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Ministry of Higher Education
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University of Kerbala
College of Education for pure Science
Department of Chemistry

Synthesis and Characterization of a Novel Nano Co-Polymer as Drug Delivery and Studying Its Ability to Inhibit the Spread of Breast Cancer

A Thesis
Submitted to the Council of College of Education for pure Science University of Karbala/ In Partial Fulfillment of the Requirements for the Degree of Master in Chemistry Sciences

By

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1443 **2021**


بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
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وَحْيُهُ وَقُلْ رَبِّ زِدْنِي عِلْمًا)
[طه: 114]

Supervisor Certification

We certify that this thesis (**Synthesis and Characterization of a novel nano co-polymer as drug delivery and studying its ability to inhibit the spread of breast cancer**) was papered under our supervision in the Department of Chemistry-College of Education for Pure Sciences/ University of Kerbala, in partial fulfillment of the requirements for the degree of Master in Chemistry Sciences by the student (**Zainab Musa shakir**).

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Prof. Dr.
Mohammad Nadhum Bahjat
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In view of the available recommendations, I forward this thesis for debate by the examining committee.

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We certify that, we read this thesis **(Synthesis and Characterization of a novel nano co-polymer as drug delivery and studying its ability to inhibit the spread of breast cancer)** and as examining committee examined the student (**Zainab Musa shakir**) in its content, and that in our opinion it is adequate (**Excellente)** with standing as a thesis for degree of master in chemistry sciences.

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Dean of the College of Education for Pure Sciences

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ZAINAB

Dedication

Specially dedicated

This humble effort

To my master, Imam Al-Hujjah, may God hasten his reappearance

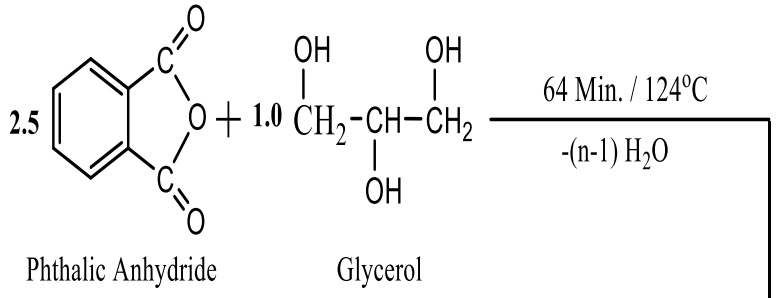
And Aba al-Fadl al-Abbas, peace be .upon him

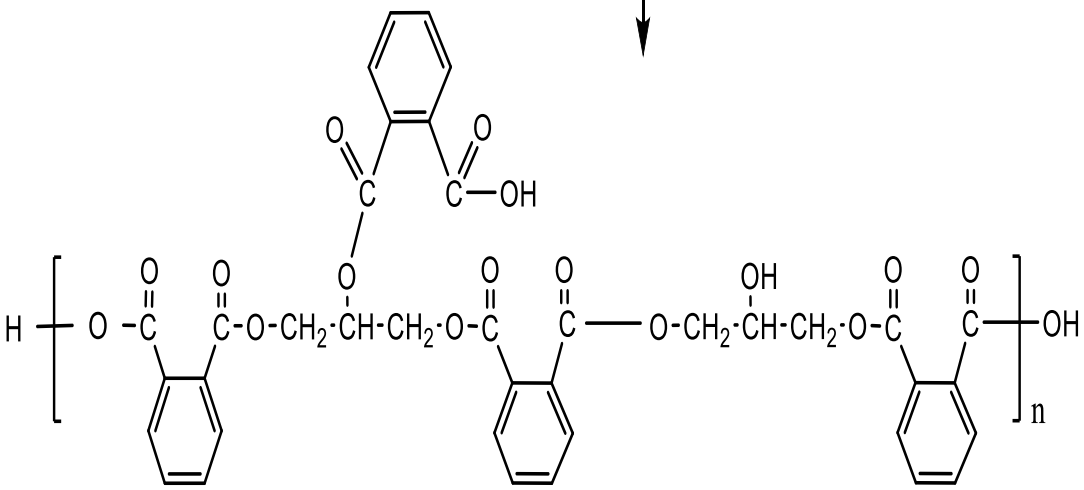
To the beat of my heart, my mother, my father, my sisters and my love

