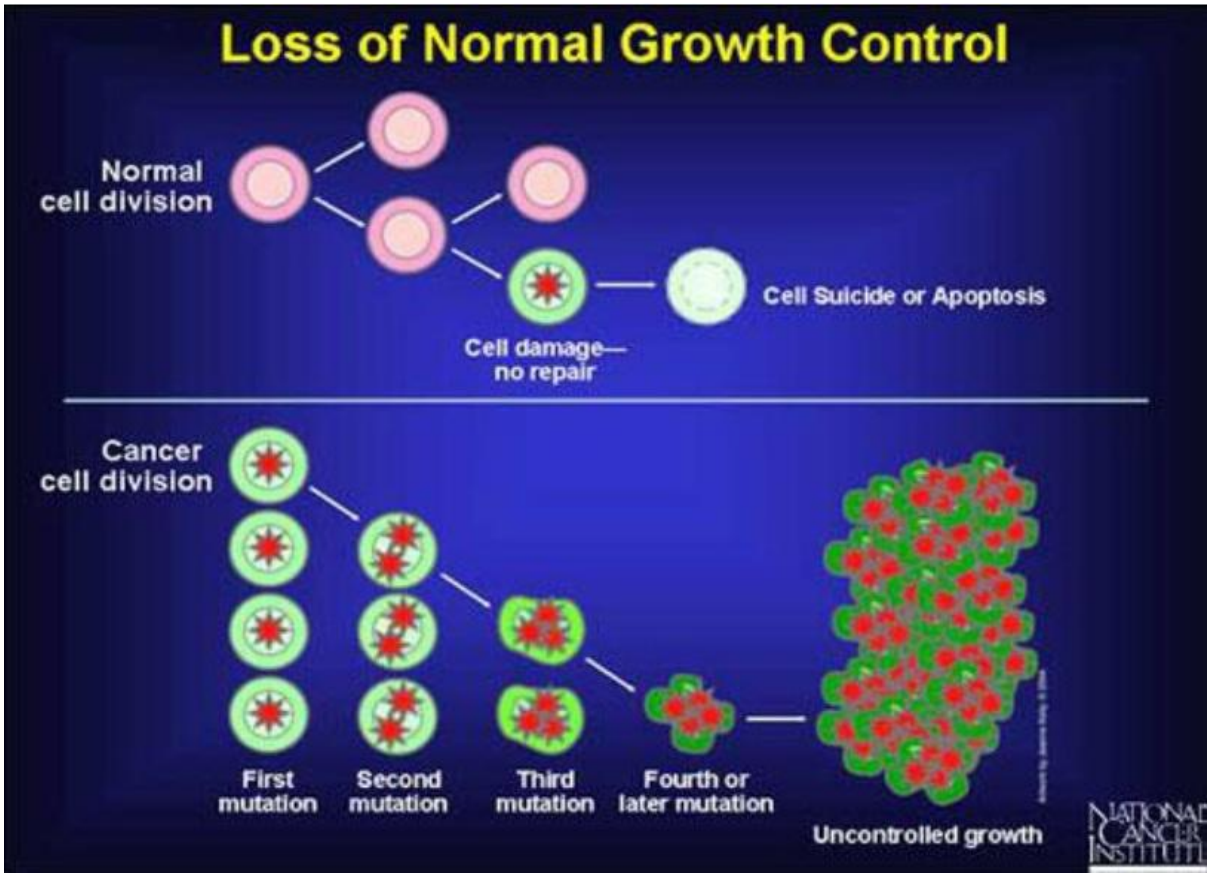


Figure (1-8): Comparison of abnormal cell division with normal healthy cells

1.13. Anticancer

Cancer treatment has evolved in recent years. Still the best option is surgery, which can survive some stages of the disease. In the advanced stage of the disease, adjuvant therapy appeared as a second option after surgery, which includes chemotherapy, radiotherapy, and immunotherapy [91].

Chemotherapy is an effective way to treat many types of cancer because it uses strong chemicals to kill rapidly growing malignant cells in the body. Chemotherapy drugs tend to be given by injection. Once the drug is given intravenously, the drug spreads directly throughout the body and thus allows access to the whole body. The air level in the system is likely to drop rapidly due to various reasons such as metabolism in the liver and excretion of glomeruli by

the kidneys. This is likely to reducing drugs the target site and thus reduce its medical effect. As chemotherapy leads to the risk of side effects, most notably loss of hair and appetite, problems in the heart, kidneys and nerves, in addition to damage to healthy cells [92, 93]. These problems appear as a result of the inaccuracy in directing the drug to kill cancer cells, a dilemma that can be solved by using what is called "Nano-medicine," which uses "nanotechnology" techniques to direct drug doses to cancer-affected cells only. The advantage that medical Nano- applications give therapies is that the drugs are delivered to the cancer cells to be treated very precisely without harming the surrounding healthy cells [94, 95].To direct the drug to cancer cells using nanotechnology accurately, the study concluded that this is achieved through 3 main rules, the first of which is that the dose of chemotherapy is placed in Nano carriers, which are nanomaterials that are used as a drug transport unit to direct it to cancer cells only. The second is that there are so-called "chemical ligands" on the surface of these vectors, and their function is to identify the third element in the process, which is the "receptors" that are present in a large amount on the surface of cancerous cells without healthy ones, and when the ligands and receptors unite together, the dose of the targeted drug is emptied into the cancer cells very precisely, without the drug reaching the healthy cells [96, 97].

1.14. Aim of the work

It is possible to create novel drug delivery methods that enhance therapeutic efficacy, safety, and customization. This could be the cause of the decrease in dosage, size, adverse effects, and biological disturbance. Benefits could also include reduced toxicity and increased specificity of action.

The aim of this work can be summarized as the following:

1. Synthesis and characterization of Nano Graft Co-polymer by FT-IR, ^{1}H-NMR, AFM, and XRD techniques.
2. Synthesis of Nano Graft Co-polymer- drug by circulating Nano Graft Co-polymer with different drugs (Amoxicillin, Aminoantipyrine, Cefotaxime, and Ceftriaxone) and characterization with FT-IR, ^{1}H-NMR, ^{13}C-NMR techniques
3. Studying of some properties of Nano Graft Co-polymer -drug such as: solubility and drug release
4. Studying of the most effective binding energy for Nano Graft Co-polymer - drugs
5. Studying the possibility of using Nano Graft Co-polymer- drugs known to be used to inhibit the rapid spread of liver cancer in HEp-2 cells line and its treatment.

CHAPTER TWO

EXPERIMENTAL PART

2. EXPERIMENTAL PART

2.1. Chemical and Techniques

2.1.1. Chemicals

Table (2-1) Show all chemical materials which are used in this work.

Table (2-1): The solid and liquid chemical materials

Materials	**Company**	**Purities**
Phthalic anhydride	ALPHA	99%
Glycerol	BDH	99.5%
Ethanol absolute	BDH	99.9%
Acetone	BDH	99.8%
Hexane	BDH	99.7%
Dimethyl sulphxide	BDH	98.9%
Dichloro methan	BDH	98%
Thionylchloride	Fluka	99.9 %
Trimethylamine	Fluka	99.5 %
Borax	BDH	99 %
KCl	BDH	99 %
Amoxicillin	SDI Company / Samarra / Iraq	99.9 %
Ampicillin	SDI Company / Samarra / Iraq	99.9 %
Cefotaxime	SDI Company / Samarra / Iraq	99.9 %
Ceftriaxone	SDI Company / Samarra / Iraq	99.9 %

2.1.2. Techniques

1. Fourier Transformer Infrared Spectroscopy (FT-IR) spectra in range 400-4000 cm^{-1} on IR Affinity-1S instrument (Shimadzu, Jaban), Department of Chemistry/College of Education for Pure Sciences / University of Kerbala, Iraq.
2. ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker AC 400 NMR spectrometer, operating at 300 MHz for H-NMR. All chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) as reference (δ=0.0 ppm); Berta laboratory for laboratory investigations, Iran.
3. UV-Spectrophotometer, UV-1800, PC–Shimadzu / College of Education for pure Sciences, University of Kerbala, Iraq
4. Atomic Force Microscope (AFM), Oxford, USA / Berta laboratory for laboratory investigations, Iran.
5. X-Ray Diffraction (XRD), Rigaku Ultima iv, Japan, Berta laboratory for laboratory investigations, Iran.

2.2. Synthesis of Nano Graft Co- polymer (S1) [98]

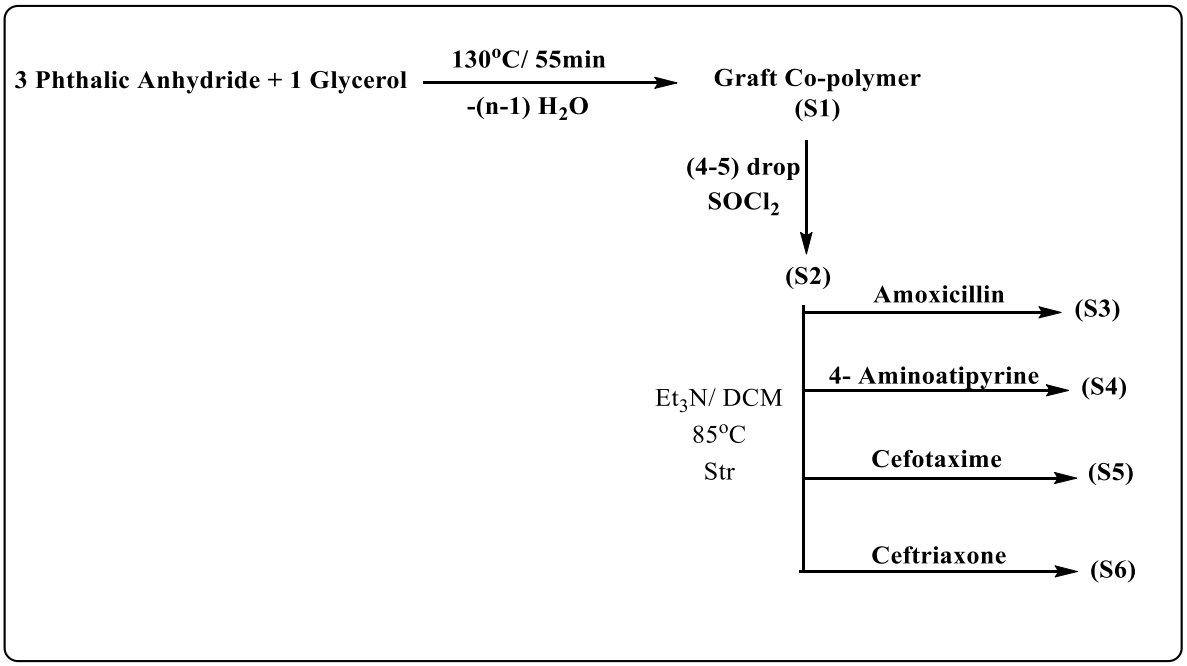
3 moles of Phthalic anhydride (0.186 mol) and DMSO (7.5 mL) were combined in a 125 mL beaker along with a thermometer. The mixture and then carefully heated to 120°C, while being continuously swirled using a magnetic stirrer. To the mixture, glycerol (0.062 mol) was added. The reaction flask is then filled with batches of about 12 mL of xylene to eliminate the water that is left over (a by-product of the esterification process). The heater turns off after fifteen minutes. A solution is obtained, which is precipitated using cold deionized water 3°C. After filtering and rinsing with additional deionized water, the precipitate is left to dry at room temperature. The precipitate is then broken down to create the nano co-polymer. Nano graft co-polymer which synthesis characterization using FT-IR, ^{1}HNMR, AFM, and XRD techniques.

2.3. Synthesis of Acid Chloride for Nano Graft Co-Polymer (S2) [98]

After mixing (0.6 g) of S1 with (4-5) drops of thionyl chloride ($SOCl_2$) and (6.0 mL) of DCM in a 25 mL beaker with a magnetic stirrer, the mixture was allowed to settle for 30 min at room temperature before being kept at 65 °C for 2 hrs. The nano graft co-polymer-acid chloride (S2) is prepared by drying out the solution for 2 hrs and raising the temperature to 85°C.

2.4. General Synthesis of Nano Graft Co-polymer- Drugs (S3-S6) [99]

Weighed 1.5 g the drugs: Amoxicillin (S3-S6) respectively, and 0.5 a mL of triethyl amine. To the previously prepared pharmaceutical ampoule, which contains 0.6 g of the compound (S2), add 8 mL of DCM and cool using ice while stirring. The contents of the ampoule are poured into a 50 mL beaker filled with distilled water ice grits and stirred with a glass stirrer until the ice melts and the sediment is filtered out. Ethylamine is then left stirring in ice for an 1 hrs at room temperature for three hours. The following scheme (1). Illustration the step of reaction:



Scheme 1. General reaction of Nano Graft Co-polymer with Drugs

2.5. Physical properties of the synthesis Nano Graft Co-polymers

2.5.1. Characteristic of Solubility [100]

The solubility of the produced composite pharmaceuticals was determined by taking very little amounts (0.01g) from the synthesized composites (S1-S6) and placing them in small test tubes with a variety of solvents (H_2O, Ethanol, Methanol, DMSO, Hexane, and Acetone).

2.5.2. Release of Drug

The drug release from the generated nano co-polymers was measured using a UV-Vis spectrophotometer in four distinct buffer solutions (2.2, 6.0, 7.0, and 8.0) at a constant temperature of 37 C. Each prepared nano Graft Co-polymer drug was submerged (0.02 g) in a 50 ml beaker. For days and even hours, the drug release was seen [101].

2.5.3. Preparation of Buffer Solutions [102, 103]

Buffer solutions were prepared using the following methods:

1. **pH=2.2**: To prepare this solution, (500mL) of (0.2M) KCl and (8.6mL) of (2M) HCl were mixed.
2. **pH=6.0**: To prepare this solution, (500mL) of (0.2M) KCl and (8.6mL) of (2M) HCl were mixed.
3. **pH=7.2**: To prepare this solution, (500mL) of (0.025M) borax [$Na_2B_4O_7.10H_2O$] and (0.43mL) of (0.1M) HCl were mixed.
4. **pH=8.0**: To prepare this solution, (500mL) of (0.025M) borax [$Na_2B_4O_7.10H_2O$] and (0.5mL) of (0.1M) HCl were mixed.

2.6. Biological Activity (Anti-Cancer Measurements)

2.6.1. Material

The materials, chemical processes, and reagents utilized are shown in Table (2-2), and the instruments utilized in biological activity are shown in Table (2-3).

Table (2-2): Materials, chemical methods and reagents

No.	Items	Company	Country
1	Trypsin/EDTA	Capricorn	Germany
2	DMSO	Santacruz Biotechnology	USA
3	RPMI 1640	Capricorn	Germany
4	MTT stain	Bio-World	USA
5	Fetal bovine serum	Capricorn	Germany

Table (2-3): Instruments used in biological activity

No.	Item	Company	Country
1	CO_2 incubator	Cypress Diagnostics	Belgium
2	Microtiter reader	Gennex Lab	USA
3	Laminar flow hood	K & K Scientific Supplier	Korea
4	Micropipette	Cypress Diagnostics	Belgium
5	Cell culture plates	Santa Cruz Biotechnology	USA

2.6.2. Molecular Docking

According to earlier studies, the proteins found in the cancer cell (1TUP) were selected from the Protein Data Bank (PDB) list. The medicine and protein were joined by the PyRx program, which also shows the strength of the link. By identifying the binding sites, the program (BIOVIA) has made it clearer how the drug binds to the essential amino acids that make up a protein chain. It details the strength and duration of the medication's bindings in addition to offering two-dimensional pictures [104].

2.6.3. Cells Culture

HEp-2 Cell line were maintained in RPMI-1640 supplemented with 10% Fetal bovine, 100 units/mL penicillin, and 100 µg/mL streptomycin. Cells were passaged using Trypsin-EDTA reseeded at 80% confluence twice a week, and incubated at 37°C [105, 106].

2.6.4. Cytotoxicity Assays [107]

Using 96-well plates, the MTT cell viability assay was performed to assess the cytotoxic effect of (S3-S6) and the impact of nano co-polymer drug manufacturing on the spread of liver cancer. 1×10^4 cells/well were used to seed the HEp-2 cell lines. Once a confluent monolayer had been formed, or after 24 hours, the cells were exposed to the experimental chemicals. Following a 72-hour treatment period, the media was removed, 28 µL of a 2 mg/mL MTT solution was added, and the cells were incubated for 2.5 hours at 37°C to determine the viability of the cells. Following the removal of the MTT solution, 130 µL of DMSO (dimethyl sulphoxide) was added to the wells to solubilize the residual crystals. The mixture was then incubated for 15 minutes at 37°C while being shaken. The assay was run in triplicate, and the absorbency was measured using a microplate reader at the test wavelength of 492 nm. The following formula was used to determine the percentage of cytotoxicity, or the inhibition rate of cell growth:

$$\textbf{Cytotoxicity} = \textbf{A-B/A} \times \textbf{100}$$

Where A and B are the optical density of control and the optical density of test.

To visualize the shape of the cells under an inverted microscope, the cell were seeded into 24-well micro-titration plates at a density of 1×10^5 cells mL^{-1} and incubated for 24 h at 37 °C. Then, cells were exposed to Cefotaxime with Nano Co-polymer drug for 24hr. After the exposure time, the plates were stained with crystal violet stain and incubated at 37 °C for 10–15 min. The stain was washed

off gently with tap water until the dye was completely removed. The cells were observed under an inverted microscope at 100× magnification and the images were captured with a digital camera attached to the microscope [108].

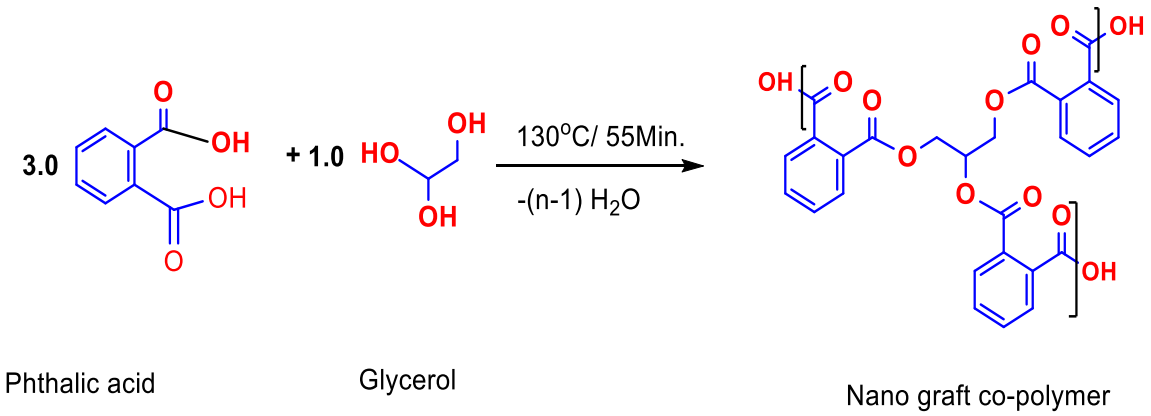
2.6.5. *Statistical analysis:*

The obtained data were statically analyzed using an unpaired t-test with GraphPad Prism 6. The values were presented as the mean ± SD of triplicate measurements[109].

Chapter Three Results and Discussions

3.1. Synthesis of a Nano Graft Co-Polymer (S1)

Nano graft co-polymer (S1) was produced by condensation polymerization. After a reaction between 3.0 moles of phthalic anhydride and (1.0 mol) of glycerol at 130°C, polymerization takes place 55 minutes later. **Equation (3-1)** explains how the process polymerizes and releases water as a byproduct as a result. Then, this nano graft co-polymer was characterized and described using FT-IR, ^{1}H-NMR, AFM, and XRD.



Equation (3-1) Synthesis of nano graft co-polymer (S1)

Figure (3-1) displays the FT-IR spectra of composite (S1). It exhibits multiple absorption bands, including a broad band at (3074 cm^{-1}) that corresponds to the (OH) group of the alcohol and the hydrogen bond, and a band at (3005 cm^{-1}) that results from the vibration of the aromatic bond (C-H). In the FT-IR spectrum, the ester bond (C=O) is represented by an absorption band at (1730 cm^{-1}), whereas the band at (1069 cm^{-1}) is connected to (C-O). ester. Two substitutions of the aromatic ring at (734 and 897 cm^{-1}) led to the development of two bands.