ZAINAB

Abstract

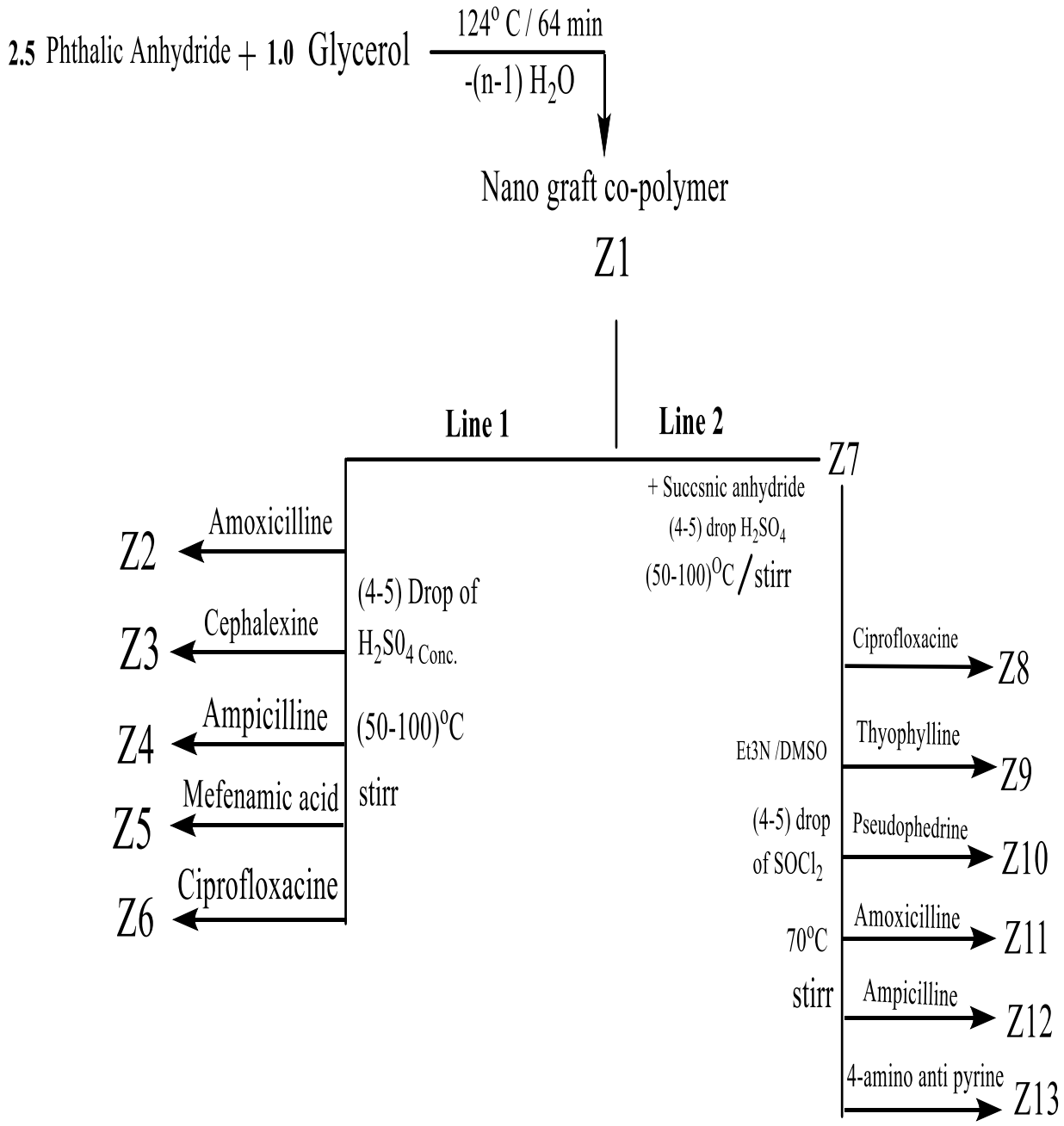
In this work, a novel nano particle graft co-polymer was synthesized using solubilization process by condensation polymerization from the reaction of one mole of glycerol with 2.5 moles of phthalic anhydride at 124°C in 64 min. with the release of water as by-product, as showed in the Equation below. The product, nano co-polymer was identified by (FT-IR, ^{1}HNMR, DSC, AFM, XRD and TEM).





(Nano graft co-polymer)

Synthesis several nano co-polymer-drugs by using different drug (Amoxicillin, Cephalexin, Ampicillin, Mefenamic acid, Ciprofloxacin, Pseudoephedrine, Theophylline and 4-Aminoantipyrine) respectively, by two different methods as shown in following scheme:



The solubility behavior and swelling ratio was studied for all the synthesis of nano graft co-polymer-drug samples in three different media pH (2.2, 7.0 and 8.0) at constant temperature 310K as function of time (hour and day).

Release of drugs (Abs.) was measured by using UV-Vis spectrophotometer in three different media pH (2.2, 7.0 and 8.0) at constant temperature 310K as function of time (hour and day).

The effect of drugs loaded on the nano co-polymer (Z3, Z4, Z5, Z6, Z8, Z9, Z10, Z11, Z12 and Z13) on inhibition of the spread of breast cancer was measured, and the results showed that the drugs had a different effect, as they varied between a high effect and a low effect. IC50 value was significantly decreased in Z8 (IC50=12.64) in comparison with pure drugs and induced an apoptotic cell death pathway. The effectiveness the synthesis nano graft co-polymer-drugs in inhibiting the spread of breast cancer was in the following order:

$$Z8 > Z6 > Z9 > Z12 > Z10 > Z3 > Z13 > Z11 > Z4 > Z5$$

$\longleftarrow$

Increasing efficacy

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List of Abbreviations

Symbol	Description
Et_3N	Triethyl ammine
EtOH	Ethanol absolute
FT-IR	Fourier Transform Infra red
DSC	Different Scanning Calorimetry
AFM	Atomic Force Microscope
XRD	X-Ray Diffraction
TEM	Transmission Electron Microscopy
T	Temperature
UV-Vis	Ultraviolet-visible
^{1}HNMR	Proton nuclear magnetic resonance
DMSO	Dimethyl sulfoxide
SOCl2	Thionyl Chloride
DDS	Drug Delivery System
PK	Pharmacokinetics
BD	Biological Distribution
ADME	Absorption, Distribution, Metabolism, Excretion
MDR	Multiple Drug Resistance
RPMI 1640	Roswell Park Memorial Institute

CHAPTER ONE

Introduction

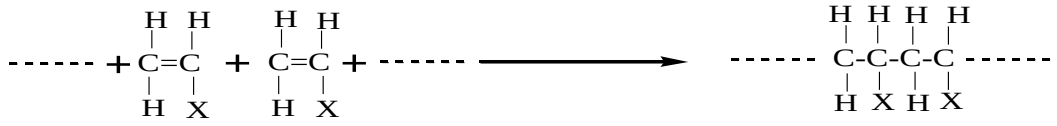
1. INTRODUCTION

1.1 Polymerization Processes

Traditionally, polymers have been classified into two main groups Addition polymers and Condensation polymers. This classification was first proposed by Carothers [1], addition polymerization, is based on whether or not the repeating unit of the polymer contains the same atoms of the monomer in its repeating unit, while condensation polymers contain fewer atoms, because of the formation of by-products during the polymerization process. The corresponding polymerization processes would then be called addition polymerization and condensation polymerization. As was mentioned earlier, this classification can lead to confusion, since it has been shown in later years that many important types of polymers can be prepared by both addition and condensation processes [2]. Recently, the emphasis has changed to classify polymers according to whether the polymerization occurs in a stepwise fashion (step growth) or by propagating from a growing chain (chain growth) [3].

1.1.1 Addition Polymerization

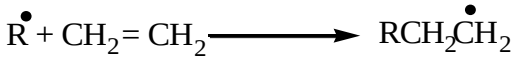
The first type of polymerization involves monomers of the type CH_2=CHX, under certain conditions, the double bond become reactive, and monomers join together (end- to- end, end-to-head or head-to-head) [4] by opening the double bond, i.e.



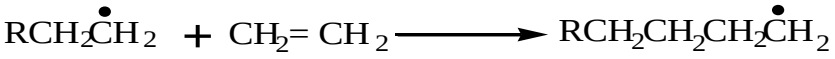
i.e. **Monomer + Monomer + ------ ⟶ Polymer**

In this linear polymer- product, the structural unit contains the same properties of atoms as does the original monomer. This type of polymer is called an addition polymer [5]. Chain-growth reactions require an initiator to start the polymerization reaction. Consider, for example, the free radical polymerization of ethylene, initiated by radical ($R^{\cdot}$) [6, 7] .

Initiation step:

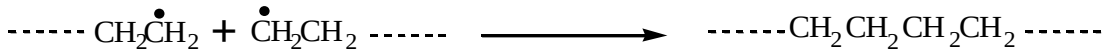


Propagation step:

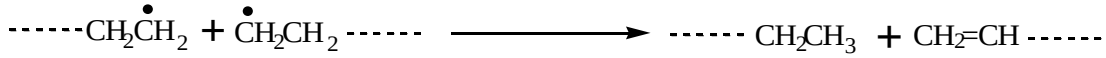


The polymerization reaction, therefore, proceeds from a reactive chain end and continues until some termination reaction such as radical coupling or disproportion renders the chain inactive. The probability of termination reaction occurring increases as monomer concentration decreases [8].

Termination step by radical coupling:

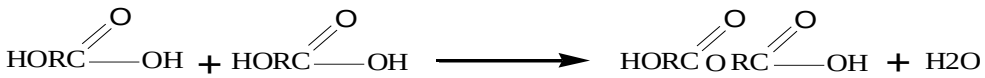


Termination step by disproportionation:



1.1.2 Condensation Polymerization

The condensation polymerization occurs when the monomer has two or more reactive, or functional groups , e.g. as in a hydroxy acid(HO-R-COOH) two molecules can react with one another with the elimination of simple , small molecule, as shown in the following example (in this case, water) [9]:



i.e. Monomer + Monomer ⟶ Dimer + Water

This type of reaction is known as condensation, and results in a dimer being formed. Another monomer can react with this dimmer to form a trimer, and so on. The product of this synthesis is a linear condensation polymer [10]. Obviously, a similar condensation reaction occurs if we have a mixture of different monomers, each of which has two reactive groups [11].

Many important commercial condensation polymers are made in this way. If the monomer has three or more reactive groups, all these can undergo a condensation reaction to give more complicated structures forming from a three-dimensional network [12]. An example for these reactions is schematically shown in Figure (1-1). In a commercial product the cross – linking reactions take place during the actual manufacture of articles from thermosetting plastics. The cross – linked network then extends throughout the article which becomes stable to heat, and can not melt or flow [13-15]:

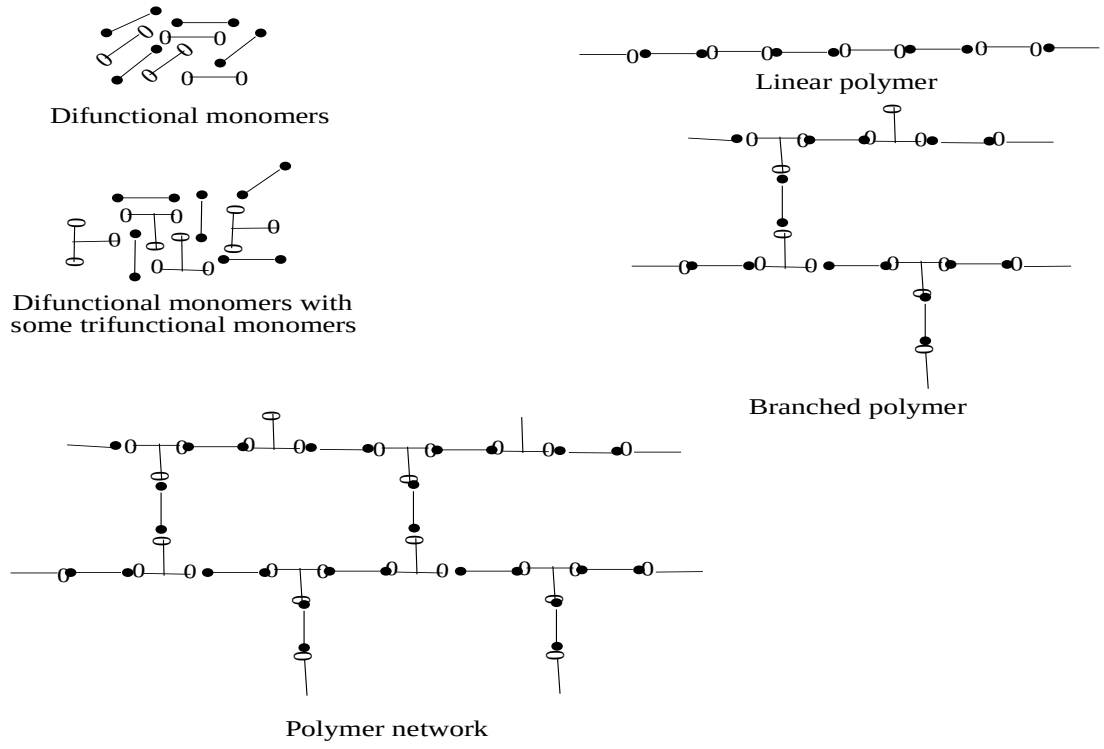


Figure (1-1): A scheme of condensation polymerization

1.2 Copolymerization

1.2.1 Addition Copolymerization

Copolymerization is the joint polymerization of two or more monomer species. High–molecular mass compounds obtained by copolymerization are called copolymers [16]. The molecular chain of a copolymer is composed of different units, in accordance with the number of initial monomers [17]. The general form of the copolymerization of two monomers can be described by Figure (1-5) [18]:

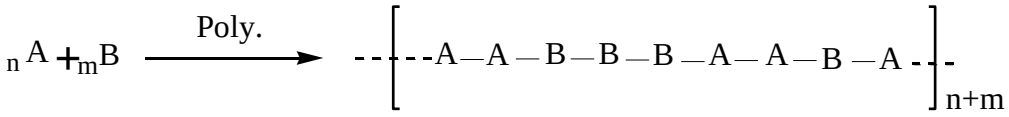


Figure (1-2): Two different monomers of copolymerization

By using different initial species and by varying their ratios, copolymers of various compositions and properties can be obtained [19].

Most copolymers are irregular in structure; the different monomeric units are randomly arranged in their molecular chains and therefore no repeating section of the chain can be singled out [20]. Copolymerization has found extensive practical usage, because it enables variation of the properties of high–molecular–mass compounds over a wide range. For instance, the copolymer of acrylonitrile and vinyl chloride, as in figure (1-6), is readily soluble in acetone, whereas poly(acrylonitrile) and poly (vinyl chloride), are soluble only in high – boiling and difficultly available solvents [21].

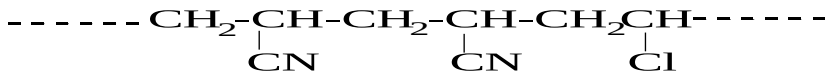


Figure (1-3): Structure of copolymer

Copolymerization is widely used in the synthetic rubber industry, and is a very important method of producing three-dimensional polymers.

Thus, polymerization of styrene in the presence of a small amount of divinyl benzene results in the three-dimensional copolymer [22].

1.2.2 Condensation Co-polymerization

If the reactants of a polycondensation have several different monomers, the result will be a copolymer [23]. The reaction of co-polycondensation has acquired great technical importance in recent years and is now widely used for the synthesis of various mixed polyesters and polyamides (e.g. containing ester and amide bonds simultaneously) and other copolymers. For instance co-polycondensation of hexamethylene-diamine, adipic acid and Terphthalic acid [24], as in the Figure (1-4):

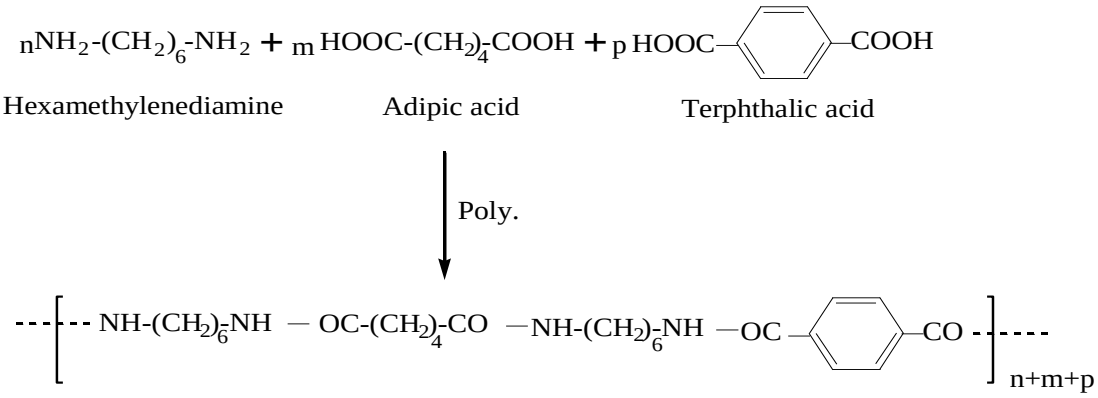


Figure (1-4): Prepared Nylon 6.6

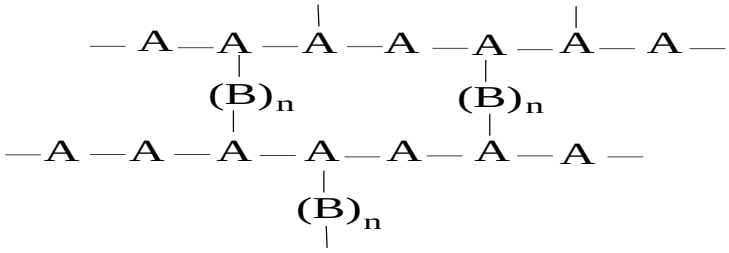
Results in a mixed polyamide of increased thermal stability; A large number of mixed polyamides are now known, containing aliphatic and aromatic diamine units, as well as, various aliphatic and aromatic dicarboxylic acid units [25]. By varying the number of aromatic radicals in the macromolecule the melting point and other physical and mechanical properties of polyamides can be varied over a considerable range [26]. The properties of the polymer can be varied over a still wider range if its molecular chain contains different bonds [27].