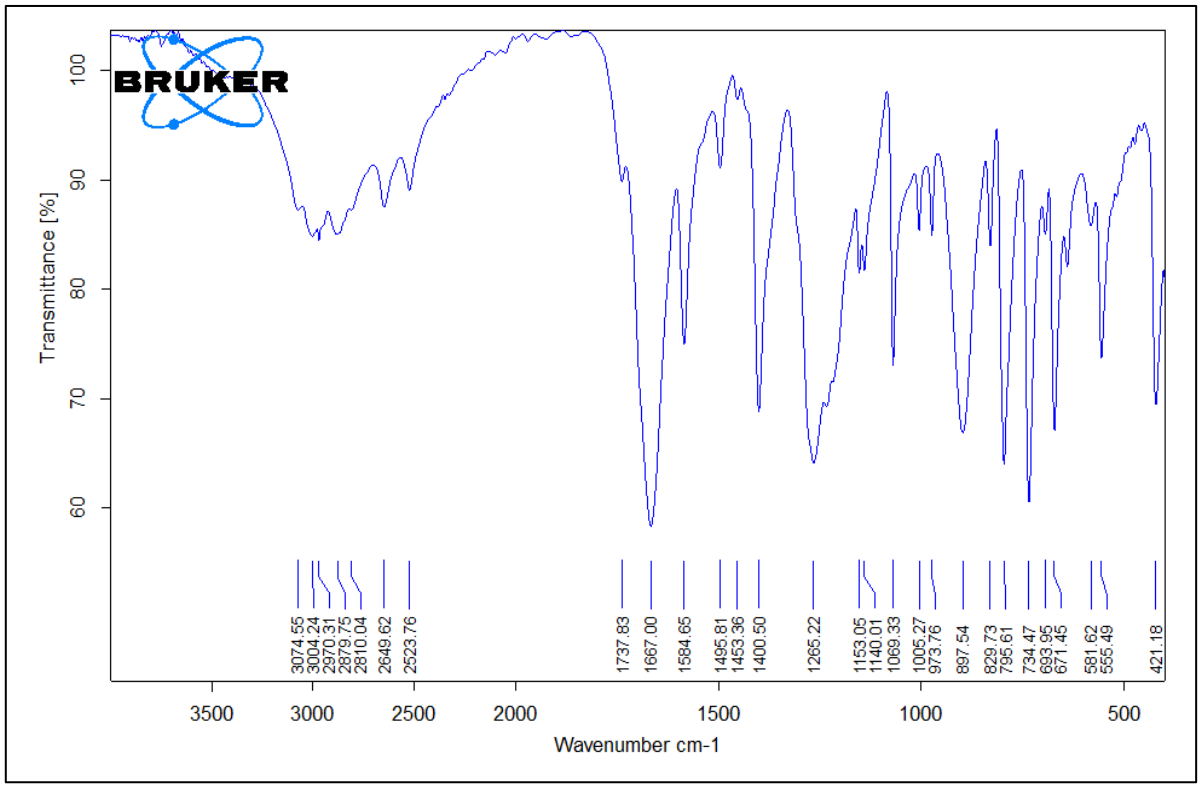


Figure (3-1) FT-IR spectra of the nano graft co-polymer (S1)

The abnormal proton in the singlet signal for the carboxylic acid group at 13.04 ppm is explained by the ^{1}H-NMR spectra displayed in **Figure (3-2)**. A multiple of methyl protons at 4.15 ppm, the absence of an aliphatic alcohol signal, signals for four methylene protons in the co-polymer structure at 4.26–4.28 ppm, and a multiple in the region 7.55–7.68 ppm attributed to all protons in the aromatic ring are indicators that a nano graft co-polymer is forming.

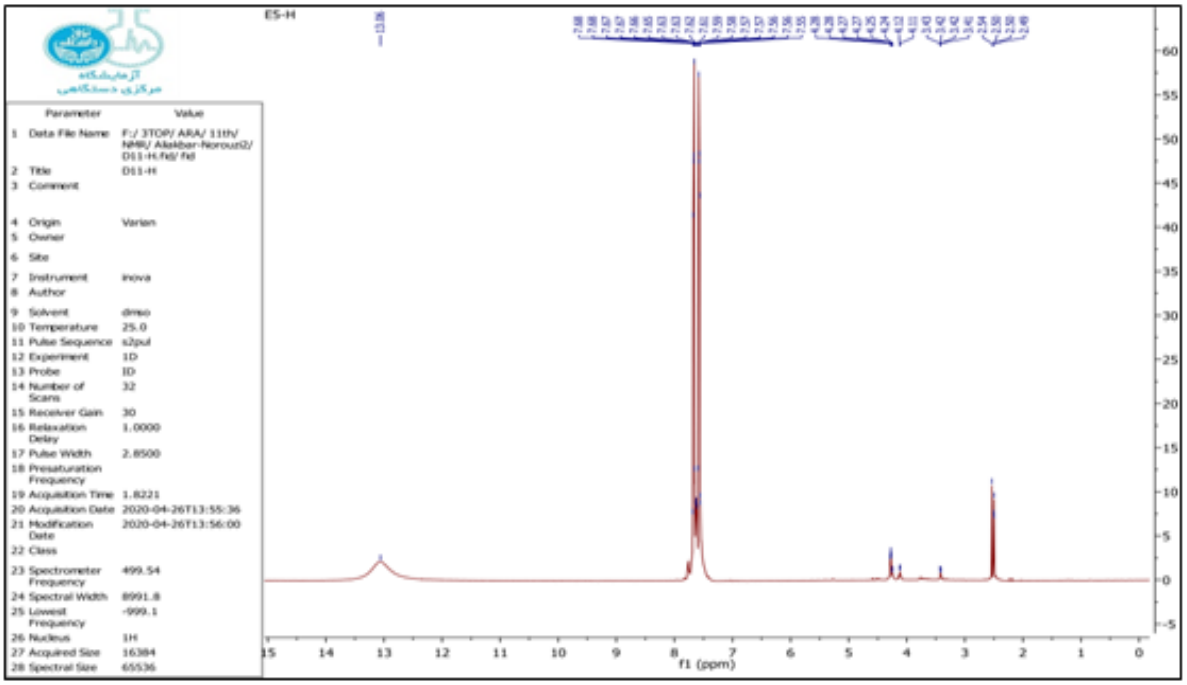


Figure (3-2) ^{1}H-NMR spectra of the nano graft co-polymer (S1)

Graft co-polymer nanoparticles (S1) exterior may be seen in **Figure (3-3, a-b)** of the AFM. The roughness coefficient of the co-polymer surface was 5.08 nm, and its square root square was 5.94 nm. This implies a strong correlation between the homogenous crystalline structure, surface roughness, and homogeneity and the big size of the nanoparticles. Moreover, the average particle height was equal to 22.04 nm, as **Figure (3-3, a)** illustrates. The results show that the molecular size of the graft co-polymer (S1) nanoparticle was 68.62 nm. The ratios of the various volumes and the overall rate of the most prevalent nanoparticle particle sizes are shown in **Table (3-1).**

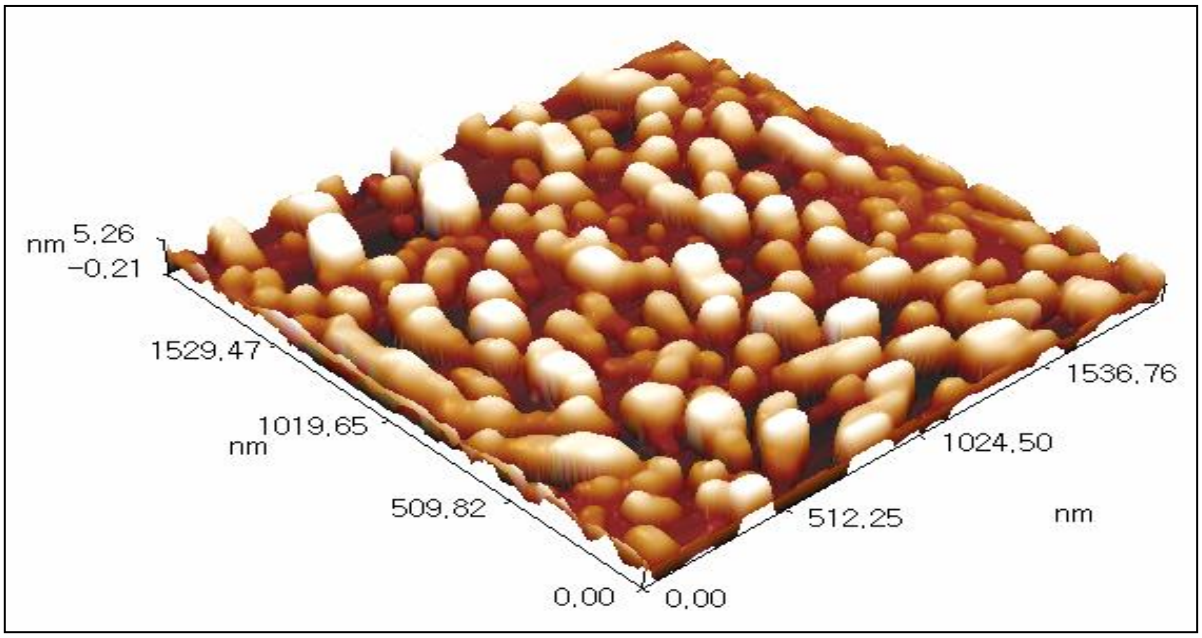
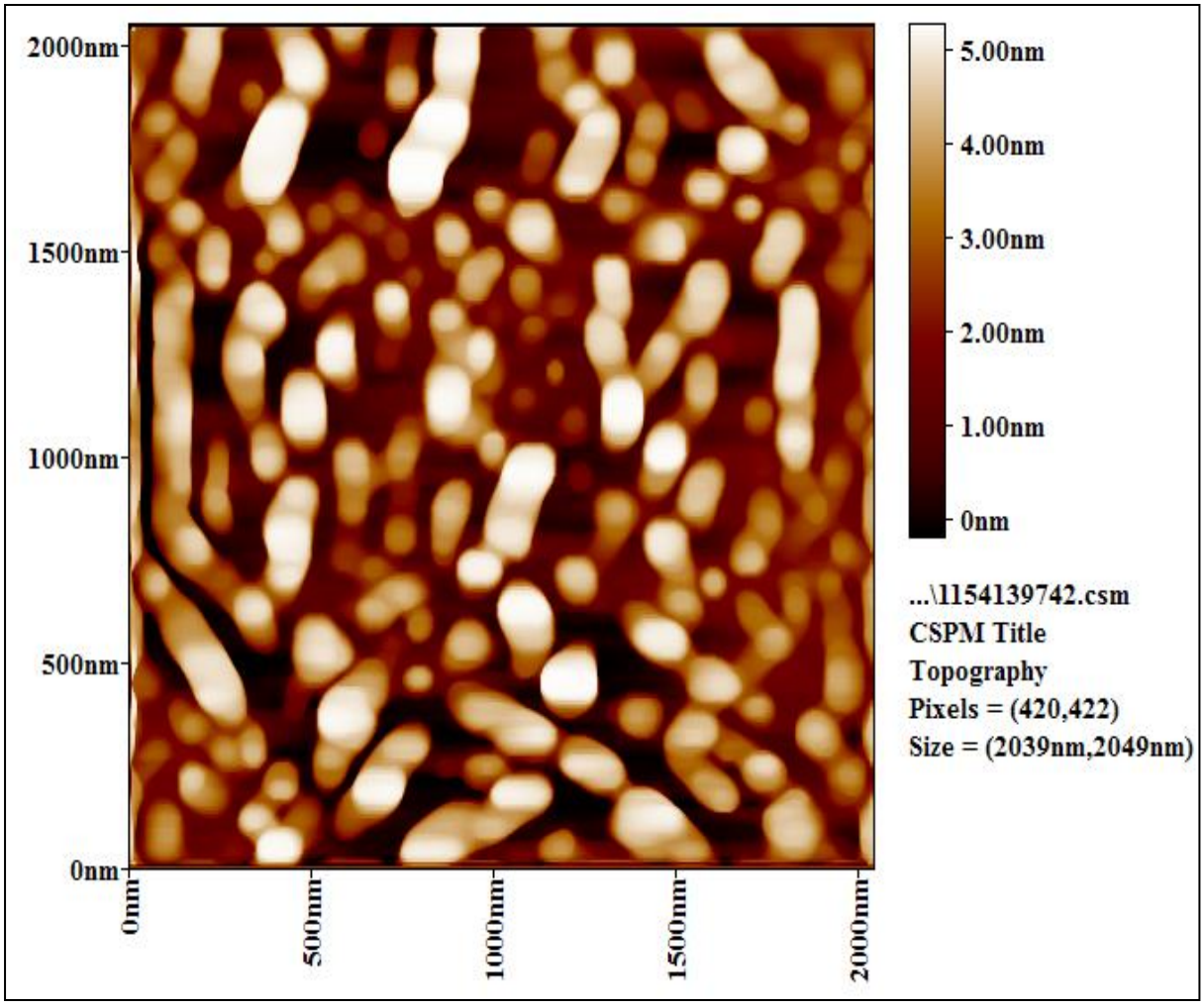


Figure (3-3, a) 3D image is displayed by the AFM of nano graft co-polymer



(3-3, b) Two-dimensional image is displayed by the AFM image for nano graft co-polymer.

Table (3-1) Displays the overall rate of the nano co-polymer nanoparticle particle sizes together with the relative proportions of the various volumes.

.

Sample: 1	**Code:** Sample Code
Line No.:lineno	**Grain No.:**264
Instrument: CSPM	**Date:** 2023-09-24
Avg. Diameter: 68.62 nm	**<=10% Diameter: 50.00 nm**
<=50% Diameter: 65.00 nm	**<=90% Diameter: 80.00 nm**

Diameter (nm)<	Volume (%)	Cumulation (%)	Diameter (nm)<	Volume (%)	Cumulation (%)	Diameter (nm)<	Volume (%)	Cumulation (%)
45.00	1.52	1.52	65.00	17.80	40.91	85.00	11.74	90.91
50.00	4.17	5.68	70.00	12.12	53.03	90.00	9.09	100.00
55.00	9.09	14.77	75.00	13.64	66.67			
60.00	8.33	23.11	80.00	12.50	79.17			

Nano graft co-polymer's x-ray diffraction (XRD) patterns revealed a diffuse halo at 2q = 20, which is connected to the intra-chain segment distance. Every polymer sample exhibits more unique peaks in its diffractogram. In contrast to polymers that are only aliphatic, the XRD pattern shows that stiff aromatic rings formed from phthalic acid lead to more rigid structures, which should result in a higher potential for crystallization. The polymer synthesis was carried out with a phthalic acid to glycerol molar ratio that produced a higher concentration of carbonyl groups. Increased phthalic acid concentrations also implied that molecular motions brought on by the stiffness of aromatic rings might aid in the ordering of polymer chains in crystalline lattices. **Figure (3-4)** illustrates how to use Origin software to obtain x-ray diffraction (XRD) for the co-polymer of nanoparticles. The aforementioned AFM measurements are consistent with the average inters planer distance (d_{hkl}) of 0.416 nm between atoms, as determined by Bragg's Law.

$$n\lambda = 2d\sin\theta \ldots\ldots\ldots \text{Bragg's Law}$$

Scherrer's equation indicates that each crystallite's average size was 68.487 nm.

$$D = \frac{k\lambda}{\beta\cos\theta} q \quad \text{…….. Scherrer's Equation}$$

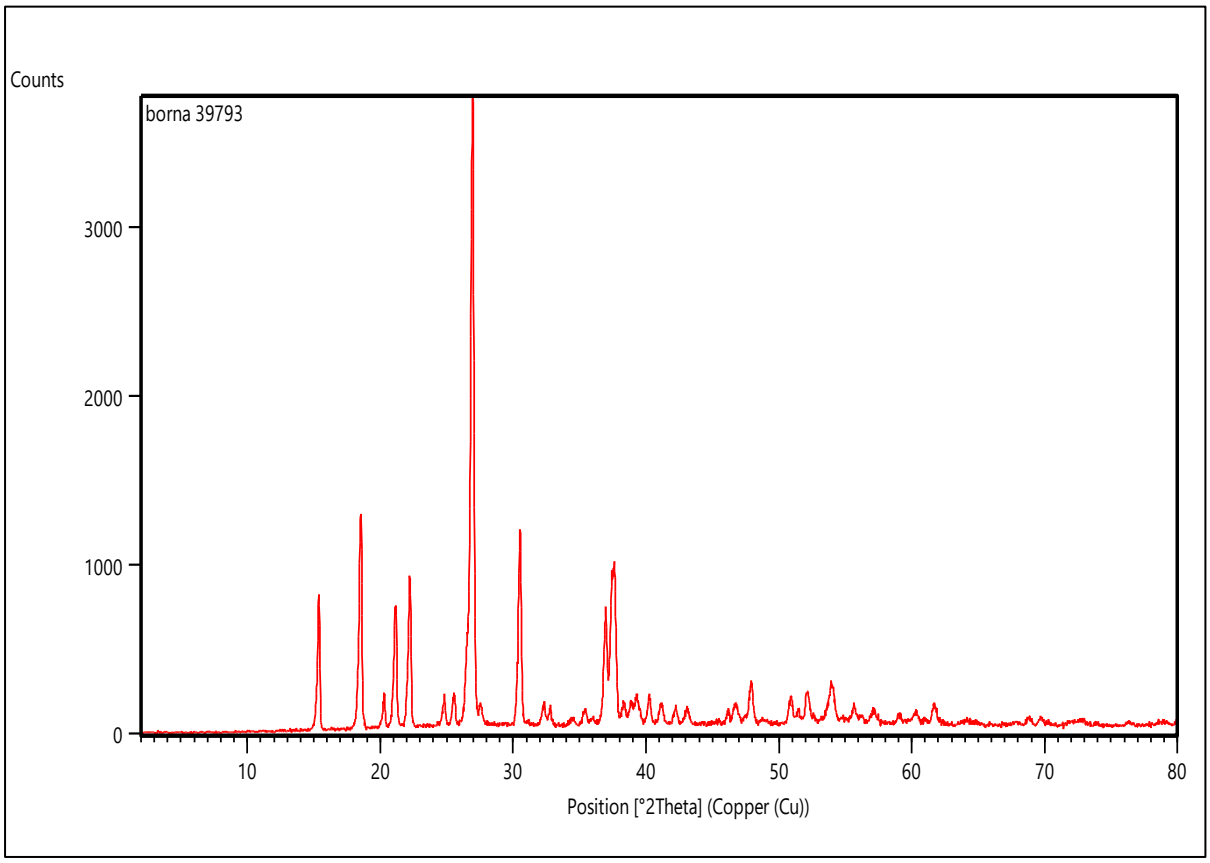


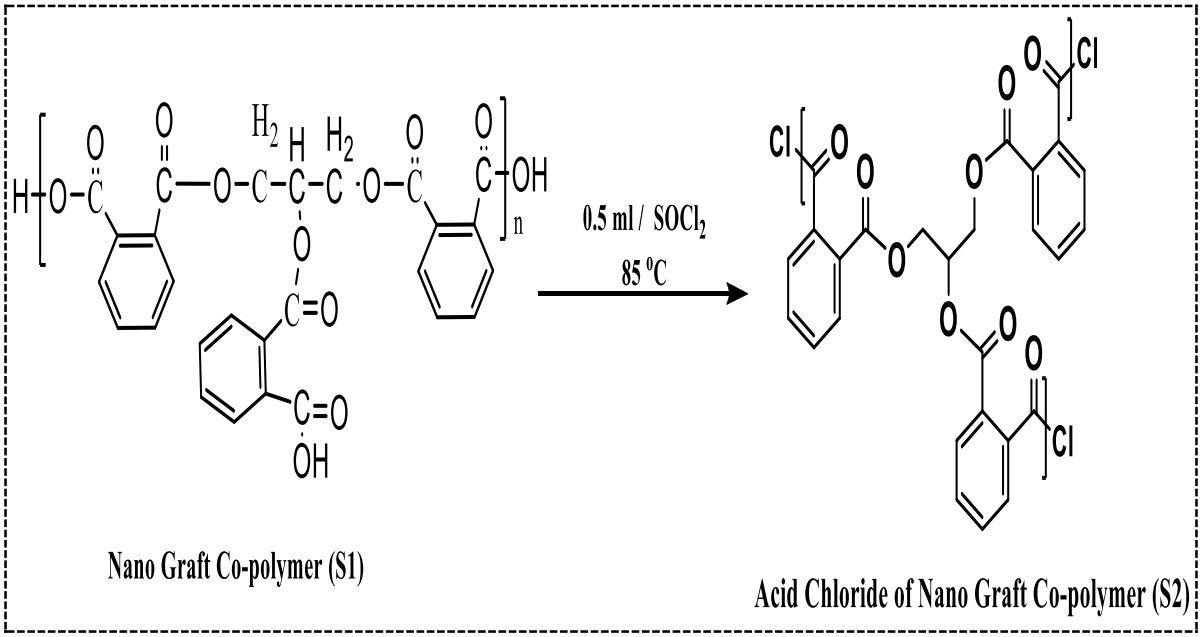
Figure (3-4) X-ray diffraction of nano graft co-polymer

Table (3-2) Lists the proportions between the crystallite diameters and the nano graft co-polymer's "d-spacing or atom-to-atom spacing

2 θ	**Θ**	**FWHM**	**D Nm**	**d hkl nm**	**D (Av.) Nm**	**d hkl (Av.) nm**
15.41888	7.70944	0.10308071	77.77159	0.57421	**68.4874**	**0.4152**
18.56158	9.28079	0.12176233	66.10961	0.477637		
21.20363	10.60181	0.11615246	69.58317	0.418681		
22.26382	11.13191	0.11743049	68.94823	0.398978		
26.9992	13.4996	0.13275784	61.54072	0.32998		
30.55913	15.27956	0.12296861	66.97155	0.292302		

3.2. Synthesis Acid Chloride of Nano Graft Co-polymer (S2)

Acid chloride of Nano graft Co-polymer was synthesized by adding $SOCl_2$ to mix reaction at 85°C according to **Equation (3-2)**. and characterized of result compound by FT-IR technique.



Equation (3-2) Acid Chloride for Nano Graft Co-polymer Synthesized

FT-IR spectra of compound (S2) in **Figure (3-5),** Appeared many main band absorption, at (3093.82 cm^{-1}) appeared of (C-H) aromatic, while (C-H) aliphatic appeared at (2904.80 cm^{-1}), and appeared band absorption at (1849.73 cm^{-1}) resulting vibration of (C=O) for acid Chloride, while (C=O) of ester appeared at (1759.08 cm^{-1}), and appeared absorption band of (C=C) at (1517.98 cm^{-1}), and absorption band of (C-O) appeared at (1478.66 cm^{-1}), while (C-Cl) appeared at (887.26 cm^{-1}).

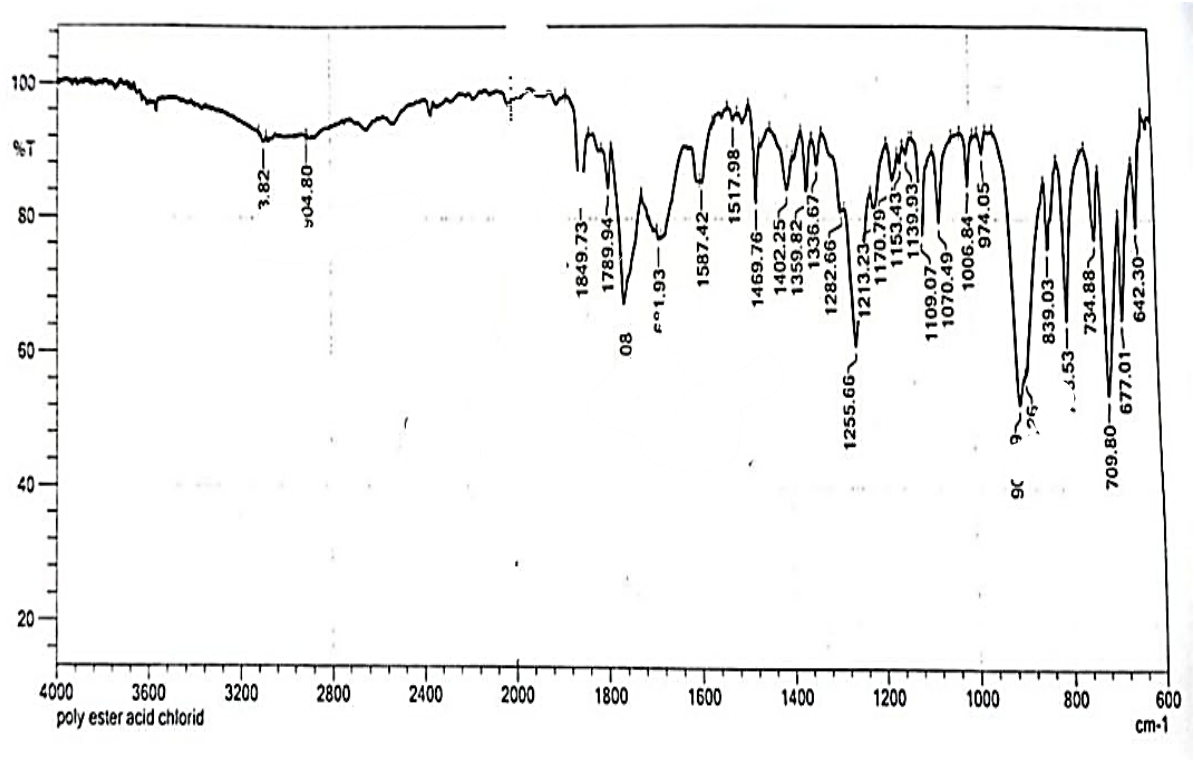
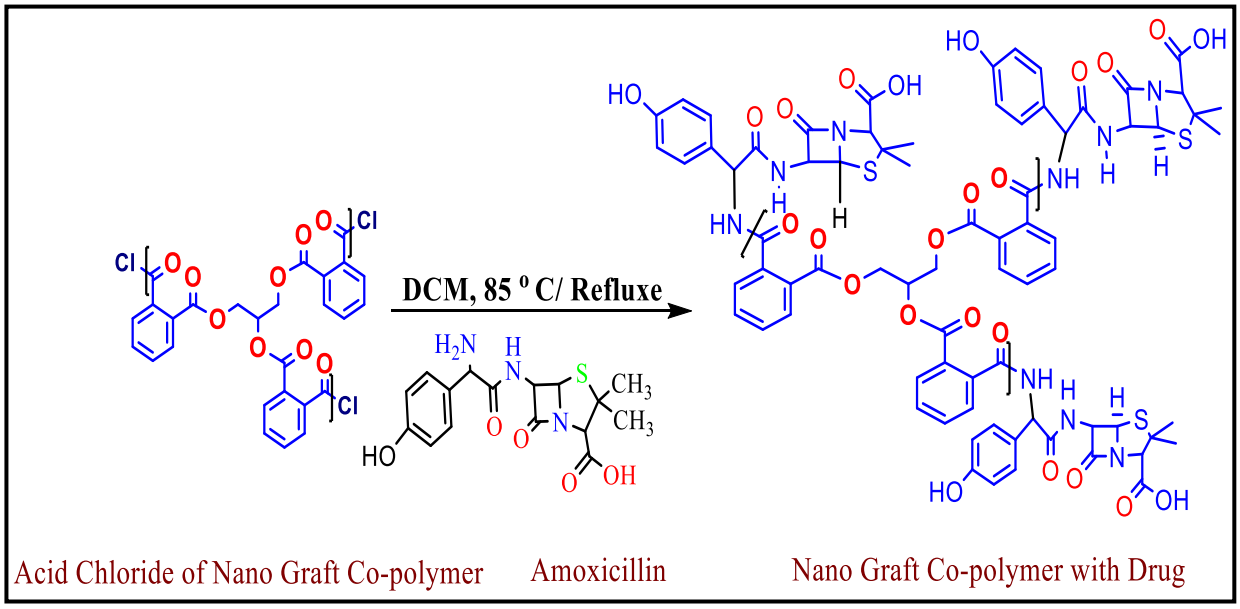


Figure (3-5) FT-IR spectra of acid chloride of nano graft co-polymer (S2)

3.3. Synthesis of Composite Nano Graft Co-Polymer-Amoxicillin Drug (S3)

About (0.6 g) of compound (S2), that reacted with (3.5 g, 0.009 mol) Amoxicillin drug and was combined to collect was added to a mixture of 0.5 mL trihydrate and 8 ml DCM at 85°C. **Equation (3-3)** represents the reaction.

FT-IR spectrum of compound (S3) is displayed in **Figure (3-6)**, where an absorption band appears at (3404.36 cm^{-1}) and is attributed to the bond (O-H) carboxyl group, (-C=O-OH) carboxyl, and absorption bands of C-H_{aliph} at (2985.81 cm^{-1}), C=O β-lactam at (1784.15 cm^{-1}), C=O-N amide at (1666.5 cm^{-1}), and absorption bands of C=C at (1565.55 cm^{-1}), C-O at (1269.16) cm^{-1}, and C-N at (1215.72 cm^{-1}), respectively.



Equation (3-3) Synthesis of the Composite (S3)**.**

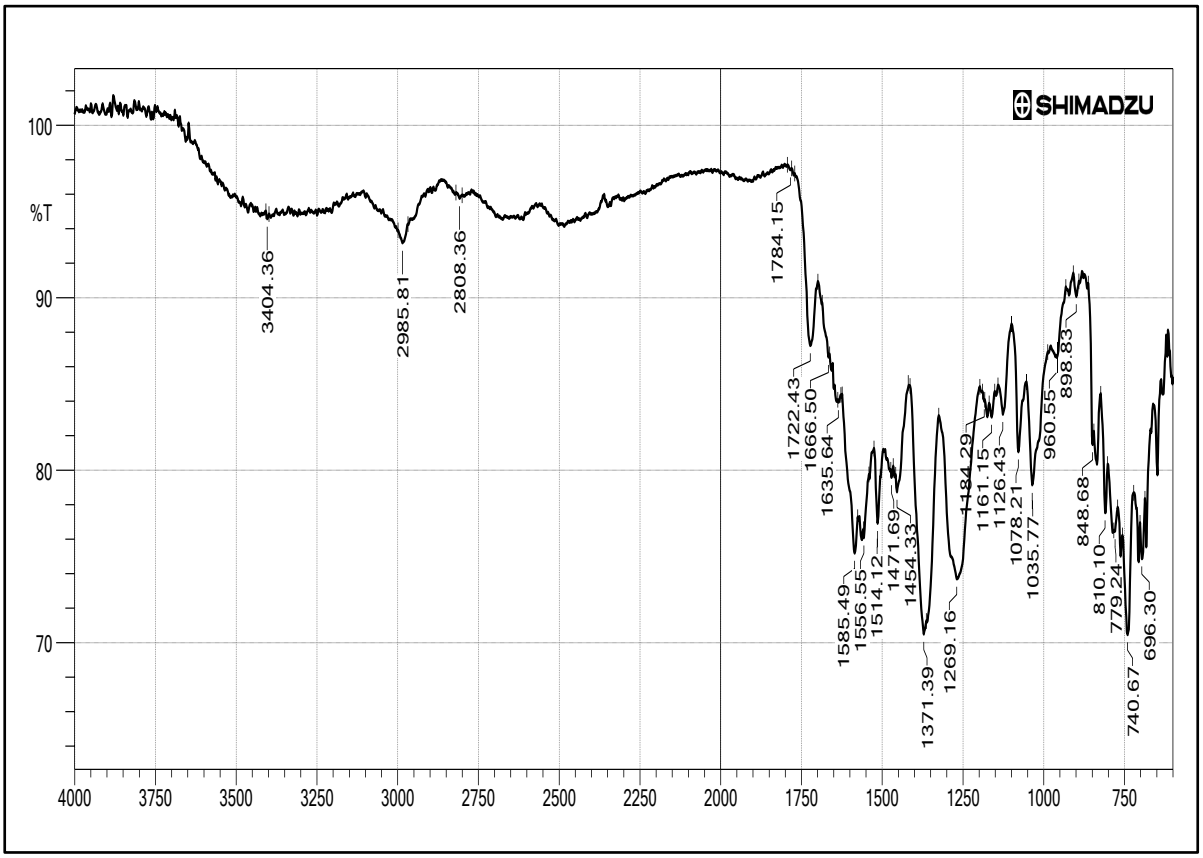


Figure (3-6) FT-IR spectra of (S3) Composite

Figure (3-7) shows the ^{1}H-NMR spectrum of compound (S3), where appearance signal of the hydroxyl that attached to the benzene ring of drug at 7.35 ppm and appearance and appear signal of the H of drug secondary amine at 7.25 ppm and appearance signal at 5.77 ppm for aromatic hydrogen, and appear signal for 1H for C-H at 3.72 ppm and appearance signal for Hydrogen of CH near S-bond at 2.98 ppm.

^{13}C-NMR spectrum of compound (S3), **Figure (3-8)** shows the presence of a signal of carbonyl amide at 133.8 ppm and a signal of 133.18 ppm for carbonyl of secondary amide, and a signal appeared at 129.11-127.29 ppm for carbons of drug aromatic ring and a signal appeared at 40.31 ppm for carbon near carbonyl amide, a signal appeared at 40.10 ppm for carbon near S-bond.

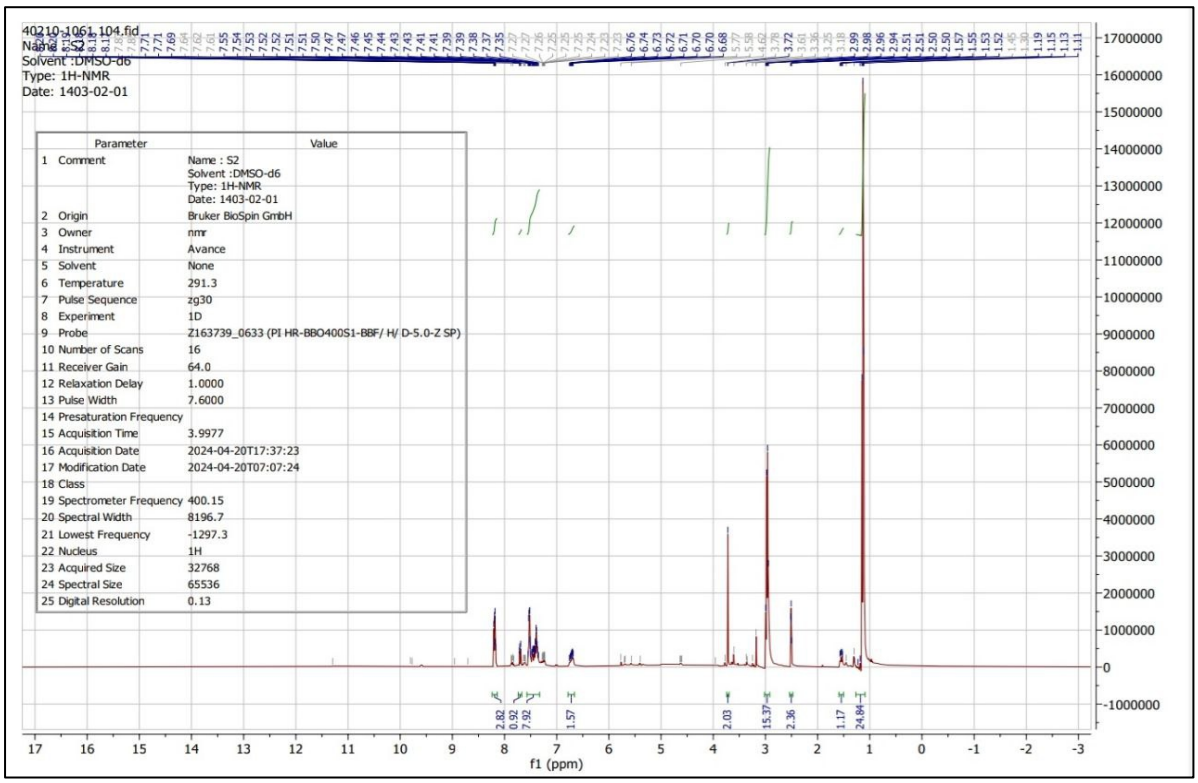


Figure (3-7) ^{1}H-NMR spectra Composite (S3)

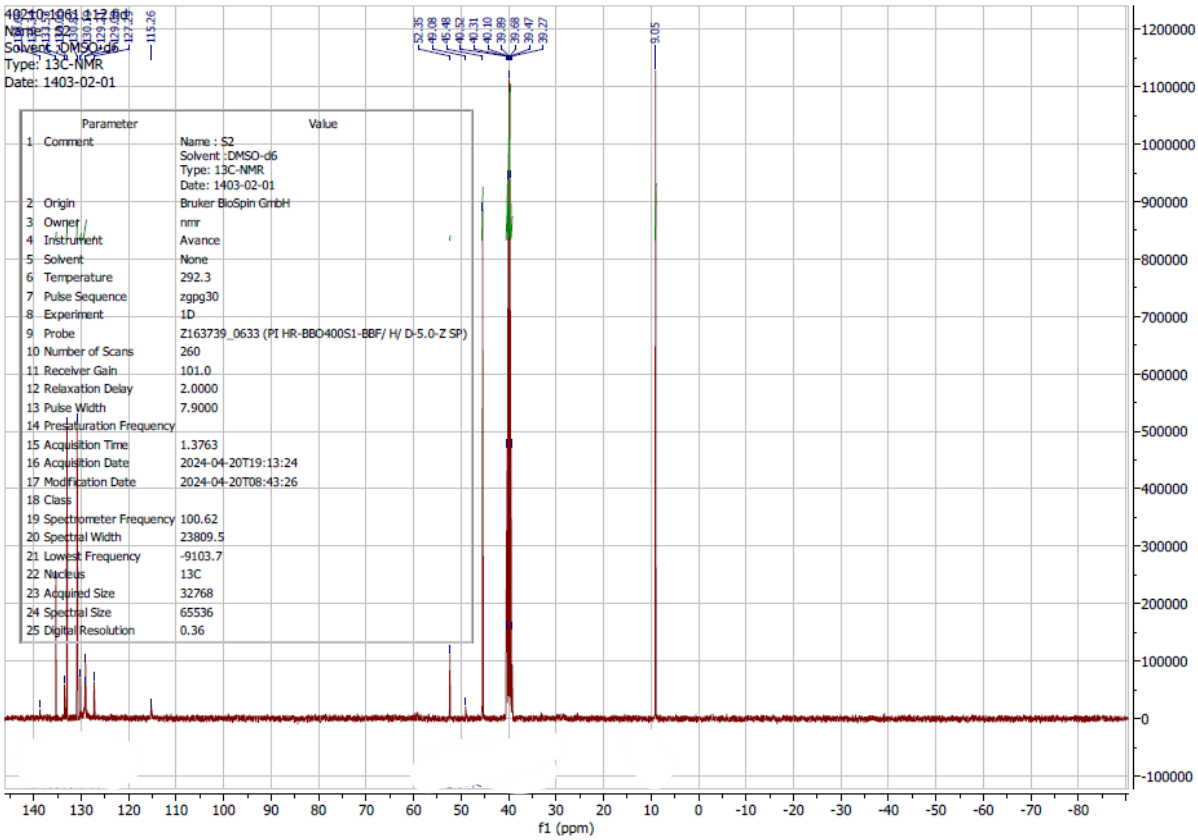
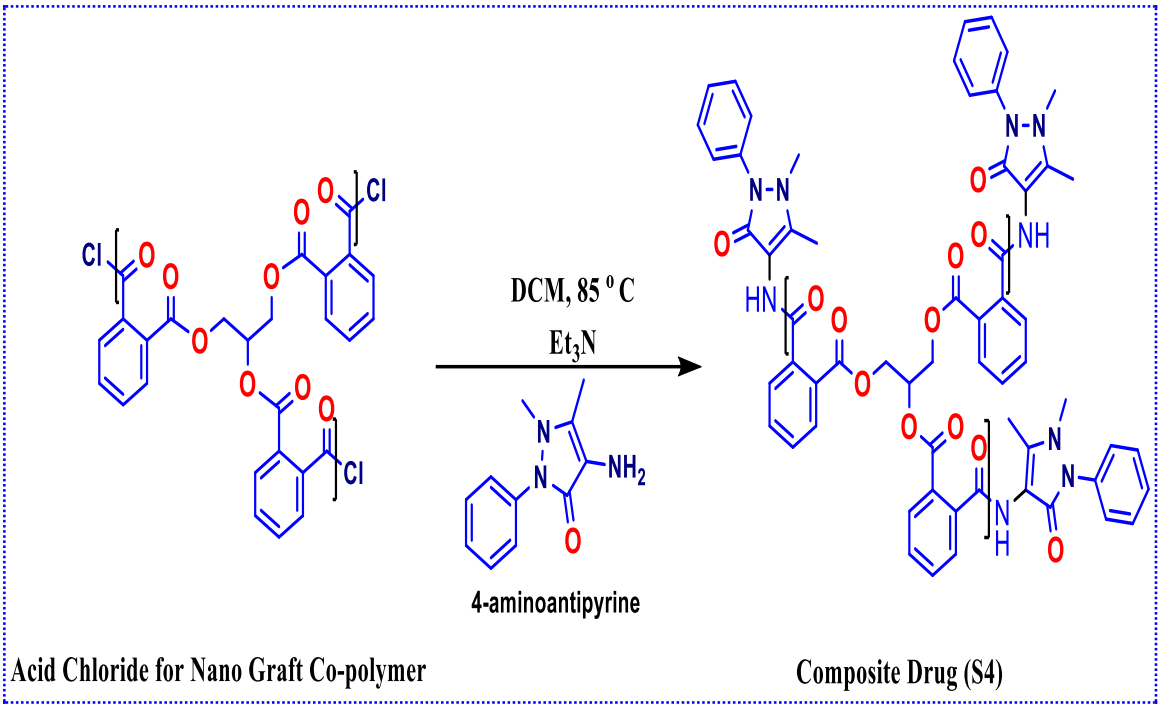


Figure (3-8) ^{13}C-NMR spectra Composite (S3)

3.4. Synthesis of Nano Graft Co-Polymer 4-Aminoantipyrine Drug (S4)

Add around 0.6 g of substance (S2) to a mixture of 0.5 a ml from ethyltriamine and 8 mL DCM at 85°C. This chemical interacted with (2 g, 0.009) mol of (4-aminoantipyrine) drug and was combined to collect. The reaction is represented by **Equation (3-4)**.

FT-IR spectrum of compound (S4), as shown in **Figure (3-9)**, exhibits the appearance of absorption bands for N-H_{amide} at (3342.64 cm^{-1}), C-$H_{aromatic}$ at (3066.82 cm^{-1}), C-$H_{aliphatic}$ at (2980.02-2887.44 cm^{-1}), and C=O amid at (1678.07 cm^{-1}), C=C ph. at (1556.55) cm^{-1}, and C-O at (1170.79 cm^{-1}) respectively.



Equation (3-4) Synthesis of the Composite (S4).

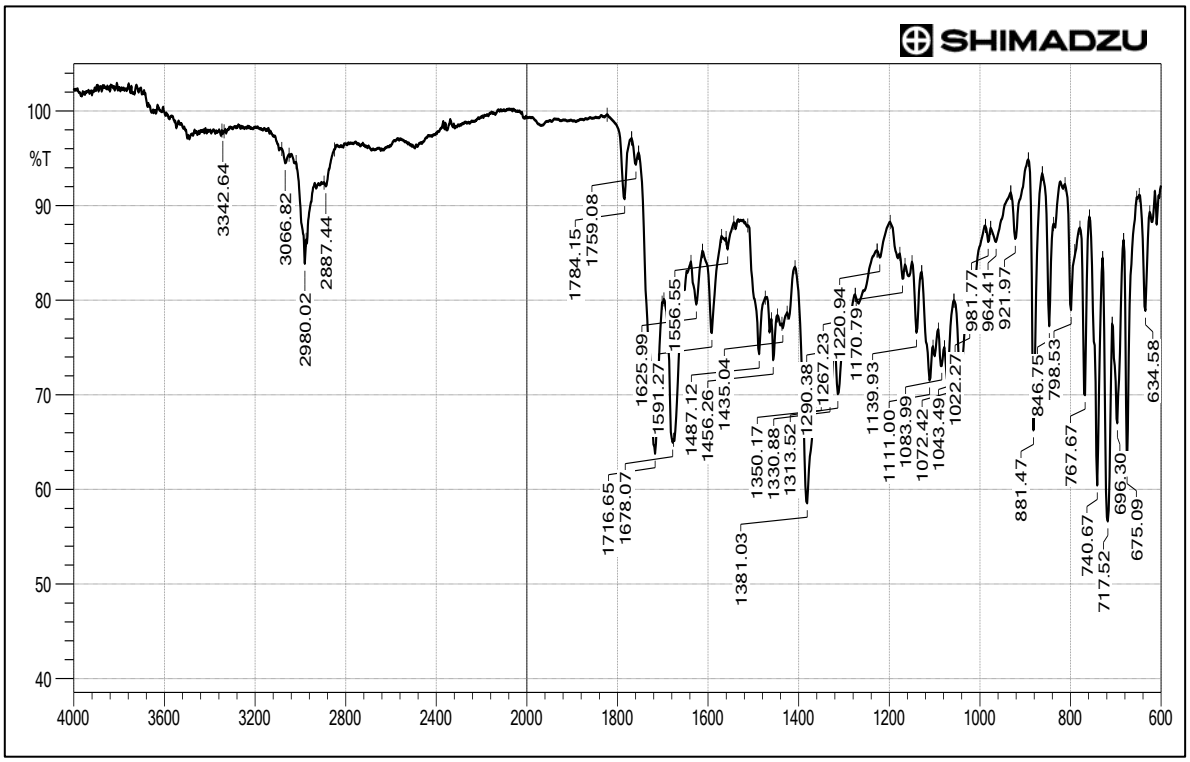


Figure (3-9) FT-IR spectra of compound (S4)

Figure (3-10). Shows the ^{1}H-NMR spectra of substance (S4), reveals that a single signal for (OH) appears at 7.54 ppm, a signal appears at 2.93 ppm for $(C{=}C\text{-}H)_{ph}$, and a signal appears at (2.5) ppm for $(C{=}C{-}H_{)\,amid}$.