The polycondensation of two substances having the same functional groups but different radicals; with a third substance containing other

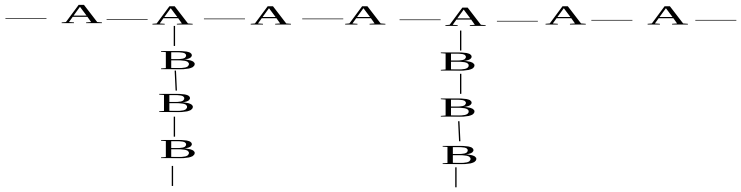
functional groups has become very popular. For example, two different dicarboxylic acids are polycondensed with a glycol or a diamine, or two diamines with one dicarboxylic acid, etc. [28]. There are several types of copolymers, they are; Block copolymers, Graft copolymers, Random copolymers and Alternating copolymers [29], Figure (1-5):

–A–A–A–A–B–B–B–B–A–A–A–

a) Alternate copolymer structure.



b) Block copolymer structure



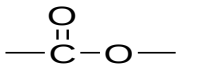
c) Graft copolymer structure

A-A-A-A-B-A-A-B-B-B-B-B-A-A-

d) Random copolymer structure

Figure (1-10): Structures of combined co-polymer

1.3 Polyester Resin

Polyesters contain esters group  in the main chain [30]. Credit for the first polyester is given to Gay- Lussac and Pelouze in 1833s and Berzelius in 1847s [31]. Polyesters are hetero chain macromolecular substances characterized by the presence of carboxylate ester groups in the repeating units of their chains [32].

The primarily deals with linear homo- and co-polyesters derived, whether actually or nationally, from the self-polycondensation of hydroxyl carboxylic acids or the polycondensation of dicarboxylic acids with dihydroxy compounds [33]. The first approach yields AB- type products having a unidirectional orientation of carboxylate ester groups in the molecular chain; the second leads to AA/ BB- type polymers with the ester groups recurring alternately in their oxycarbonyl and carbonyloxy forms [34]. In homo polyesters the carboxylate ester groups are spaced regularly along the chains, but in co-polyesters their separations may vary with the nature of the intervening skeletal groups [35].

Observations on polyesters were recorded from as early as 1833s, but their first significance through empirical appearance was with the glycerylphthalate (Glyptal) coating and impregnating materials of the world War- One period [36]. The rational study of polyesters dated from the 1990s with Kienle's [37], observations, which led to the evolution of alkyd resin technology, and more outstandingly, with research of Carothers who began with polyesters, laid the foundations of step-polymerization chemistry and the relationships among molecular structure, molar mass, and polymer properties. These principles were later elaborated systematically by Flory [38]. The resulting concepts formed the basis of Carother's [39], discovery of Nylon- 6,6 in 1935s and that of poly (ethylene terephthalate) by Winfield and Dickson[40], in 1946s events which led in a large degree to the growth of the modern synthetic textiles industry.

Other seminal discoveries were those of the late 1930s leading to the development of unsaturated polyester casting and laminating resins, and of impact- resistant polycarbonate resin in the mid- 1950s [41].

1.3.2 General preparation of polyester resin

Saturated and unsaturated polyesters are conveniently prepared by melting co-polyesterification at elevated temperatures above the melting point of the resulting polyesters [42, 43].

Unsaturated polyester resin is step- growth polymers formed by the interaction of stoichiometric mixture of saturated and unsaturated dibasic acids or anhydrides with dihydric alcohols or oxides [44]. The unsaturated acid component is fundamental to the reactivity of the low molecular weight polymers formed and is derived primarily from 1, 2-olefinic dibasic acids such as maleic acid or anhydride [45].

The commercial resins have established a significant position within the plastics industry [46]. They are typically solutions of unsaturated polyester polymers dissolved in unsaturated co- reactant liquid monomers such as styrene, to enhance reactivity and proccessibility [47]. Free-radical catalysts initiate cross-linking reactions involving the unsaturated polymer and the unsaturated co- reactant monomer, rapidly transforming the low viscosity resin into a rigid thermoset plastic state, and comprising a three- dimensional polymer network [48].

1.4 Nanoparticles polymers

Polymer nano science is the study and application of nano science to matrix polymeric nano particles, where nanoparticles are those with at least one dimension less than 100 nanometers [49]. The transition from fine particles to nanoparticles causes a change in their physical and chemical properties.

Two major factors in this are the increase in the ratio of surface area to volume, and particle size. An increase in the ratio of the surface area to volume, which increases as the smaller the size of the particles,

leads to an increasing dominance of the behavior of atoms on the surface area of the particle over the interior of the particle. This affects the properties of the particles when they interact with other molecules. Because of the high surface area of nanoparticles, the reaction with other particles inside the mixture is more and this increases strength, heat resistance, etc., and many factors change for the mixture. An example of a nano polymer is the silicon nanoparticles that exhibit completely different properties, they are 40-100 nm in size and are much more difficult than silicon, their hardness between rubies and diamonds [50].

Various methods are used to prepare polymeric nano-particles, which are evaporation of solvents, spontaneous emulsification, diffusion of solvents, or polymerization. Methods of preparing polymeric nanoparticles are classified under three techniques [51]:

1. Preparation of nanoparticles from a dispersion of preformed polymers, including solvent evaporation, nano precipitation, emulsification, salting out, dialysis, and supercritical fluid.

2. Polymerization of monomers, including emulsion, miniemulsion, microemulsion, interfacial polymerization, and controlled/living radical polymerization.

3. Ionic gelatin or coacervation of hydrophilic polymers.

The choice of a suitable method for the production of polymeric nanoparticles depends on various factors, such as particle size, the types of solvents and polymers used for synthesis, the scope of application, etc. For controlled / sustainable release in drug delivery systems; Polymeric nanoparticles can be either nanocytes or nanoparticles [50].

Nanoparticles Polymer has a matrix structure consisting of biodegradable and biologically compatible polymers of synthetic or natural origin. The most widely used synthetic polymers are polylactide, polylactide–polyglycolide copolymers, polycaprolactones, and polyacrylates, Lactide–glycolide copolymer is an extensively explored copolymer. Among the various natural polymers, alginate and albumin or chitosan have been widely explored. Several formulation and process parameters that affect the release volume and coil and the stability of polymeric nanoparticles are drug solubility, drug-to-polymer ratio, molecular weight, polymer composition, solvent, pH, homogeneity speed, and mixing time [52].