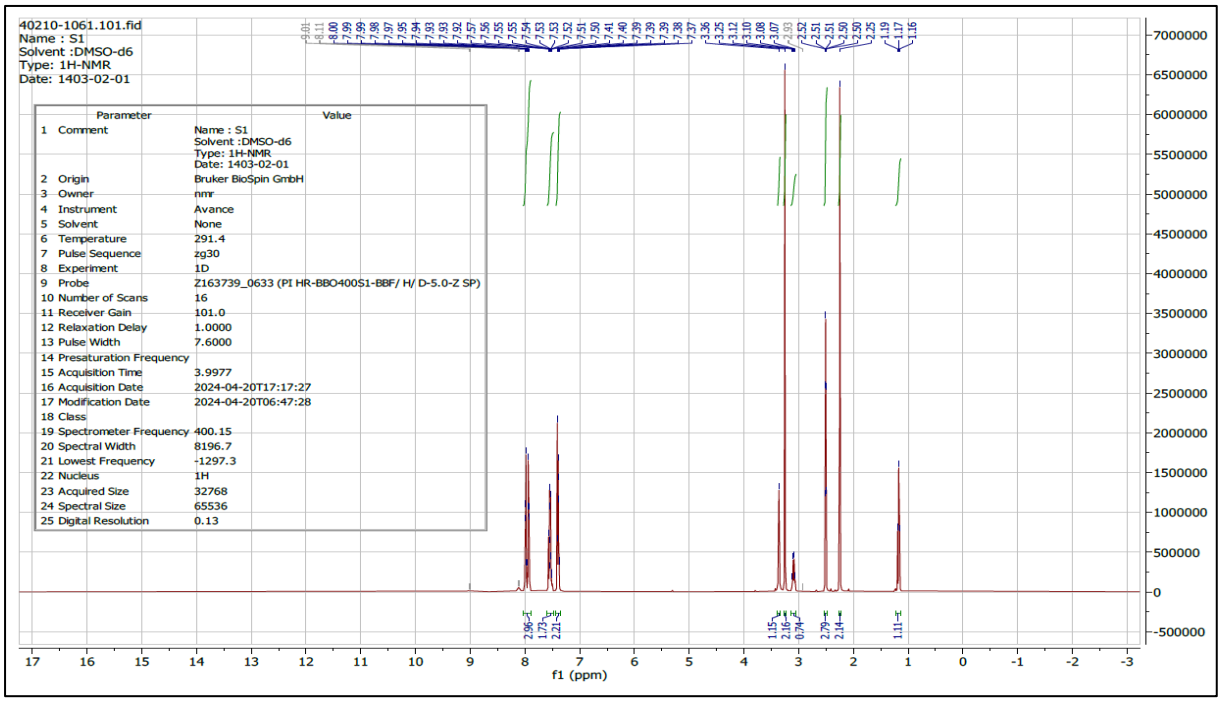


Figure (3-10) ^{1}H-NMR spectra compound (S4)

^{13}C-NMR spectra **Figure (3-11)**; It appears at a signal of 167 ppm for the C=O amide, a signal of 130.80 ppm for (CO), and a signal of 40 ppm for (R-CH_3).

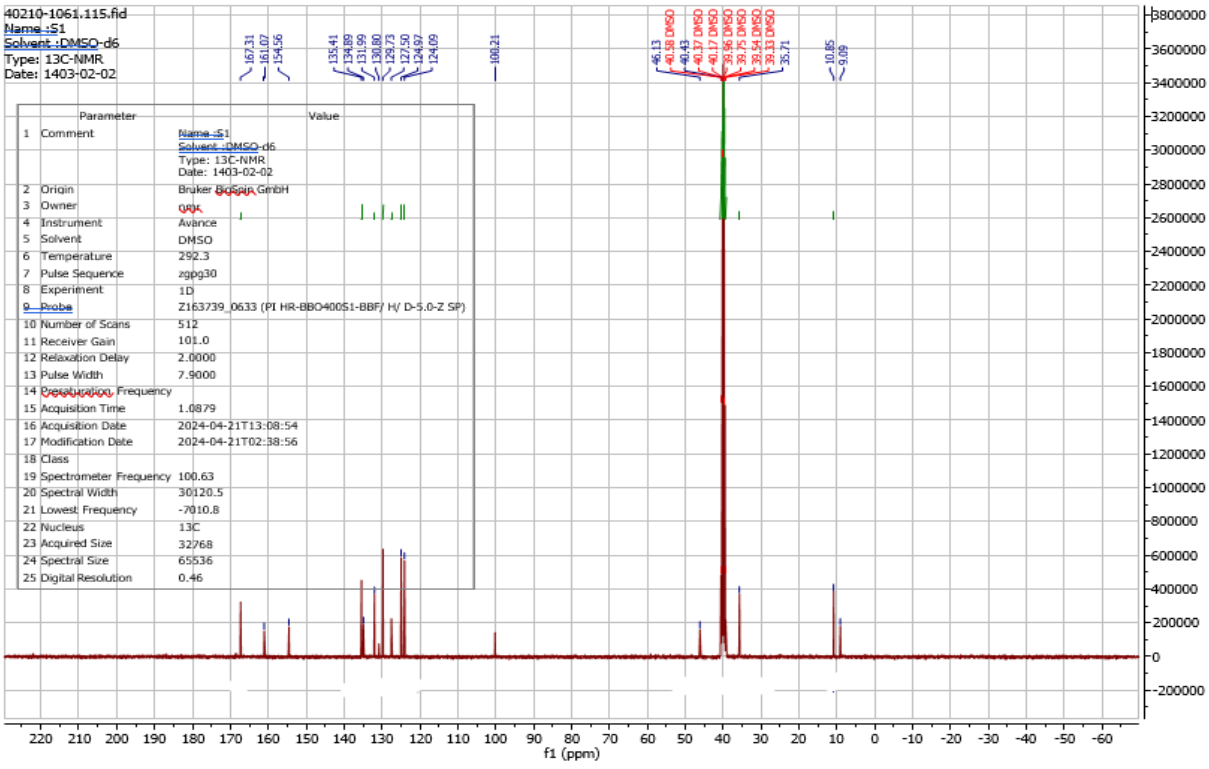
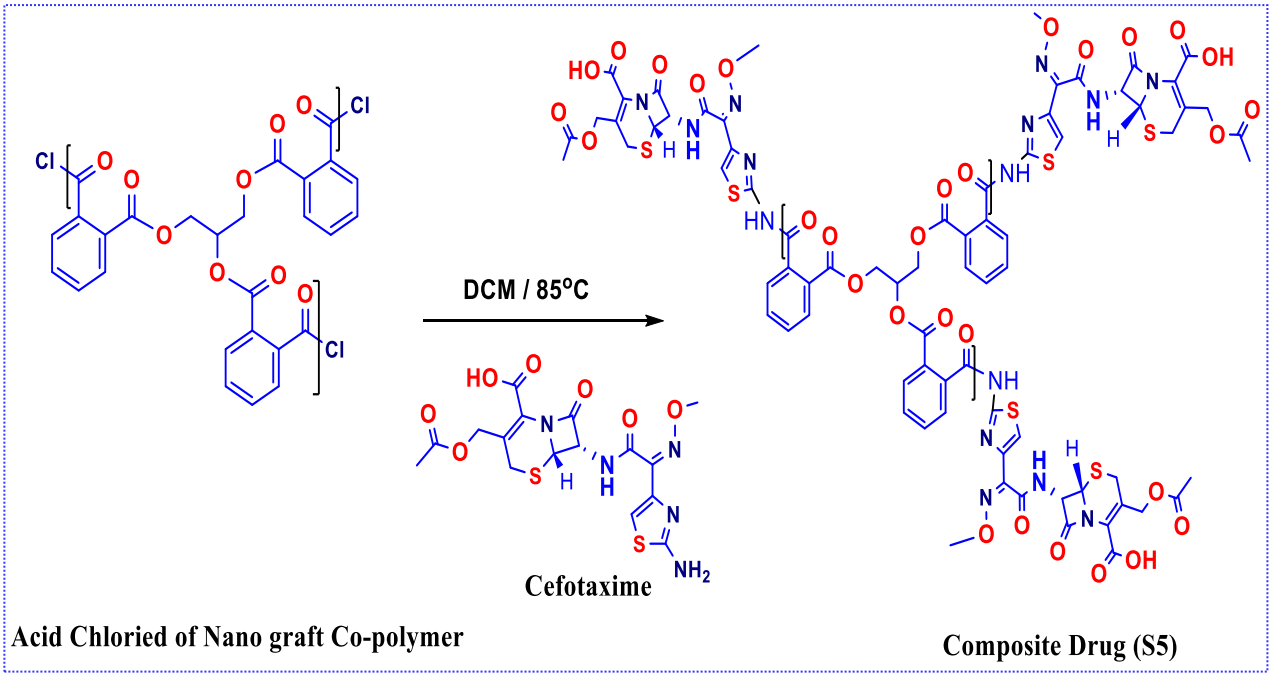


Figure (3-11) ^{13}C-NMR spectra of compound (S4)

3.5. Synthesis of Nano Graft Co-Polymer- Cefotaxime Drug Composite (S5)

About (0.6 g) of compound (S2), that reacted with (4.53 g, 0.009 mol) Cefotaxime drug and was combined to collect was added to a mixture of 0.5 mL trihydrate and 8 ml DCM at 85°C. **Equation (3-5),** represents the reaction.



Equation (3-5) Synthesis of the Composite (S5)

Figure (3-12). Shows the compound's FT-IR spectra (S5). The FT-IR spectrum shows a group of bands, where we notice the appearance of the band that falls between (3309.85-3194.12 cm^{-1}), which belongs to... Secondary amine group (N-H). As for the band that appeared at (3028.24 cm^{-1}), it belongs to the aromatic (C-H) group. As for the aliphatic (C-H) group, it appeared at (2985.81 cm^{-1}). The FT-IR spectrum also shows the appearance of a new and distinct band at (1791.87 cm^{-1}), which belongs to the beta-lactam ring present in the drug cefotaxime. The carboxyl (C=O) band can be seen at (1716.65 cm^{-1}), while the amide (C=O) band appears in the range (1598.99-1683.86 cm^{-1}). We also notice in the spectrum the (C=C) band, which is located at (1541.12 cm^{-1})

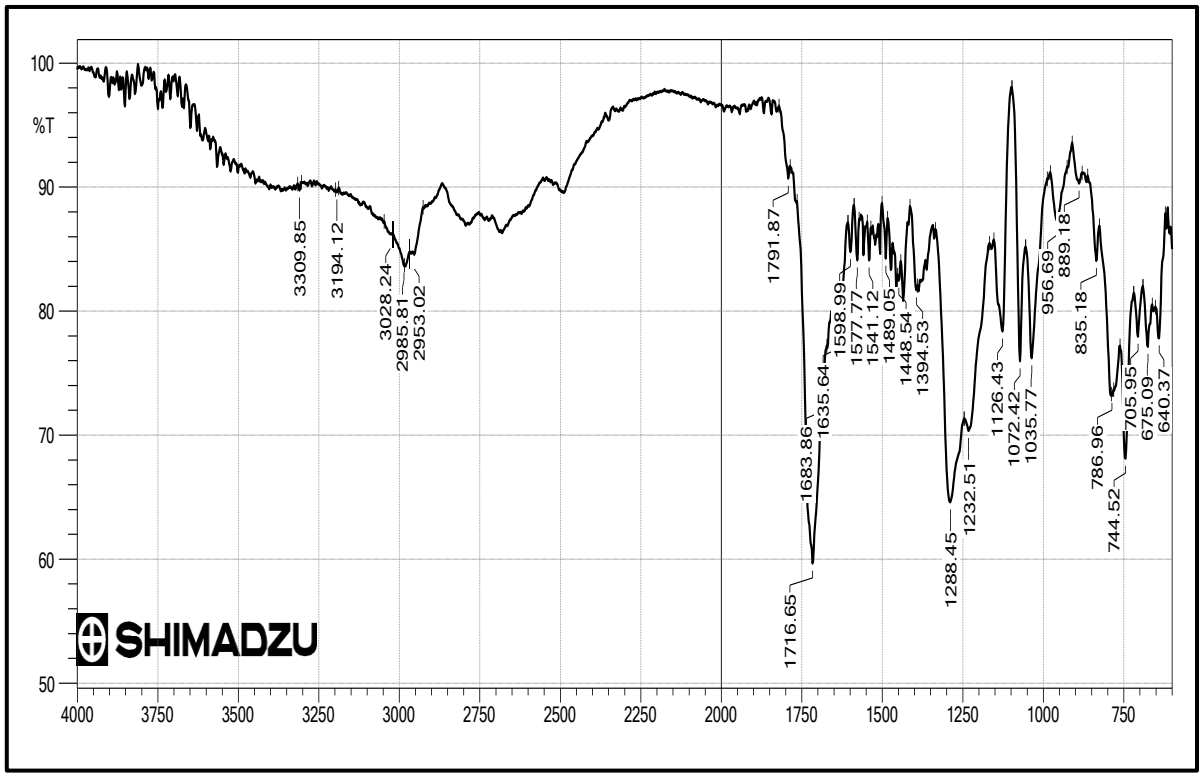


Figure (3-12) FT-IR spectra compound (S5)

Figure (3-13). Shows the ^{1}H-NMR spectrum, which explain the singlet signal at (10.49 ppm) of characteristic proton in the carboxylic acid group. Moreover, the multiple in the region (7.77-7.66 ppm) attributed to all protons in the aromatic ring, the signals at (3.68-3.57 ppm) for the four methylene protons of co-polymer, and multiple at 3.88ppm of the methyl protons, but aliphatic alcohol signal has disappeared indicating the formation of a graft co-polymer. Regarding the signal observed at (2.5 ppm), it bound the solvent (DMSO-d^{6}).

Figure (3-14), showed ^{13}C-NMR indicated the appearance of a signal at (131.89 ppm) of (N-C=O amide), at 45.69 of (C=C-H), and a signal of (40.35 ppm) (CO).

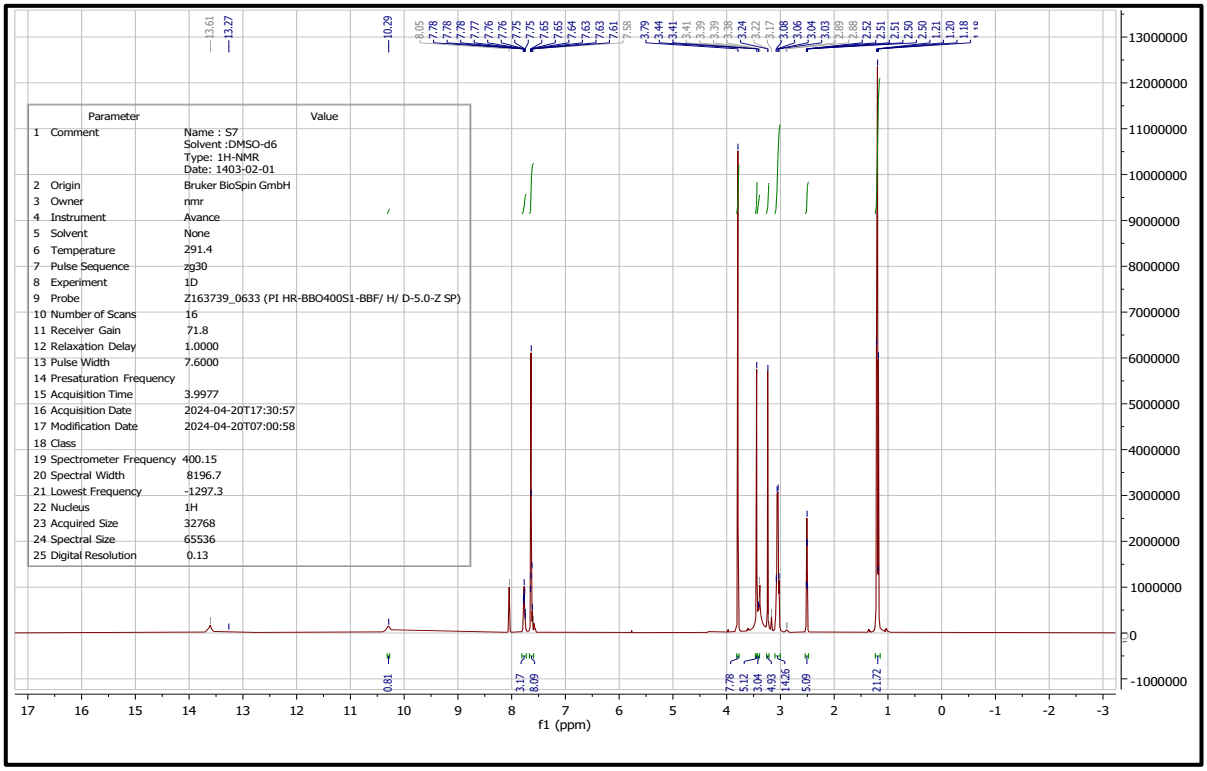


Figure (3-13) ^{1}H-NMR spectra compound (S5)

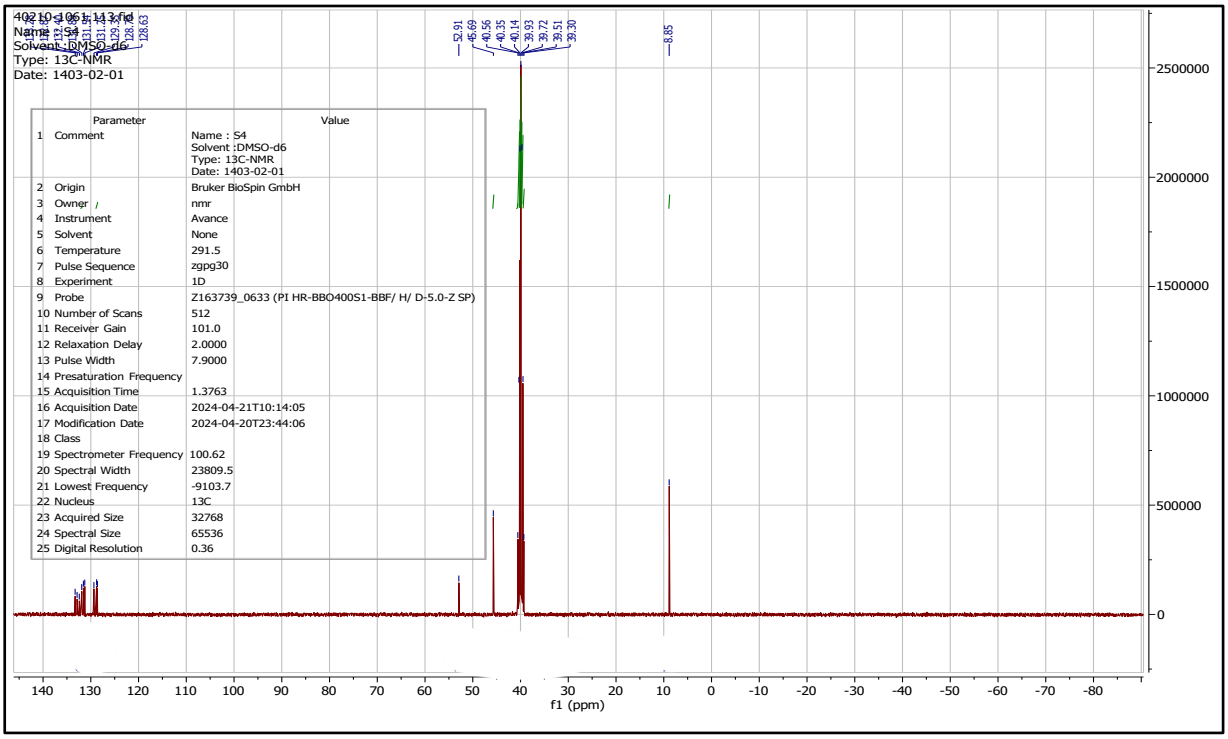
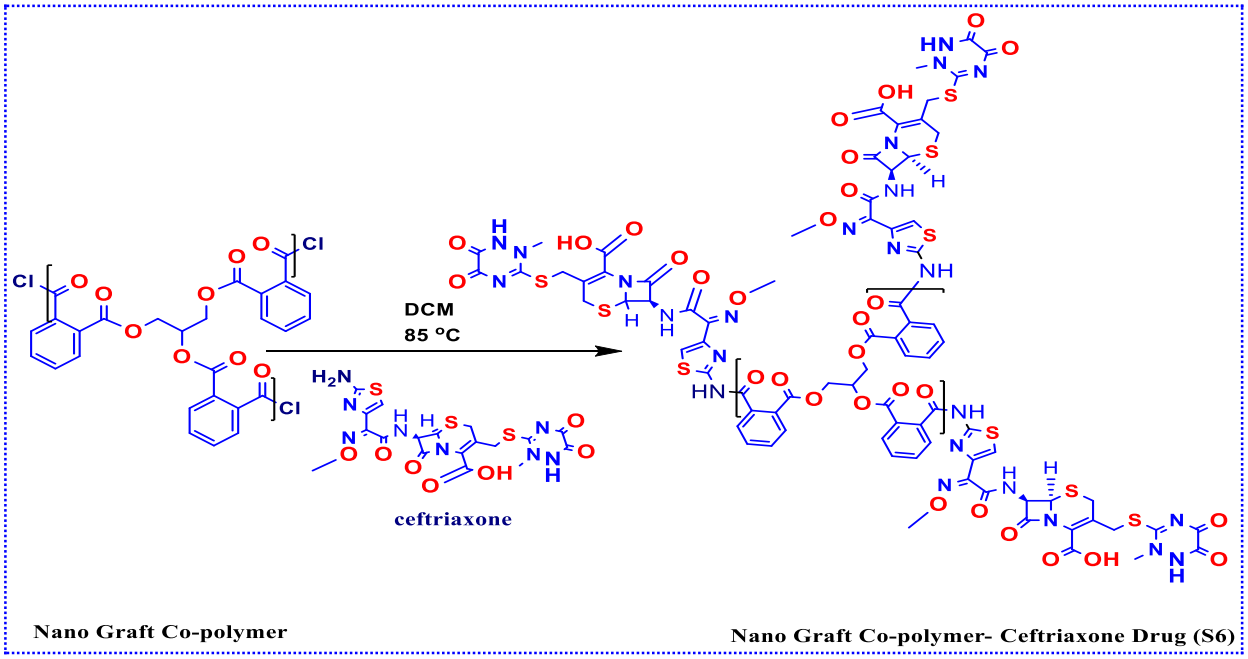


Figure (3-14) ^{13}C-NMR spectra compound (S5)

3.6. Synthesis of Nano Graft Co-Polymer- Ceftriaxone Drug Composite (S6)

About (0.6 g) of compound (S2), that reacted with (5 g, 0.009 mol) Ceftriaxone drug and was combined to collect was added to a mixture of half mL trihydrate and 8 ml DCM at 85°C. **Equation (3-6),** represents the reaction.