Nanoparticles Polymer are solid colloidal molecules with a size between 10-100 nm, and are made of biodegradable polymers or copolymers that are biocompatible and compatible, as the drug can be locked or encapsulated inside the carrier, physically adsorbing on the carrier surface or chemically bound to the surface. These nanostructures are known for their attractive properties, such as small size, biological degradation, water solubility, non-toxicity, long shelf life, and stability during storage. These properties make it a point of interest for the delivery of drugs, proteins, DNA or genes to specific target tissues or organs. Consequently, it is applied in anti-cancer treatment, vaccine and gene therapy, diagnosis, and many other uses in the medical file [53].

The previously study dealt with preparation of graft co-polymer by reaction of one mole of glycerol which has three hydroxyl groups, with two moles of Terphthalic acid monomer, which have two groups from carboxylic acid. This reaction will give one point of hydroxyl group that can react with fumaric acid to form graft co-polymer which can make cross-linking with the added monomer [54].

Another study [55], dealt with preparing a new carrier polymer through two steps, which included modification of polyacrylic acid (P1) with ethanol amine producing N-ethanol acrylic amide polymer (P2) then reacting it with Mefenamic acid would give Mefenamate ester polymer (P3) as a new drug carrier polymer. Ethanol amine was used as spacer between polyacrylic acid and Mefenamic acid, which could have a potential use as a carrier for drug delivery system

Other studies [56], concerned with preparation two groups of nano composite material, from unsaturated polyester resin (UPE). This study includes the effect of selected volume fraction (0.5%, 1%, 1.5%, 2%, 2.5%, 3%) for both reinforcement nano materials. Experimental investigation was carried out by analyzing the thermo-physical properties like thermal conductivity, thermal diffusivity and specific heat for the polymeric composites samples, as well as the hardness test. The results showed that the values of (hardness, specific heat) increased as the nanoparticle content in composite samples increased for both groups' nanocomposites, whereas the values of thermal conductivity and thermal diffusion decrease for both of groups composites. In another study unsaturated polyester/nano ceramic composite were manufactured and the study of the effect of addition of filler (nanoparticles SiO_2 treated with silane) at different weight ratios (1, 2, 3, 4 and 5) %, on electrical, mechanical and thermal properties. Materials were mixed with each other using an ultrasound, and then the mixture was poured into the molds to suit all measurements. The electrical characteristics were studied within a range of frequencies (50-1M) Hz at room temperature, the mechanical properties at the filler ratio (2%) [57].

1.5 Drug polymers

Polymers are useful as therapeutic agents, that exhibit pharmacological properties, before that, they can be utilized as carriers for selective and sustained delivery vehicles for small molecule or macromolecular (e.g. proteins, genetic materials, etc) pharmaceutical agents [58]. Chemical modifications can cause a change in the properties of biodegradable polymers. A large group can be obtained, and many adjustments can be made with other industrial polymers that are correctly formed [59]. There are industrial polymers that have many therapeutic activities, and the researchers focused on stimulating polymers with therapeutic properties by attaching a polymer to a drug by means of a covalent adherence, so polymers have become of great importance in pharmacological applications, especially in drug delivery [60]. Natural and synthetic polymers have been used extensively in the manufacture and development of pharmaceutical products and have several applications including: masking undesirable taste, drug delivery, altering the flow characteristics of the active pharmaceutical product, modifying drug release properties and inhibiting the crystallization of active pharmaceutical products [61]. The work of pharmacological polymers in the body always depends on the hydrolysis of the enzymatic divisions of the modified drug from the polymer and this allows benefiting from delayed and continuous drug release for a long time while reducing side effects. And polymers, this condition include the slow release of water-soluble drugs, the rapid release of low-water-soluble drugs [62].

Biodegradable polymers with response properties or effective combinations have been widely achieved for liberation control and drug delivery applications, biodegradable polymers such as poly (alpha-acetic acid) with effective carboxyl groups can be combined with drugs via an

amide or ester to form a degradable molecular auxiliary drug to reduce From the side effects of free drugs, drugs can be released by the decomposition of degradable polymers [63]. Most medications require many daily doses in order to achieve the appropriate concentration required. Therefore, focus was placed on the delivery of the drug to be prolonged effect, that the prolonged system of effect provides a steady release of the drug over a longer period of time and therefore, there are appropriate regular concentrations within the therapeutic window in order to reduce side effects and reduce the number of times the drug was taken and the patient's acceptance of the drug improved [64].

Industrial polymers are of great importance in the delivery of the drug as a therapeutic agent, usually polymers show good pharmacokinetic movement compared to drugs with small molecules and have a longer time for diffusion and the ability to target tissue like proteins and polynucleotide acids. If the polymer is not a drug in itself, it plays an ineffective role as a drug carrier, reducing immunity, toxicity or degradation with the possibility of a negative targeting function in this case, the polymer should be non-toxic. Soluble in water and should be safe throughout the entire delivery stages of the drug (before and after release of the drug) [65].

1.6 Drug loaded

Over the past few decades, nanoparticle (NP) formulation has been the subject of extensive research. The choice of a suitable NP formulation technique is dependent on the physicochemical properties of the drug, such as solubility and chemical stability. Different NP manufacturing methods enable modification of the physicochemical characteristics such as size, structure, morphology and surface texture, but also affect the drug

loading, drug entrapment efficiency and release kinetics [66]. This review covers an update on the state of art of the manufacturing of polymeric NPs from preformed polymers. Both, conventional methods for NP preparation, such as spontaneous formulation and emulsification-based methods, and new approaches in NP technology are presented. A comparative analysis is given for polymer, drug and solvent nature, toxicity, purification, drug stability and scalability of the method. The information obtained allows establishing criteria for selecting a method for preparation of NPs according to its advantages and limitations. The drug loaded polymeric material containing a therapeutic drug can be applied to a structure of an intravascular stent. A therapeutically effective amount of a therapeutic drug is incorporated into such a layer of polymeric material, without significantly increasing the thickness of the stent, to avoid interfering with the function of the stent. The drug loaded polymer coating of the stent can formed to include pores, can be multi-layered to permit the combination of a plurality of different drug containing materials in a single stent, and can include a rate controlling membrane to allow for controlled retention and delivery of selected drugs within the affected blood vessel upon implantation [67]. The layer of polymeric material is manufactured by combining the selected polymeric material with a relatively high loading of the therapeutic drug in a thermal process, such as co-extrusion of the therapeutic drug with the polymeric material [68]. The therapeutic drug is dispersed and incorporated into the polymer as small particles, preferably having a maximum cross-sectional dimension of 10 microns [69].