Equation (3-6) Synthesis of the composite (S6)

Figure (3-15), displays the FT-IR spectrum of the compound (S6), where the spectrum showed many absorption bands, where an absorption band appeared between (3317.56-3271.27 cm^{-1}) belonging to the alcoholic (OH), while the absorption band that appeared at (3045.60 cm^{-1}) belongs to the aromatic (C-H) bond, while the aliphatic (C-H) appeared at the absorption band located between (2981.95-2951.09 cm^{-1}), and the spectrum also showed an absorption band at (1770.65 cm^{-1}) resulting from the vibration of the beta-lactam ring present in the drug ceftriaxone. As for the acidic (C=O) it appeared at (1714.72 cm-^{1}), the amide (C=O) appeared at (1681.93-1647.21 cm^{-1}), and the acidic (C=C) appeared at (1435.04-1556.55 cm-^{1}).

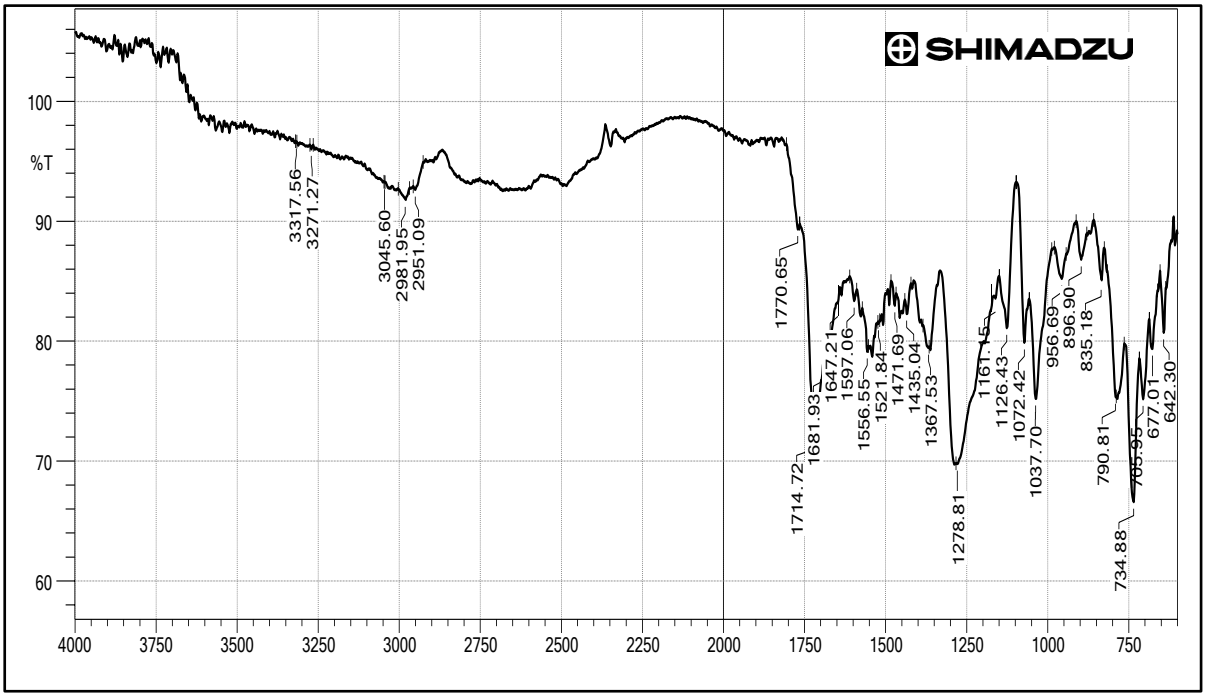


Figure (3-15) FT-IR spectra compound (S6)

The ^{1}H-NMR spectrum appears in **Figure (3-16),** where the spectrum showed a number of signals. The signal that appeared at (13.04 ppm) belongs to the acidic (OH), and the signal that appeared at (7.87 ppm) belongs to the amide (C=O). As for the signal that appeared at 3.90 ppm, it goes back to (-N- C=O), and the signal that appeared at (2.5 ppm) goes back to the solvent group DMSO-d^{6}**.**

Figure (3-17), showed the ^{13}C-NMR indicated the appearance of a signal at (168.67 ppm) of (N-C=O amide), and at (131.51 ppm) of (C=C-H), at a signal of (44.69 ppm) from (CO). At (39.89 ppm) of (DMSO-d^{6}).

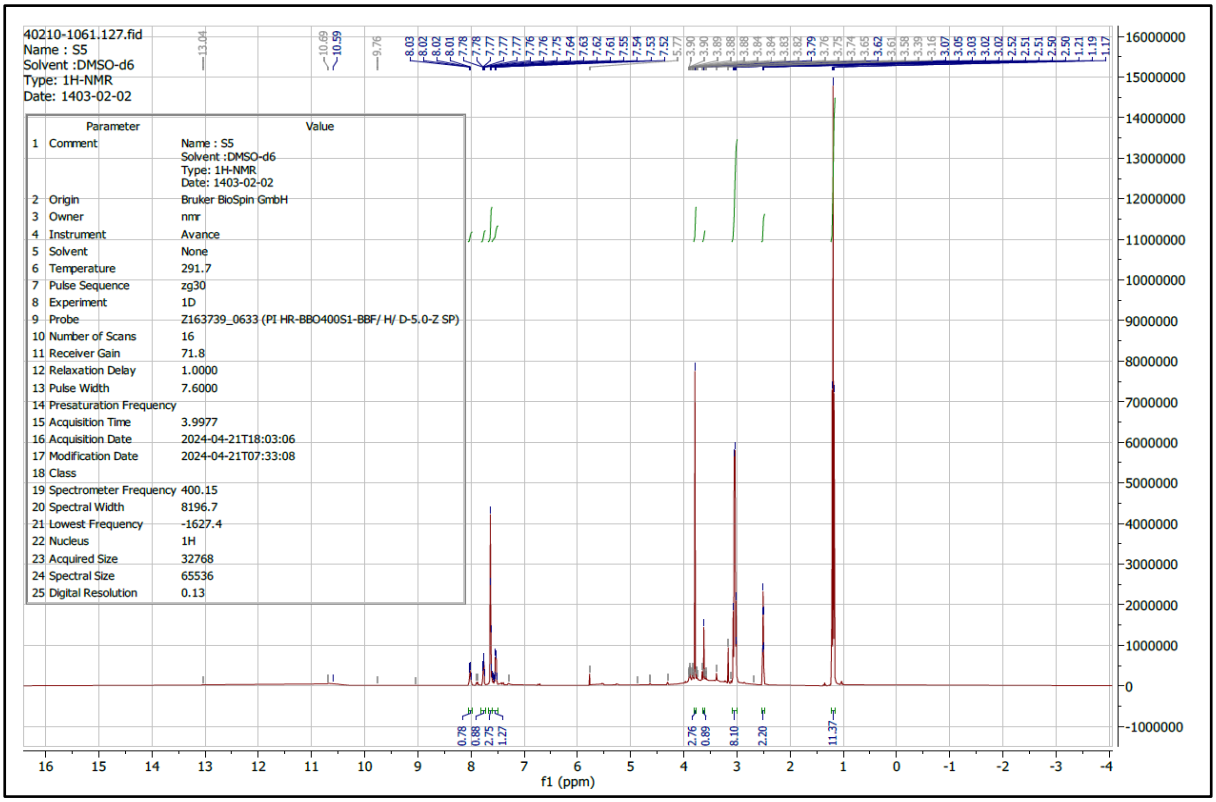


Figure (3-16) ^{1}H-NMR spectra compound (S6)

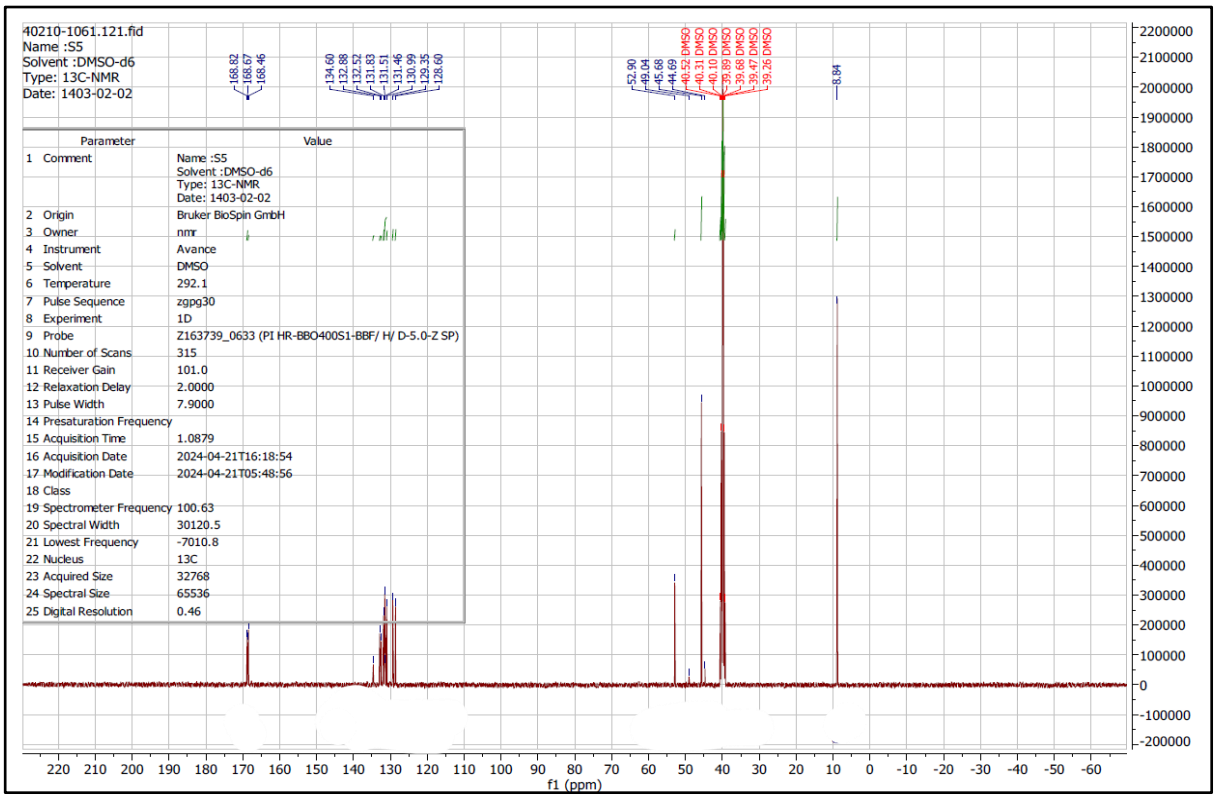


Figure (3-17) ^{13}C-NMR spectra compound (S6)

3.7. Solubility of Drug

It was investigated how soluble the polymer was in several solvents, including acetone, DMSO, ethanol, methanol, and water. As displayed in **Table (3-3)**, for created nano co-polymers, the solubility of the polymers was observed, with some solids totally dissolved (+), others partially dissolved (partial), and another solid not dissolved (-).

Table (3-3) Solubility of synthesis nano Compounds

Types of Nano Compound	H_2O	EtOH	MeOH	DMSO	Hexane	Acetone
S1	Partial	partial	partial	+	_	+
S2	Partial	+	+	+	_	+
S3	Partial	+	+	+	_	+
S4	Partial	_	_	+	_	+
S5	Partial	+	+	+	_	+
S6	Partial	_	_	+	_	+

3.8. Release of Drug

Release the drug from the synthesized nano co-polymer pharmaceuticals were measured in four distinct buffer solutions (2.2, 6.0, 7.0, and 8.0) at a constant temperature of 37 °C using a UV-Vis spectrophotometer. The drug release from the synthesis nano co-polymer-drugs is shown in **Tables (3-4) to (3-7)** and **Figures (3-18) to (3-25)**.

Table (3-4) Release of drug per time (hour and day) of Nano composite in pH=2.2 at 37 °C

Time	Release of drug (λ)			
(Hour)	Types of Nano Graft Co-polymer Drug			
	S3	S4	S5	S6
1	0.963	0.295	0.330	0.186
2	1.062	0.313	0.355	0.180
3	1.205	0.343	0.380	0.2
4	1.3	0.380	0.406	0.209
5	1.312	0.432	0.460	0.235
6	1.312	0.432	0.460	0.235
(Day)				
1	1.450	0.504	0.650	0.232
2	1.407	0.650	0.700	0.245
3	1.607	0.859	0.967	0.257
4	1.973	0.979	1.22	0.257
5	2.337	1.242	1.320	0.258
6	2.532	1.443	1.553	0.258
7	2.666	1.553	1.667	0.259
8	2.666	1.553	1.667	0.259

Table (3-5) Release of drug per time (hour and day) of Nano Graft Co-polymer-drugs in pH=6.0 at 37 °C

Time	Release of drug (λ)			
(Hour)	Types of Nano Graft Co-polymer Drug			
	S3	S4	S5	S6
1	0.863	0.195	0.230	0.086
2	1.052	0.213	0.255	0.080
3	1.105	0.243	0.280	0.1
4	1.2	0.280	0.306	0.109
5	1.212	0.332	0.360	0.135
6	1.212	0.332	0.360	0.135
(Day)				
1	1.349	0.404	0.55	0.132
2	1.303	0.550	0.8	0.145
3	1.504	0.759	0.95	0.157
4	1.862	0.879	1.15	0.157
5	2.237	1.142	1.35	0.158
6	2.432	1.343	1.662	0.158
7	2.566	1.553	1.695	0.159
8	2.566	1.553	1.695	0.159

Table (3-6) Release of drug per time (hour and day) of Nano Graft Co-polymer-drugs in pH=7.2 at 37 °C

Time	Release of drug (λ)			
(Hour)	Types of Nano Graft Co-polymer Drug			
	S3	S4	S5	S6
1	0.545	0.319	0.098	0.164
2	0.645	0.388	0.123	0.219
3	0.797	0.473	0.128	0.255
4	0.89	0.567	0.135	0.298
5	0.961	0.644	0.137	0.373
6	0.972	0.644	0.144	0.432
(Day)				
1	1.101	0.731	0.181	0.381
2	1.221	0.842	0.155	0.424
3	1.359	0.991	0.163	0.459
4	1.473	1.212	0.172	0.568
5	1.598	1.334	0.184	0.691
6	1.656	1.466	0.189	0.781
7	1.722	1.557	0.192	0.891
8	1.822	1.657	0.212	0.891

Table (3-7) Release of drug per time (hour and day) of Nano Graft Co-polymer-drugs in pH=8.0 at 37 °C

Time	**Release of drug (λ)**			
(Hour)	**Types of Nano Graft Co-polymer Drug**			
	S3	**S4**	**S5**	**S6**
1	0.485	0.412	0.101	0.197
2	0.652	0.559	0.122	0.271
3	0.777	0.666	0.163	0.354
4	0.877	0.732	0.171	0.421
5	0.931	0.846	0.184	0.462
6	0.987	0.946	0.196	0.494
(Day)				
1	1.328	0.993	0.241	0.568
2	1.441	0.999	0.262	0.698
3	1.571	1.163	0.291	0.781
4	1.683	1.303	0.321	0.803
5	1.791	1.544	0.341	0.909
6	1.965	1.671	0.388	1.212
7	2.188	1.799	0.402	1.331
8	2.313	1.899	0.402	1.431

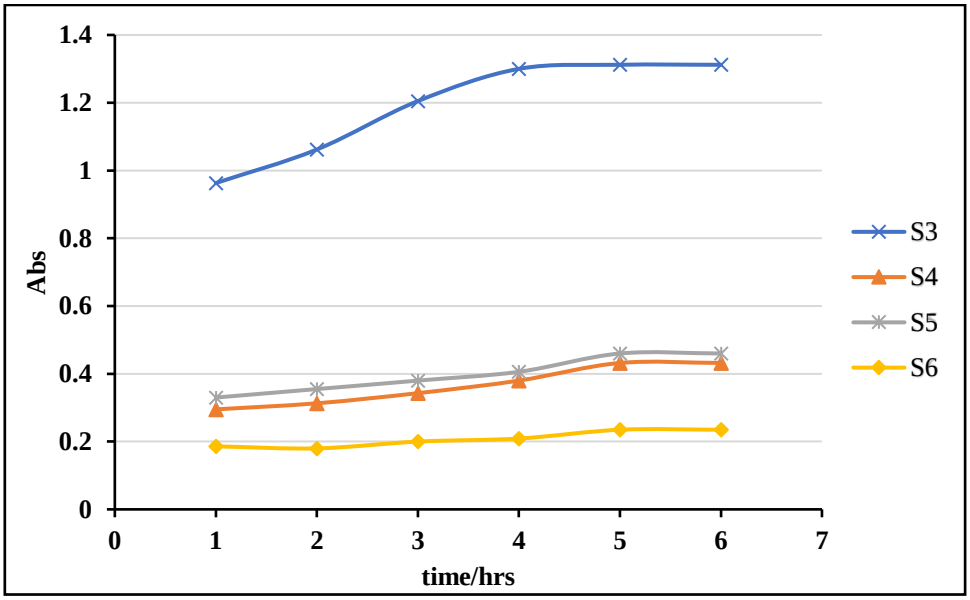


Figure (3-18) Release of Drugs from Nano Co-polymer per time (hrs) at pH=2.2 and 37 °C

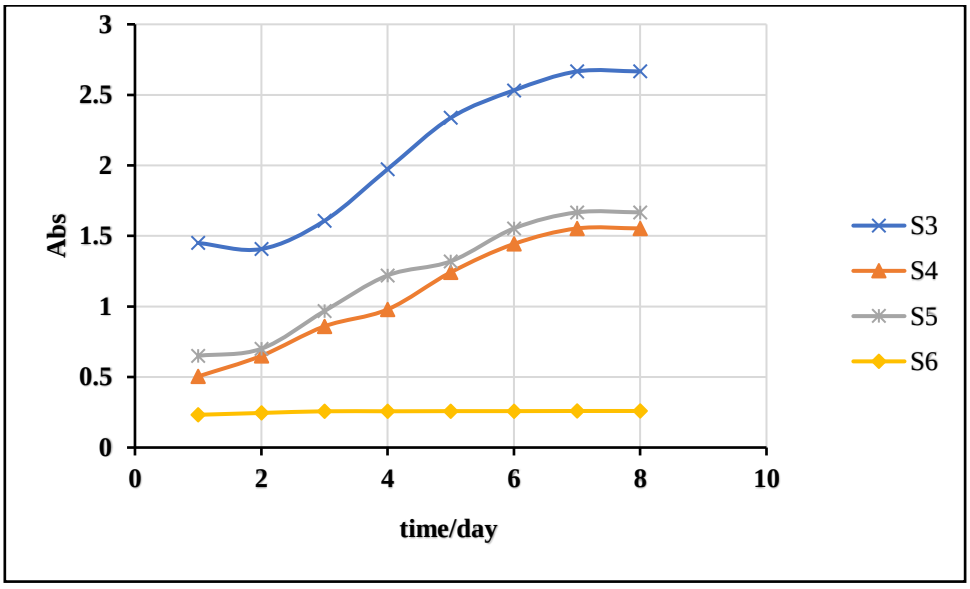


Figure (3-19) Release of Drugs from Nano Co-polymer per time (day) at pH=2.2 and 37 °C

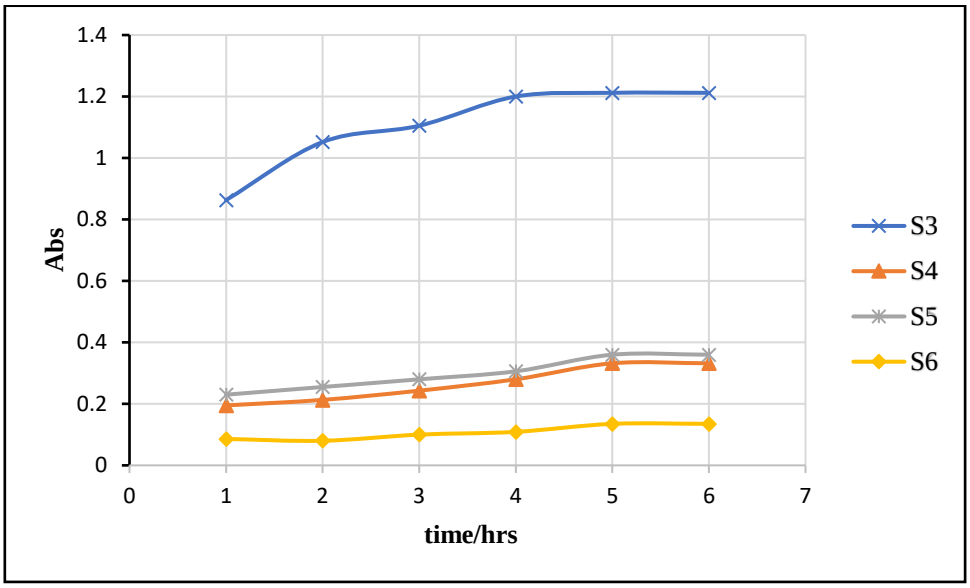


Figure (3-20) Release of Drugs from Nano Co-polymer per time (hrs) at pH=6.0 and 37 °C

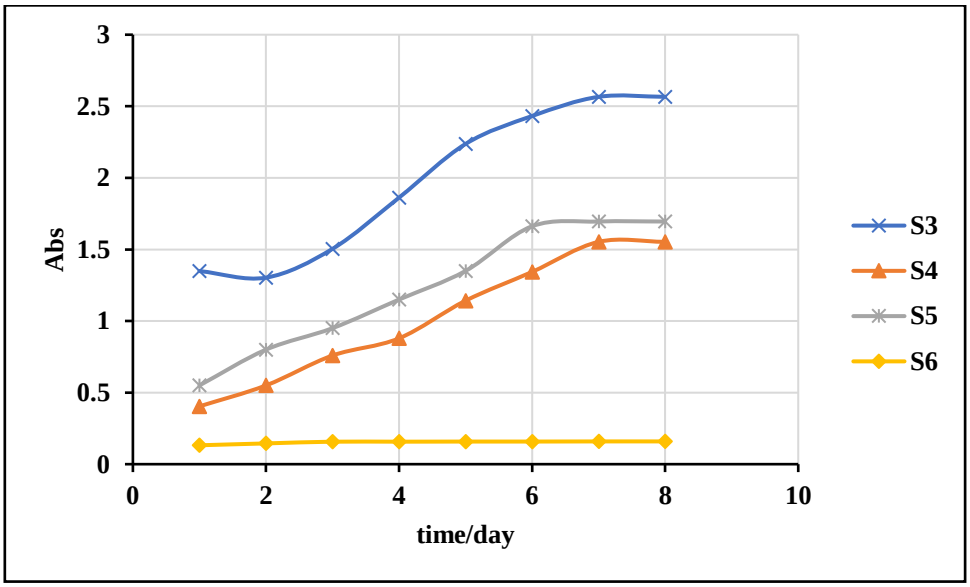


Figure (3-21) Release of Drugs from Nano Co-polymer per time (day) at pH=6.0 and 37 °C

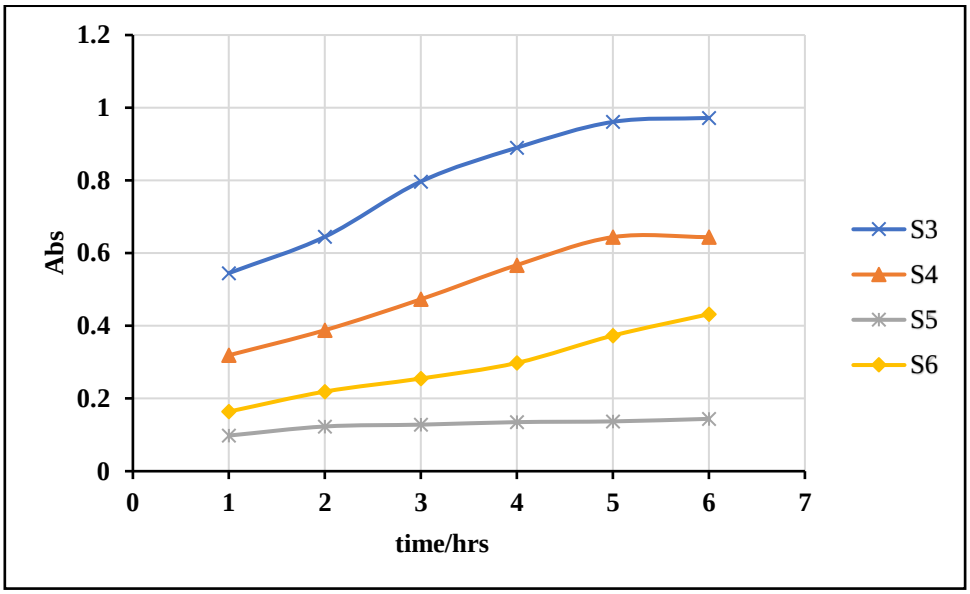


Figure (3-22) Release of Drugs from Nano Co-polymer per time (hrs) at pH=7.2 and 37 °C

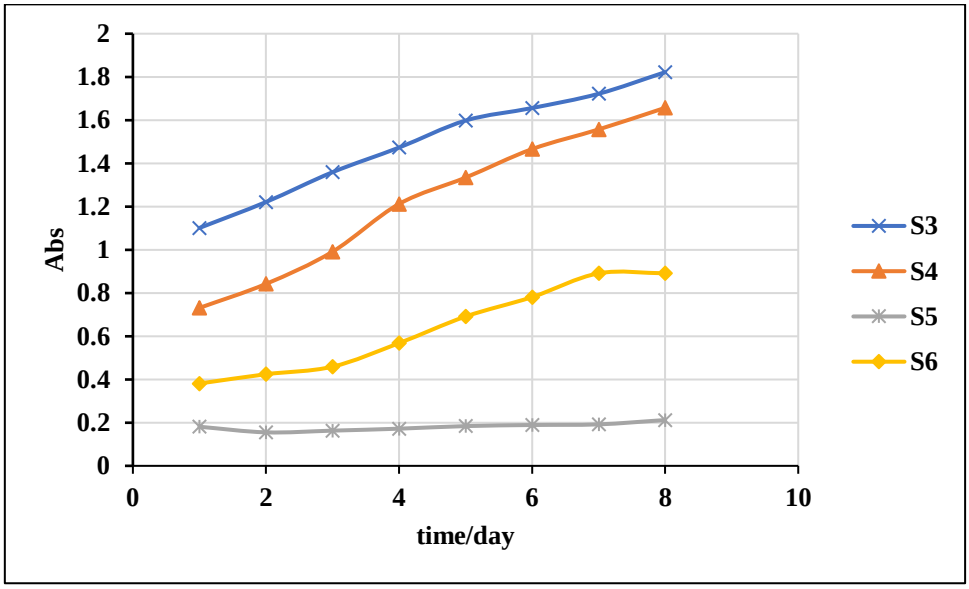


Figure (3-23) Release of Drugs from Nano Co-polymer per time (day) at pH=7.2 and 37 °C

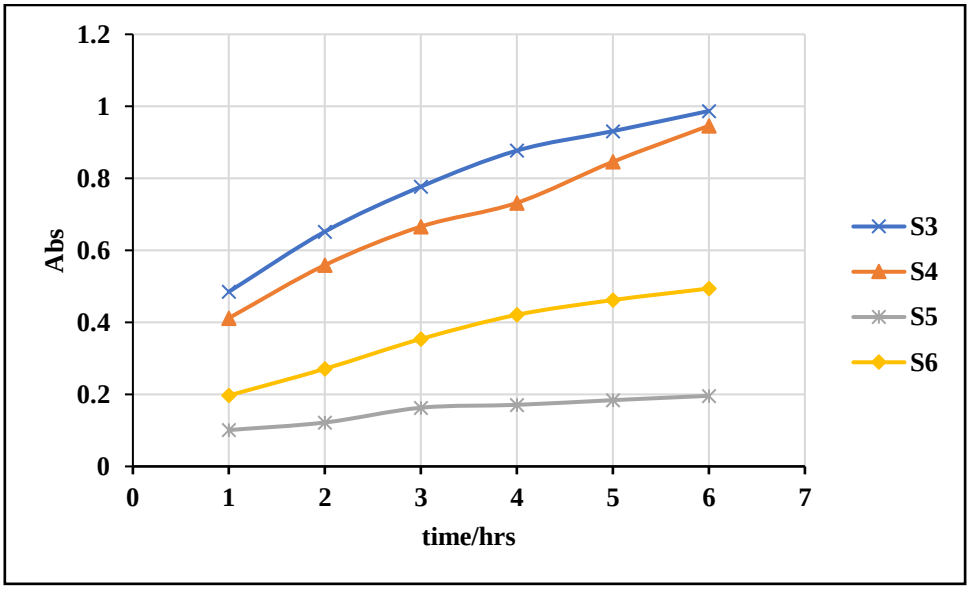


Figure (3-24) Release of Drugs from Nano Co-polymer per time (hrs) at pH=8.0 and 37 °C

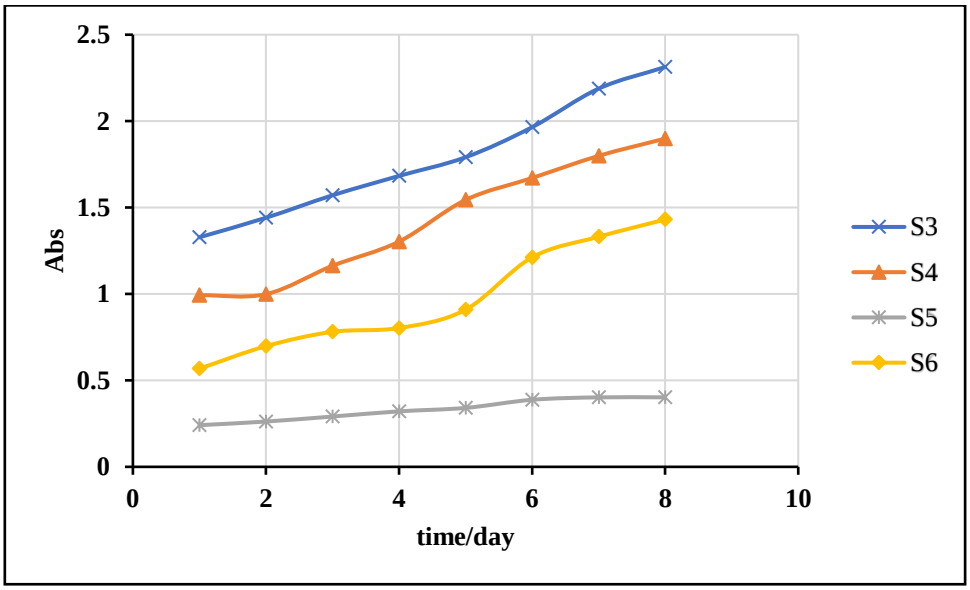


Figure (3-25) Release of Drugs from Nano Co-polymer per time (day) at pH=8.0 and 37 °C

3.9. Molecular Docking Study

A specific kind of computational modelling called molecular docking makes it easier to anticipate the optimal binding orientation of a ligand to a receptor when the two interact to create a stable complex [110]. Most fascinating example is the protein ligand interaction because of its applications in medicine. A ligand is a small chemical that interacts with protein binding sites. Molecular docking is frequently used in modern drug design to study drug-receptor interactions. Binding can occur in a variety of different mutual conformations. A common method for predicting the binding orientation of therapeutic candidates for small molecules to their protein targets and thus the small molecule's affinity and activity is molecular docking [111].

3.9.1. Molecular Docking of Compound (S3)

Table (3-8) shows the binding energy of the drug (S3) with the amino acids present in the protein, as well as the minimum and maximum limits (RMSD). **Figure (3-26)**. Shows the binding of the drug (S3) with the amino acids contained in the protein of the liver cancer line, and these acids are: the amino acids and cysteine (Cys) which carries the serial numbers (I:58, I:12), and glycine (Gly) which carries the serial number (A:219), and aspartic (Asp) which carries the serial number (I:10) which are linked to the drug by a hydrogen bond in dark green. Also, a yellow (pi-sulfur) bond appeared for cysteine (Cys) which carries the serial numbers (I:22, I:14, A:191, A:220). As for the amino acids that appeared with a light pink bond called a (pi-alkyl) bond, they belong to the amino acid lysine (Lys) which carries the serial number (A:224) and the amino acid proline (Pro) which carries the serial numbers (I:61, I:20). As for the amino acid aspartic (Asp) which carries the serial number (I:10), it is linked to a carbon-hydrogen bond (C-H) which is very light green. As for the remaining amino acids that appeared in light green when they are molecularly bound, they are linked to the protein by van der Waals force.

(Tyr – Ser – Pro – Asn – Cys – Gln – Phe – Glu – Gly)

Table (3-8). Shows the binding energy of drug (S3)

Ligand	Binding Affinity (kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
1d6r_Fragment_uff_E=1978.53	-7.2	0	0.0	0.0
1d6r_Fragment_uff_E=1978.53	-7.1	1	3.778	10.469
1d6r_Fragment_uff_E=1978.53	-6.9	2	4.305	7.329
1d6r_Fragment_uff_E=1978.53	-6.8	3	3.357	9.103
1d6r_Fragment_uff_E=1978.53	-6.8	4	3.615	6.861
1d6r_Fragment_uff_E=1978.53	-6.8	5	2.895	7.394
1d6r_Fragment_uff_E=1978.53	-6.8	6	3.415	9.589
1d6r_Fragment_uff_E=1978.53	-6.7	7	3.631	10.547
1d6r_Fragment_uff_E=1978.53	-6.7	8	15.296	20.652

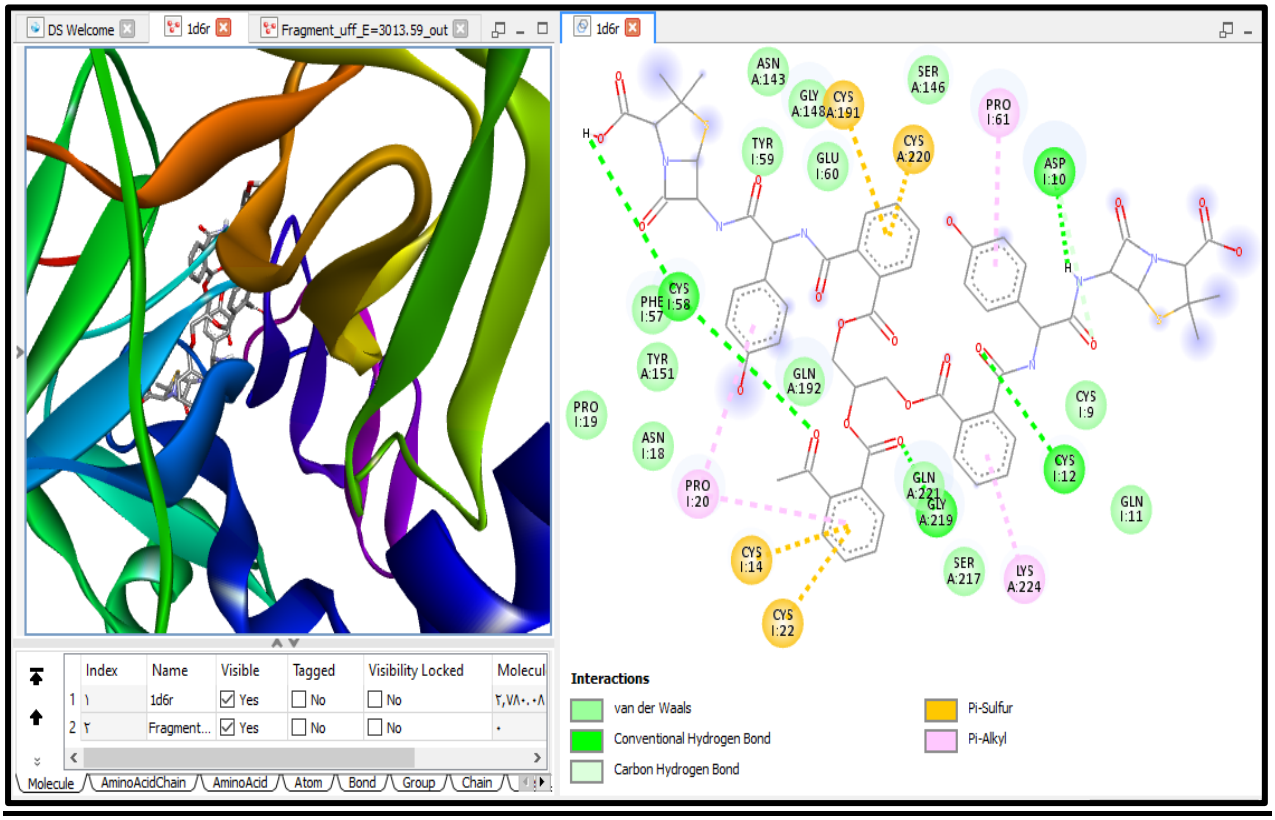


Figure (3-26) Shows the association of drug (S3) with amino acids.

3.9.2. Molecular Docking of Compound (S4)

Table (3-9) shows the binding energy of the drug (S4) with the amino acids present in the protein, as well as the minimum and maximum limits (RMSD). **Figure (3-27)** shows the binding of the drug (S4) with the amino acids contained in the protein of the liver cancer line, including: the amino acids threonine (Thr) which carries the serial number (A:151), glycine (Gly) which carries the serial numbers (A:148, A:219), and glutamine (Gln) which carries the serial numbers (A:221, A:192), which are linked to the drug by a hydrogen bond in dark green. Also, a yellow (pi-sulfur) bond appeared for the cysteine acid (Cys) which has the serial number (I:14). As for the amino acids that appeared with a light pink bond, called a (pi-alkyl) bond, they belong to the amino acid cysteine (Cys) which has the serial numbers (I:22, I:12) and the amino acid proline (Pro) which has the serial numbers (I:61, I:20). As for the amino acids glycine ((Gly) which has the serial number (A:219), serine ((Ser) which has the serial number (A:146) and aspartic (Asp) which has the serial number (I:10), they are linked by a carbon-hydrogen (C-H) bond that is very light green in color. As for the remaining amino acids that appeared with a light green color when they are molecularly bound, they are linked to the protein by the force of van der Waals. This is consistent with what is stated in the references.

(Thr– Ser – Lys– Phe– Glu– Asn – Cys)

Table (3-9) Shows the binding energy of the drug (S4)

Ligand	Binding Affinity (kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
1d6r_Fragment_uff_E=2182.61	-7.5	0	0.0	0.0
1d6r_Fragment_uff_E=2182.61	-7.3	1	2.87	7.476
1d6r_Fragment_uff_E=2182.61	-7.2	2	3.236	8.453
1d6r_Fragment_uff_E=2182.61	-7.1	3	3.882	7.197
1d6r_Fragment_uff_E=2182.61	-7.0	4	17.717	22.561
1d6r_Fragment_uff_E=2182.61	-7.0	5	3.074	7.395
1d6r_Fragment_uff_E=2182.61	-6.9	6	2.456	8.369
1d6r_Fragment_uff_E=2182.61	-6.8	7	1.735	4.262
1d6r_Fragment_uff_E=2182.61	-6.8	8	2.378	10.109

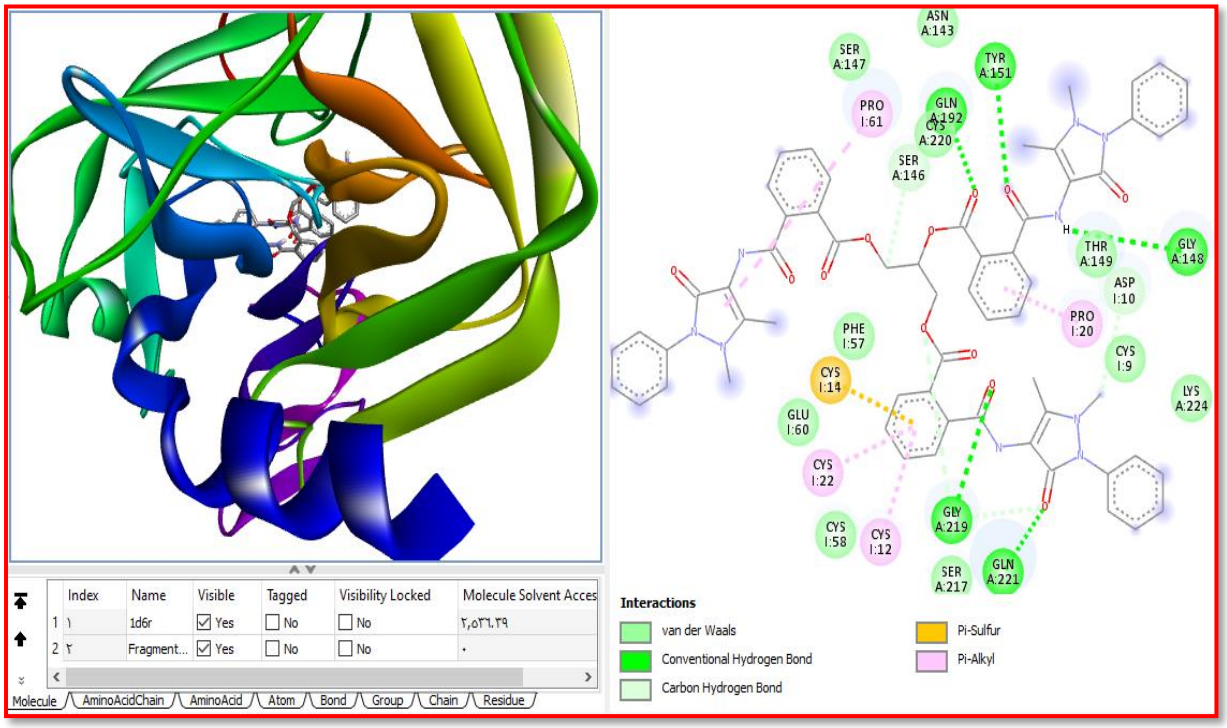


Figure (3-27) Shows the binding of drug (S4) to amino acids.

3.9.3. Molecular Docking of Compound (S5)

Table (3-10) shows the binding energy of the drug (S5) with the amino acids present in the protein, as well as the minimum and maximum limit (RMSD). **Figure (3-28)** shows the association of the drug (S5) with the amino acids contained in the protein of the liver cancer line. These acids include: the amino acids glutamine (Gln), which has two serial numbers (A:221, A:192), and asparagine (Asn), which has the two serial numbers (I:18, A:74), which are linked to the drug by a dark green hydrogen bond. Likewise, a yellow bond (pi-sulfur) appeared for cysteine (Cys), which has two serial numbers. (I:22, I:14). As for the amino acids that appeared with a light pink bond, they are called (pi-alkyl) bonds. They belong to each. Of the amino acid proline (Pro), which has the serial number (I:20), the amino acid lysine (Lys), which has the serial numbers (A:224, A:222), and the amino acid tyrosine (Tyr), which has the serial number (A:151). As for the amino acid glycine (Gly), which has the serial number (A:219), it is linked by a carbon-hydrogen bond (C-H) that is very light green in color. As for the rest of the amino acids that appeared in light green color when molecularly bound, they bound to the protein with a van der Waals force.