1.7 Drug release

Control systems seek to improve the effectiveness of pharmacotherapy. This improvement includes reducing side effects and

increasing the therapeutic activity for a longer period and reducing the number of times taking the drug during the treatment period such as repeated injections. This can achieve two types of control over drug liberation, which is time and distribution [70].

It is the process of leaving the drug to its pharmaceutical form to become available for distribution, disposal, absorption and metabolism and eventually becomes ready for the pharmacological action and the liberation is divided into [69, 70]:

1) Direct liberation: It is the immediate availability of the drug for the pharmacological action or absorption as the drug is allowed to dissolve without prolonging dissolution, delay, or absorption of the drug.

2) Modified liberation. There are many patterns of modified pharmaceutical forms of liberation, including prolonged liberation. A prolonged therapeutic effect of the drug is achieved by continuous release during a period of time that extends after applying a single dose. The benefit of these forms is to reduce the number of times taking the drug at least twice from it in forms with direct liberation.

1.8 Drug delivery system

Polymeric drug delivery systems have been considered in many applications to supplement standard methods for medical treatments and it has appeared that these drug delivery systems are less and less difficult than mechanical pumps because the drug can be stored as a pow. Medication delivery systems are one of the human health care applications and are an ever evolving field of medical material science, and the medication delivery system controls the duration and rate of drug

delivery and targets specific areas of the body, and is designed to maintain therapeutic levels during the treatment period [71].

There are new systems for drug delivery that can Control it as it responds to environmental conditions such as light, visible or ultraviolet radiation, pH, and the electric field, and some chemicals are explored [72]. Drug delivery systems are important in controlling the rate of drug release in the body and the focus of optimal treatment, and that monitoring the drug concentration through direct tracking of the dyes associated with the drug molecules may be difficult because the drug signals may result from unedited drugs, or drugs that are absorbed by the cells or free medicines that show low-intensity signal [73].

The drug delivery system includes binary conjugation (drug-polymer conjugation) and depends only on the mechanism of ineffective targeting and it certainly faces real restrictions on its specificity. One of the suggested methods for eliminating these restrictions is to include an antibody or to target targeting in the drug-polymer association, depending on the preparation method. Either joint, physical, or covalently bonded with the polymer [74]. The system for delivering medicine through the stomach improves the delivery of the tightly controlled drug that has a narrow absorption window through the continuous release of the drug for a long period before arriving at its place of absorption to ensure optimal biological availability [75].

There are three advantages offered by polymeric drug delivery products, namely: drug stability, continuous drug delivery, a lower rate of release depending on the properties of the drug. In systems whose prevalence is controlled, the release rate decreases with time [76]. The appropriate drug delivery system can alter the behavior of chemotherapy

release factors and thereby improve the effectiveness of anti-cancer activity [77]. The way in which the medicine is delivered has an effect on the therapeutic efficacy of the drug, some medications have a better range of concentrations in which they derive the greatest therapeutic benefit, that the concentration of the drug above or below this range is toxic or does not produce a therapeutic benefit [78]. Many of the traditional pharmacological features can be improved using drug delivery systems (DDS). They include particle transporters that consist of fats. Medication delivery systems are designed to change pharmacokinetics (PK) and the biological distribution (BD) of the related drugs or to act as a medicine reservoir (i.e. liberating systems) Continuing) or both [79]. Several drug delivery vectors have evolved to improve the performance of many anti-cancer drugs by enhancing their effectiveness as well as the efficiency of cell absorption [80]. Although there is a significant development in drug delivery systems to overcome difficulties in conventional diagnosis and treatment, there are many problems that need to be resolved, for example, enhancing water solubility and stabilizing anti-cancer drugs to prolong their spread in the blood and targeting cancerous tissues because most anti-cancer drugs have susceptibility Low solubility in water, selective low tumor and side effects of healthy tissue [81].

There are important things in developing drug delivery systems, namely that drug carriers must have a good compatibility with life and be able to target specific harm to improve drug efficacy and reduce side effects [82].

Nanoparticles are used as a drug delivery system as they can be easily manufactured, degradable biological properties and low cellular toxicity, and new drug delivery systems are being developed and

explored to improve drug delivery efficiency as well as low cellular toxicity [83].

1.9 Biological activity

Biochemical activity or pharmacological activity in pharmacology describes the beneficial effects of a drug or a drug on living matter. When a drug is a complex chemical mixture, this activity is done through the active substance of the drug; the biochemical activity plays a chemical role because it suggests the uses of compounds in medical applications. Chemical compounds may exhibit some toxic and negative effects that may prevent their use in medical applications [84]. Activity is generally dose-dependent. The activity critically depends on meeting ADME standards. To be effective, the compound should not only be active against the target but also have the ADME properties needed to make it suitable for use as a medicine. The substance is biologically active if it interferes with or affects any cellular tissue in the human body, and the drug activity is taken to describe the beneficial effects, the toxicity of the substance as well as the candidate's effects on the drugs [85]. The good relationship between observed and predicted biological activities allows for the formation of new derivatives from the compound (the most active group molecule) with improved pharmacological properties [86]. The interactions of living organisms against bio toxicity threats have been developed, for example, in the concept of survival attraction as driven by the butterfly diffraction phenomena, which are closely related to the phase-by-stage disaster [87].