(Tyr – Thr – Trp – His – Ser – Pro – Asn – Cys – Ile – Asp – Phe – Gly)

Table (3-10) Shows the binding energy of drug (S5)

Ligand	Binding Affinity (kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
1d6r_Fragment_uff_E=3383.71	-8.0	0	0.0	0.0
1d6r_Fragment_uff_E=3383.71	-7.8	1	5.448	13.779
1d6r_Fragment_uff_E=3383.71	-7.8	2	4.7	8.681
1d6r_Fragment_uff_E=3383.71	-7.8	3	2.995	18.779
1d6r_Fragment_uff_E=3383.71	-7.7	4	5.606	11.197
1d6r_Fragment_uff_E=3383.71	-7.7	5	6.113	11.2
1d6r_Fragment_uff_E=3383.71	-7.6	6	5.983	11.767
1d6r_Fragment_uff_E=3383.71	-7.6	7	4.865	10.061
1d6r_Fragment_uff_E=3383.71	-7.5	8	5.585	13.333

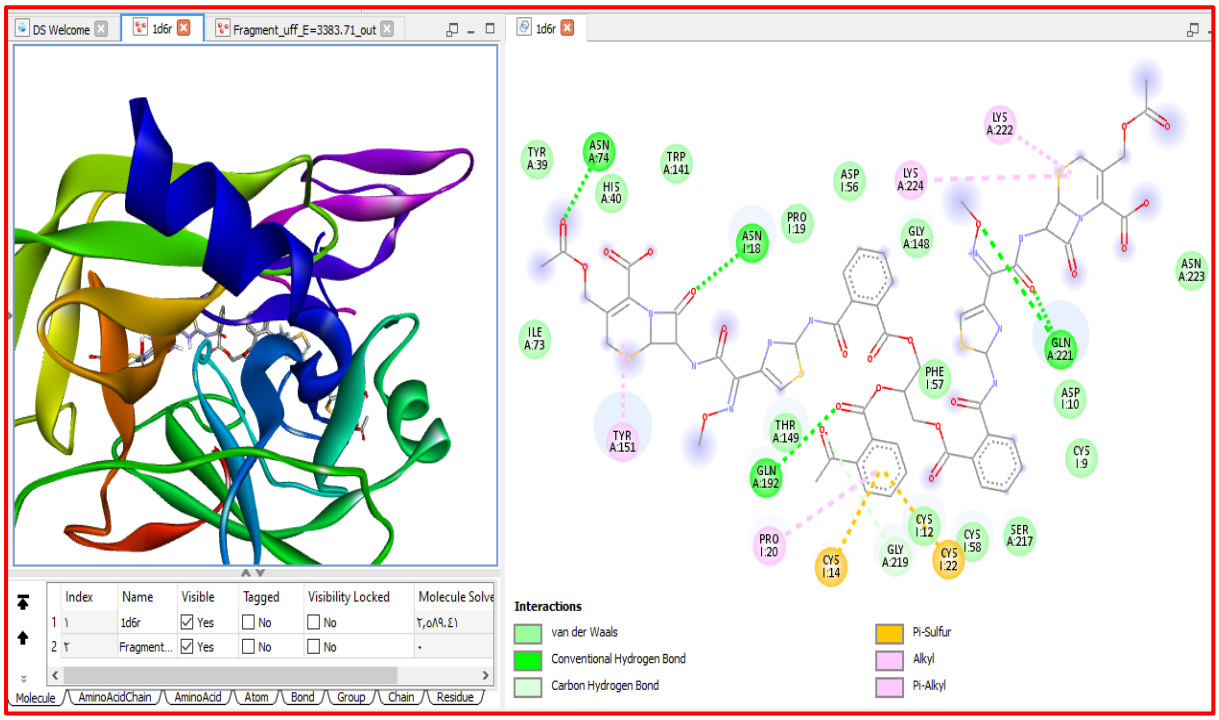


Figure (3-28) Shows the association of drug (S5) with amino acids

3.9.4. Molecular Docking of compound (S6)

Table (3-11), shows the binding energy of drug (S6) with the amino acids present within the protein, as well as the minimum and maximum limit (RMSD). **Figure (3-29)** shows the association of the drug (S6) with the amino acids contained in the protein of the liver cancer line. These acids include: the amino acids glutamine (Gln), which has the serial number (A: 192), and asparagine (Asn), which has the serial number (I). :18), and cysine (Cys), which has the serial number (I:12), and glycine (Gly), which has the serial number (A:219), and aspartic acid (Asp), which has the serial number (I:10), and serine. (Ser), which has the serial number (A:217), and the threonine (Thr), which has the serial number (A:149), which is linked to the drug by a dark green hydrogen bond. As for the amino acids that appeared with a light pink bond called the (bay-alkyl) bond, they belong to the amino acid proline (Pro), which has the serial number (I:20), and the amino acid tyrosine (Tyr), which has the serial number (A). :151). As for the amino acid proline (Pro), which has the serial number (I:20), it is linked by a carbon-hydrogen bond (C-H) that is very light green in color. As for the rest of the amino acids that appeared in light green color when molecularly bound, they bound to the protein with a van der Waals force.

(Tyr – His – Pro – Asn – Cys – Glu – Phe – Gln)

Table (3-11) Shows the binding energy of drug (S6)

Ligand	Binding Affinity (kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
1d6r_Fragment_uff_E=2009.82	-8.9	0	0.0	0.0
1d6r_Fragment_uff_E=2009.82	-8.8	1	3.399	8.272
1d6r_Fragment_uff_E=2009.82	-8.7	2	5.028	13.501
1d6r_Fragment_uff_E=2009.82	-8.6	3	14.0	21.499
1d6r_Fragment_uff_E=2009.82	-8.5	4	4.36	14.176
1d6r_Fragment_uff_E=2009.82	-8.5	5	2.336	3.853
1d6r_Fragment_uff_E=2009.82	-8.5	6	4.484	8.482
1d6r_Fragment_uff_E=2009.82	-8.4	7	16.48	18.637
1d6r_Fragment_uff_E=2009.82	-8.4	8	15.979	17.936

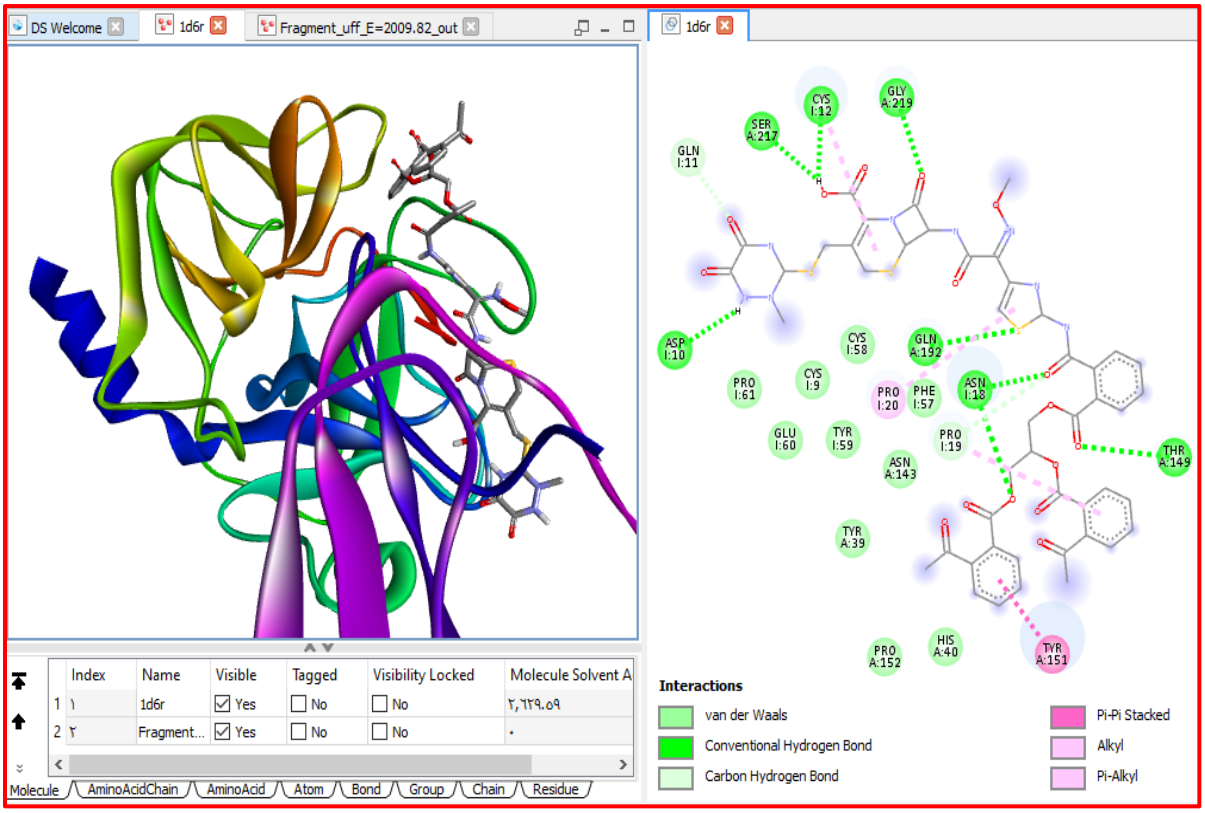


Figure (3-29) Shows the association of drug (S6) with amino acids.

Previous studies have shown that the presence of hydrogen bonds is important in the composition of proteins because their stability is affected by the presence of hydrogen bonds [112], as well as the positioning of nano-loaded drugs in the active sites and their association with a number of amino acids that make up the protein [113]. Also, the more hydrogen bonds there are, the more the drug is associated with the amino acids, and thus the effectiveness of the nano-loaded drug increases [114].

3.10. Anti- Cancer Measurements

Figures from **(3-30) to (3-33)**. displays the viability findings of the MTT colorimetric experiment utilizing HEp-2 human liver cancer cells following exposure to varying doses of Nano Graft Co-polymers-Drugs at concentrations of 12.5, 25, 50, 100, and 200 µg/mL for 72 hours. The MTT assay was then used to measure the cytotoxicity. Results showed that treatment with Nano Graft Co-polymers-Drugs strongly suppressed cell growth for the human liver cancer cell line (HEp-2), with a concentration-dependent reduction. As seen in **Figure (3-30)**, the inhibitory concentration value (IC50) of the (S3) chemical was 36.932 µg/mL, the lowest possible. Therefore, Nano Graft Co-polymer-amoxicillin may be a promising anticancer drug due to its unique qualities, which include biocompatibility, high selectivity, increased cytotoxicity, and smooth synthesis [115].

The following sequence of efficacy was demonstrated by the production of Nano Graft Co-polymer-drugs against the spread of liver cancer:

$$S3 > S4 > S6 > S5$$

Table (3-12) Effectiveness the synthesis Nano Graft Co-polymer- drugs composites to inhibiting the spread of liver cancer

No.	Nano Graft Co-polymer Drugs	IC50 (µg/mL)
1	S3	36.932
2	S4	41.268
3	S5	49.551
4	S6	47.351

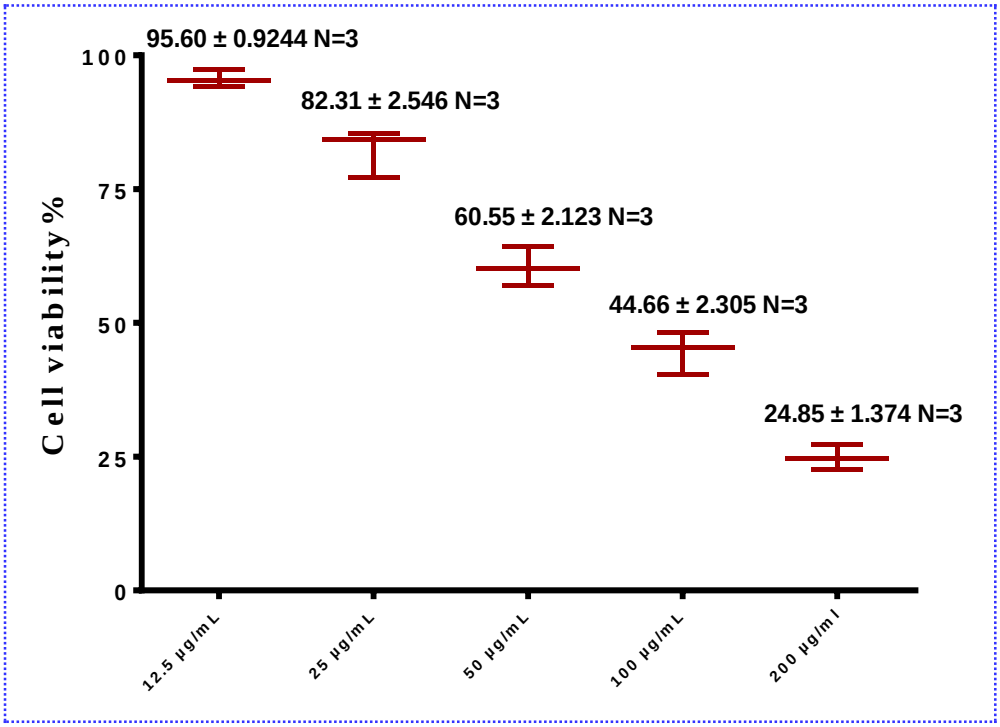


Figure (3-30) Cytotoxicity of S3 in HEp-2 cells. IC50=36.932 µg/mL

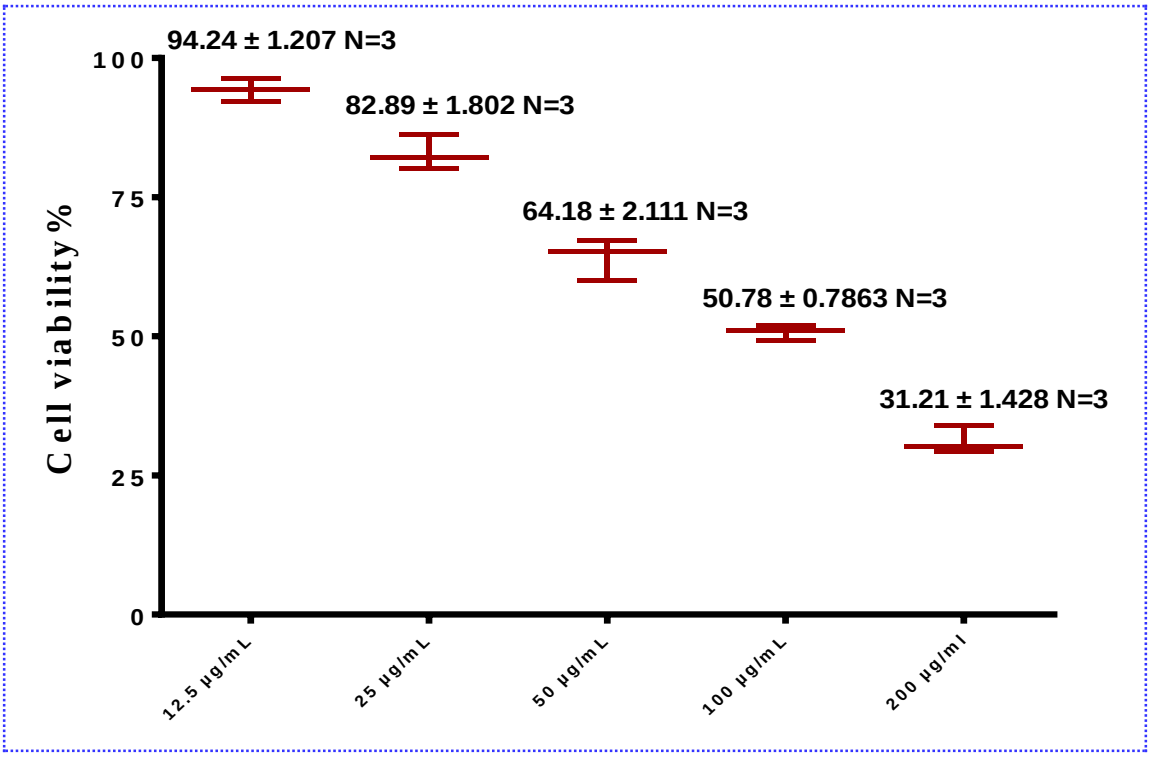


Figure (3-31) Cytotoxicity of S4 in HEp-2 cells. IC50=41.268 µg/ml

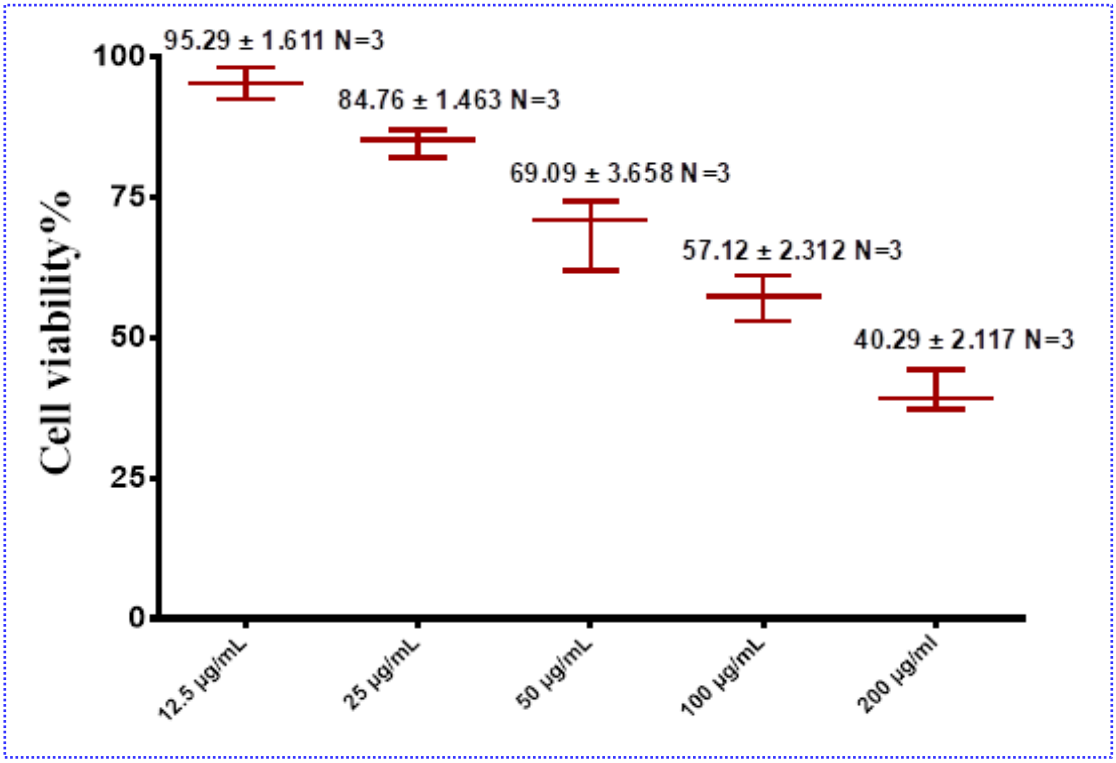


Figure (3-32) Cytotoxicity of S5 in HEp-2 cells. IC50=49.551 µg/ml

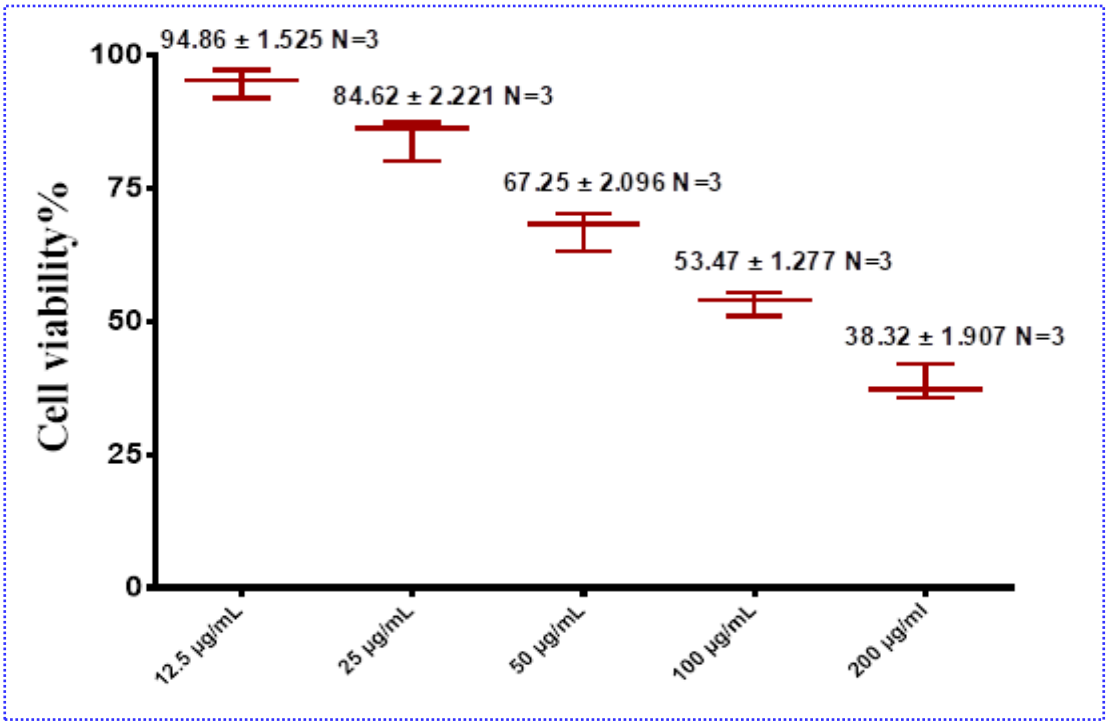


Figure (3-33) Cytotoxicity of S5 in HEp-2 cells. IC50=47.351 µg/ml

The following **figures** from **(3-34)** to **(3-38)** display the morphological changes in HEp-2 cells line before and after treated with Nano Graft Co-polymer- Drugs composites.

In cases when the efficiency rises with increasing nano drug composite concentrations [116] and in cancer cells, its toxicity reduces [117], the spread of it declines. As depicted in **Figure (3-34)** before to treatment, the cells occupy the form, exhibiting semi-regular shapes[118], a large quantity, and lack of swelling [119]. **Figures** from **(3-35)** to **(3-38)** demonstrate the small quantity and uneven shape of the cells during treatment exposure, together with the existence of swollen cells and black dots signifying the residual swelled cells that burst following treatment exposure [120].

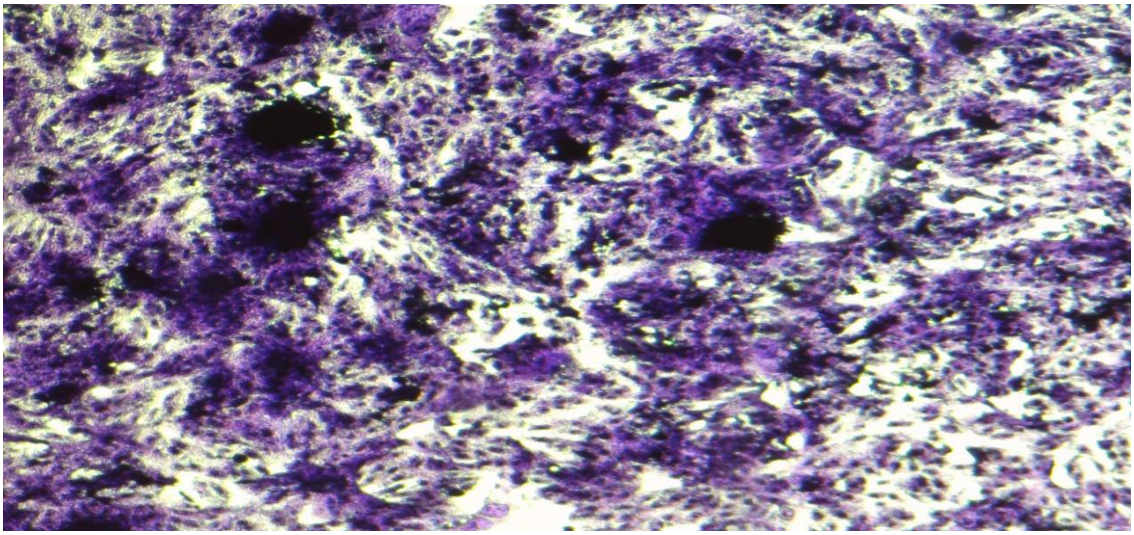


Figure (3-34) Control Un-treated HEp-2 cells

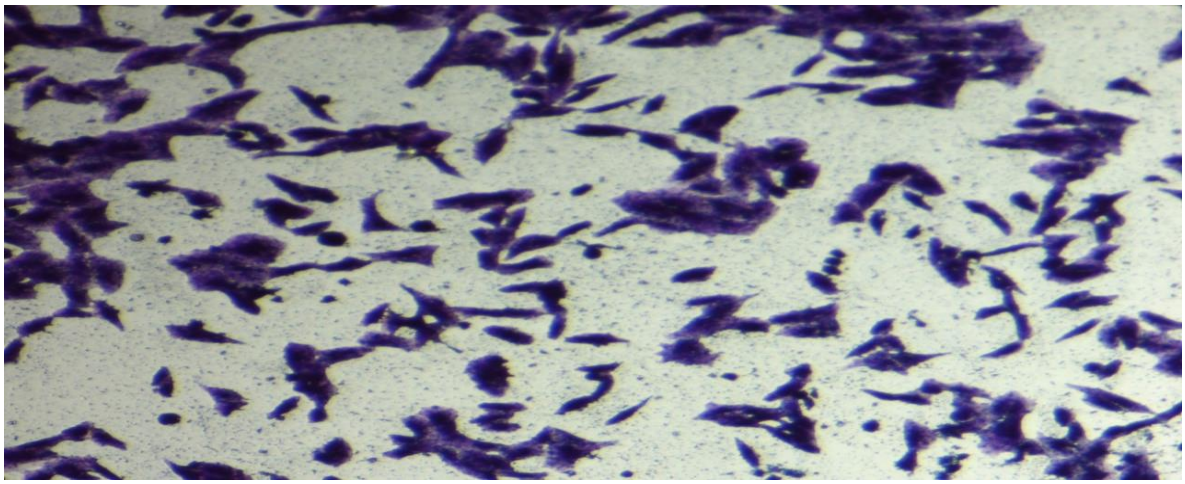


Figure (3-35) Morphological changes in HEp-2 cells after treated with S3

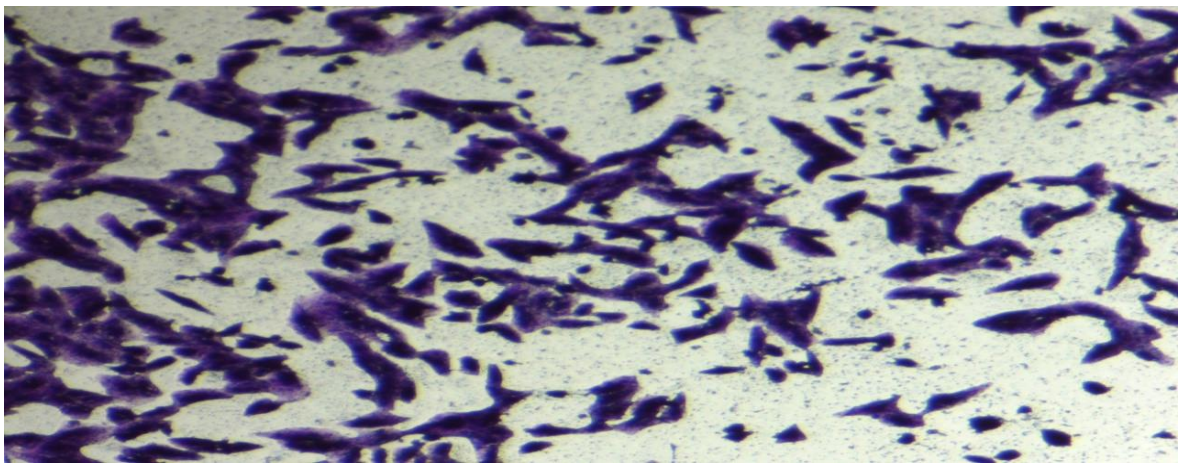


Figure (3-36) Morphological changes in HEp-2 cells after treated with S4

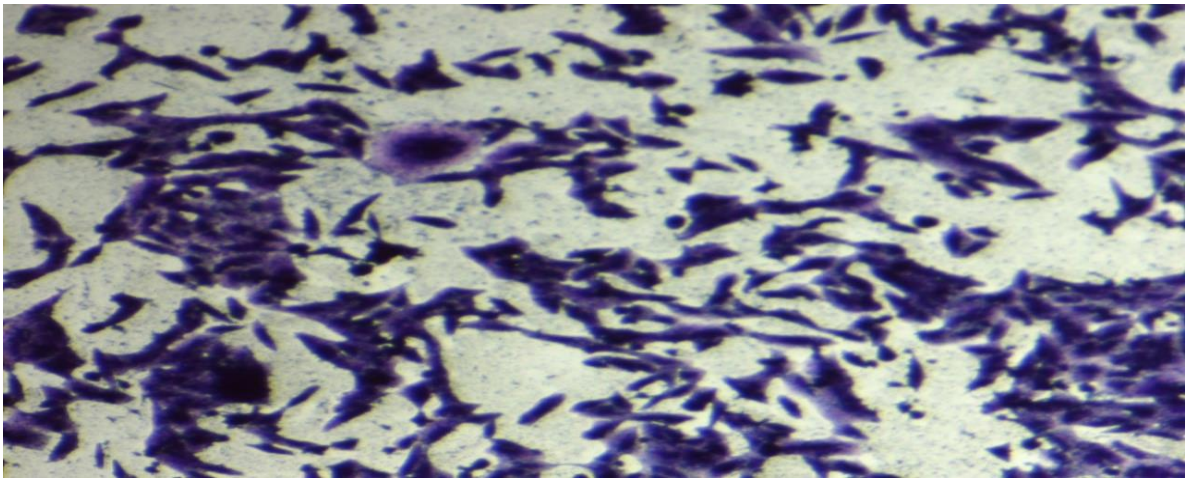


Figure (3-37) Morphological changes in HEp-2 cells after treated with S5

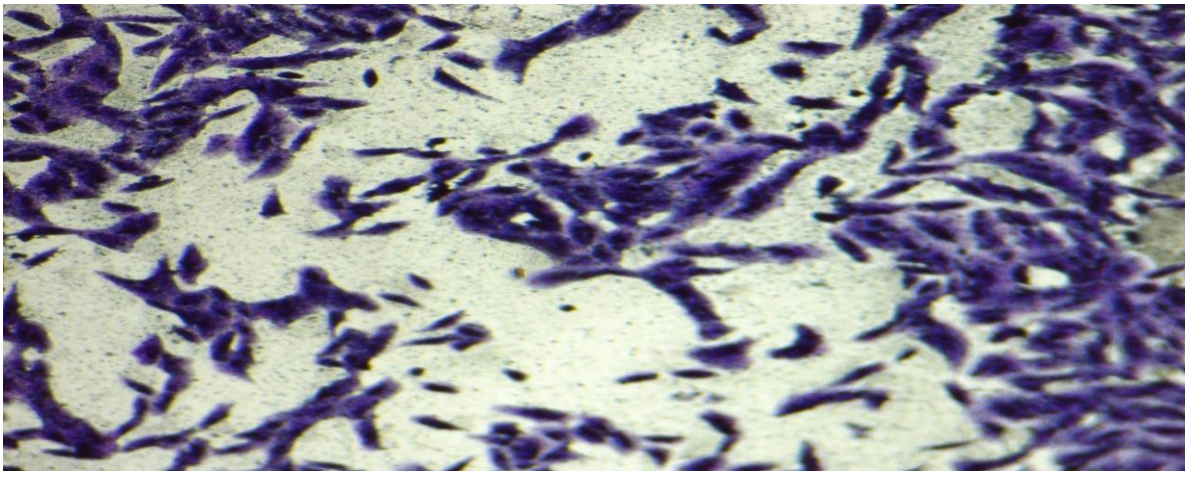


Figure (3-38) Morphological changes in HEp-2 cells after treated with S6

CONCLUSIONS

1. Synthesis of nano graft co-polymer by condensation polymerization, and characterize by FT-IR, ^{1}HNMR, AFM, and XRD techniques.
2. Synthesis of novel nano graft co-polymer-drug composites by condensation polymerization, and characterize by FT-IR, ^{1}HNMR, AFM, and XRD techniques
3. Different solvents were used to test these novel nano graft co-polymer-drugs composites solubility.
4. Drug release behavior of these novel nano co-polymer-drugs composites was assessed at various acid values (pH = 2.2, 6.0, 7.0, and 8.0).
5. Biological efficacy of the produced novel composites was investigated by examining how well they inhibited the growth of liver cancer.
6. Incredible thing about this work is that the drugs used in it were linked to a novel nano composites and used to treat liver cancer. The drugs showed remarkable results in treating and healing the affected cells as well as preventing the cancer from spreading. The drugs used in this work are well-known and used by people on a daily basis to treat specific diseases. As seen below, the medications bound with the nano co-polymer were the most successful in treating and preventing the spread of liver cancer in infected cells.

S3 > S4 > S6> S5

Recommendation

1. The creation of additional novel pharmacological co-polymers by establishing links between the polymer and the medication, as well as the potential to combine other medications to boost efficacy and prolong drug life, particularly in chronic conditions requiring daily doses, as well as to lessen toxicity and assess drug release in the individual patient.
2. The characteristics of certain pharmacological polymers synthesized at the nanoscale and potential veterinary applications can be studied.
3. Conduct in-depth research on the biological activity of various bacteria and fungus.
4. Handling of the flaws in medications that taste bitter and are marked by offensive smells or reduced water solubility.
5. Pharmaceutical polymers are characterized and assessed to determine what qualities make them useful for a range of medical applications.

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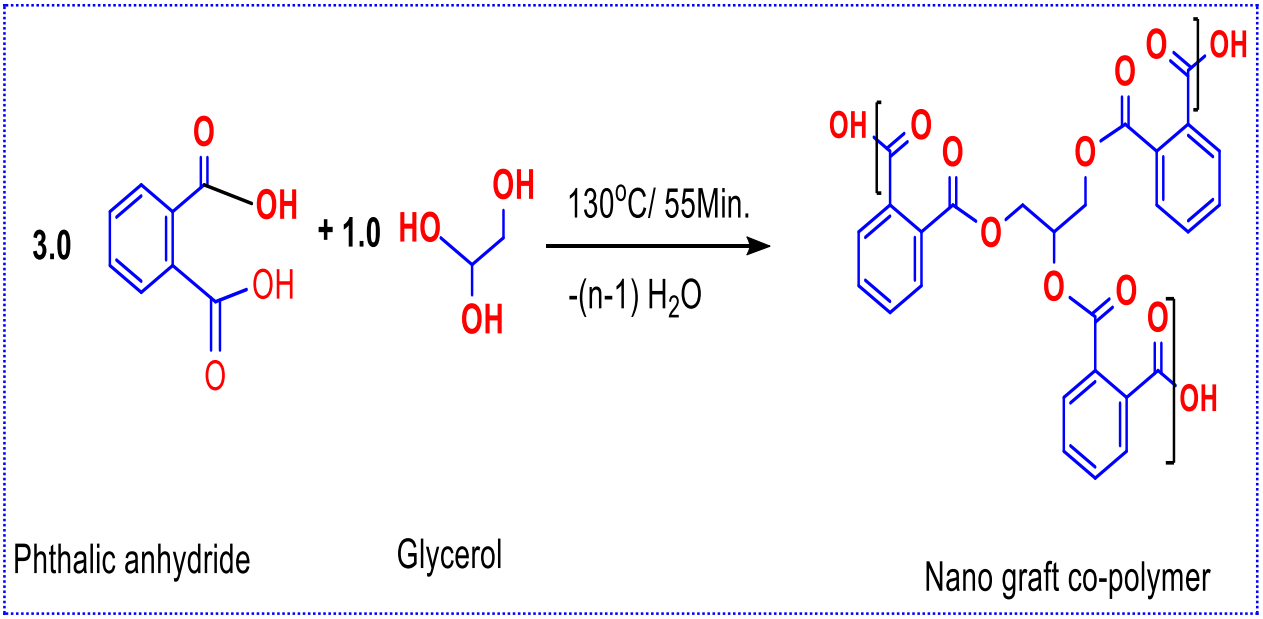
الخلاصة

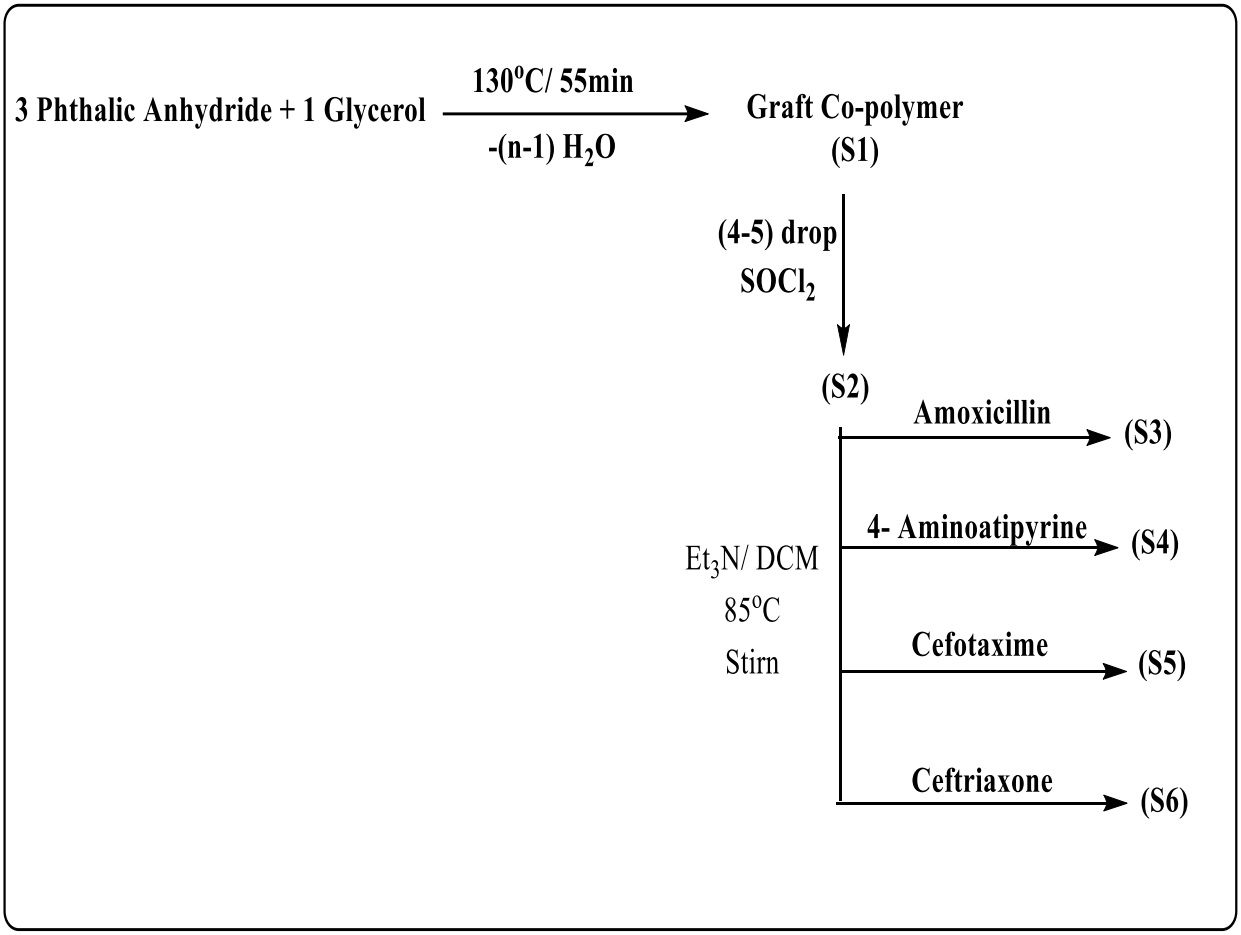
في الدراسة الحالية تم تحضير بوليمر نانوي جديد، عن طريق تفاعل مول واحد من الجلسرين مع ثلاثة مولات من أنهدريد الفثاليك عند 130°C في 55 min ، كما هو موضح في المعادلة أدناه . تم تشخيص البوليمر النانوي المحضر باستخدام تقنيات (FT-IR، H-NMR ، AFM و XRD).



تم ربط البوليمر النانوي المطعم ببعض الأدوية الشائعة مثل (أموكسيسيلين، 4-أمينوأنتيبيرين، سيفوتاكسيم، سيفترياكسون) على التوالي كما هو موضح في المعادلة، وتم تشخيص متراكبات البوليمر النانوي الدوائية باستخدام تقنيات (FT-IR, ^{1}H-NMR, ^{13}C-NMR). وكما في المخطط التالي ادناه .

تمت دراسة خصائص قابلية ذوبان متراكبات البوليمر النانوي المطعم المرتبط ببعض الأدوية في مذيبات مختلفة (H_2O، إيثانول، ميثانول، هيكسان، ثنائي مثيل سلفوكسيد، وأسيتون).

باستخدام مطياف الأشعة فوق البنفسجية المرئية، تمت مراقبة إطلاق الأدوية (Abs.) كدالة للوقت (ساعة ويوم) عند قيم pH مختلفة (2.2، 6.0، 7.2، و8.0) عند درجة حرارة ثابتة تبلغ 37°C .



تمت دراسة الالتحام الجزيئي الأكثر كفاءة لمتراكبات للبوليمر النانوي الدوائي المطعم ، ونوع وطول الاصرة ، والتنبؤ بتفاعلات ارتباط البروتين، وإعداد الموقع النشط للبروتين المستهدف فيما يتعلق بربط الأدوية ببروتينات خلايا سرطان الكبد.

تم فحص تأثير الأدوية المركبة المذكورة أعلاه على سلالة خلايا سرطان الكبد. عندما تم الجمع بين العديد من الأدوية الشائعة ومتراكبات البوليمر النانوي الدوائي، اوضحت بياناتنا نتائج إيجابية. إن مبرر ذلك هو أن الدواء يجب أن يستمر في العمل لفترة زمنية كبيرة حتى يستهدف مناطق معينة من الجسم بكفاءة أكبر، وفي نفس الوقت يمنع الآثار الضارة على مناطق أخرى من الجسم. انخفضت نسبة هذه الخلايا بشكل كبير، مما يشير إلى أن متراكبات البوليمر النانوي الدوائي كانت فعالة بيولوجيًا للغاية في منع انتشار سرطان الكبد بسرعة في جميع أنحاء الخلايا. وعلاوة على ذلك، كانت فعالية متراكبات البوليمر النانوي المطعم في منع انتشار سرطان الكبد كالاتي:

$$S3 > S4 > S6 > S5$$

جامعة كربلاء
كلية التربية للعلوم الصرفة
قسم الكيمياء

تحضير وتشخيص متراكبات نانوية دوائية ودراسة قابليتها على تثبيط سرطان الكبد

رسالة مقدمة إلى مجلس كلية التربية للعلوم الصرفة، جامعة كربلاء

وهي جزء من متطلبات نيل درجة الماجستير في علوم الكيمياء

كُتبت بواسطة:

سرور فالح حسن جمعه

بكالوريوس كيمياء/ كلية التربية للعلوم الصرفة / جامعة كربلاء 2018

بإشراف

أ. د. محمد ناظم بهجت البياتي

م. د. زياد طارق حبيب

جمادى الأولى 1446هـ تشرين الثاني 2024 م