1.10 Anticancer

Cancer is a range of diseases characterized by abnormal growth and spread of abnormal cells and is considered one of the most serious

diseases in the world, where it represents the second most cause of death in the united States and Europe after cardiovascular diseases according to the facts of cancer numbers 2016[88] . Most type's recurrent cancers are cancers of the colon, prostate, breast, lung and rectum as a sex function. The lung cancer is most common in men and breast cancer is prevalent in women, cancer. Despite the great progress that has been made against cancer, this disease remains a major year health concerns and a huge burden on all communities [89]. Cancer management includes surgery, chemotherapy and radiotherapy. The development of chemical resistance is an underlying and persistent problem during chemotherapy. Cytotoxic drugs are selectively targeted, not exclusively, actively targeted the proliferating cells include such diverse groups as clotting factors, division, DNA and metabolite control, and exchange factors [90]. Inhibitors is the resistance of the components to non-response to inhibition of tumor growth caused by drugs; which can be obtained as a cellular response to exposure to drugs or may be inherent in subpopulation of heterogeneous cancer cells which may include variable membrane transport that includes a p-glycoprotein product of the multidrug gene (MDR) as well as other enzyme target change and associated proteins, reduced drug activation, drug disruption due to association with increased glutathione [91], enhanced DNA repair, increased drug degradation due to variable expression of drug metabolism enzymes, drug interaction, Cell redistribution, and apoptosis in apoptosis due to a changing cell cycle [92].

1.11 Test techniques

1.11.1 Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) is a thermal analytical technique in which the difference in the amount of heat required to increase the sample and reference temperature is measured as a function of temperature. The sample and reference are kept at about the same temperature throughout the experiment. Generally, the temperature program for DSC analysis is designed to increase the sample carrier temperature linearly as a function of time. The reference sample must have a well-defined heat capacity over the temperatures to be scanned [93].

DSC is widely used to examine polymeric materials to determine thermal shifts. Important thermal shifts include the glass transition temperature (Tg), crystallization temperature (Tc), and melting temperature (Tm). The observed thermal shifts can be used to compare materials, although shifts alone do not uniquely define the composition. The formation of unknown substances can be supplemented with complementary techniques such as infrared spectroscopy. Melting points and glass transition temperatures are available for most polymers of standard classifiers, and the method can demonstrate the degradation of the polymer by lowering the expected melting temperature. Tm is based on the molecular weight of the polymer and its thermal history [94].

1.11.2 Atomic Force Microscope (AFM)

The atomic force microscope (AFM) is a very high-resolution type of scanning microscope (SPM), with precision fixed to the order of nanometer fractions, more than 1,000 times better than the optical diffraction limit. Information is collected by "feeling" or "touching" the

surface using a mechanical probe [95]. AFM is used for quantitative and qualitative data based on various properties such as morphology, size, surface roughness, texture, strength between the sharp probe tip (<10 nm) and the sample surface, with a 0.2-10 nm probe - the sample separation is measured. The probe is attached to a cable that deflects upon reaction; this deflection is measured by the reflection of the laser beam by the method of "beam bouncing"; So the topography of the surface is measured directly with cantilever deviations. The topography map takes the form of different peaks represented by different hues (red, orange, yellow, etc.) or gray tones. In this way an image of a multi-colored surface topology can be produced that can be very useful [96].

Sample properties such as size of parts, mechanical properties such as hardness or adhesion force, and electrical properties such as conductivity or surface voltage can be measured [97].

AFM has many advantages over SEM. Unlike electron microscopy, which provides a two-dimensional projection or two-dimensional image to a sample, AFM provides a three-dimensional surface appearance. In addition, the samples viewed do not require any special treatments (such as metal / carbon coating) that will alter the sample or be irreversibly damaged, and do not usually suffer from the shipment of artifacts in the final image, AFM can provide higher resolution than SEM [98].

1.11.3 X-Ray Diffraction (XRD)

X-ray diffraction (XRD) is a powerful technique for characterizing crystalline materials, Provides information about preferred crystal structures, phases, orientations (texture), and other structural parameters such as average grain size, crystallization, stress, and crystal defects. X-ray diffraction peaks are produced by constructively interfering with

a monochromatic ray of X-rays scattered at specific angles from each group of lattice planes in the sample [99].

X-rays can be considered waves of electromagnetic radiation. Atoms are spread by X-ray waves, primarily through the electrons of the atoms. Just as the ocean wave hits the lighthouse, the secondary circular waves emanating from the lighthouse are produced, so the x-rays that strike the electron produce secondary spherical waves emitted by the electron. This phenomenon is known as flexible scattering, and the electron (or lighthouse) is known as a scatter. A uniform set of scatters produces a uniform set of spherical waves [100]. Although these waves cancel each other in most directions through destructive interference, they add constructively in some specific directions, determined by Bragg's law:

$$\mathbf{n\lambda = 2dsin\theta}$$

Where d is the spacing between the diffracting levels, θ is the angle of incidence, n that is an integer, and λ is the wavelength of the beam. These specific trends appear as diffraction pattern spots called reflections. Consequently, X-ray diffraction is caused by an electromagnetic wave (X-rays) that collides with a uniform set of scattering (the repeated arrangement of the atoms inside the crystal) [101].

1.11.4 Transmission Electron Microscopy (TEM)

The transmission electron microscope (TEM) is widely used for decades to study the morphology of synthetic polymers. It remains an essential tool, especially due to the inherent ability of these materials to hierarchically structure themselves on multiple length ranges and produce morphologies that lead to progress in functionality and application, as the most detailed and powerful technology was available to photograph materials. TEM allows a qualitative evaluation of the internal structure

and spatial distribution of various stages through direct visualization, along with the occurrence of intercalated and exfoliated nano composites, and the formation of sintered structures. Although TEM represents a powerful tool for describing nano composites, problems related to preparing a tough sample and modifying the latter should be considered [102,103]. When preparing samples for studies of nano composites, ultrathin samples (<100 nm) are produced and used for TEM imaging. This is a common method for preparing samples for polymeric materials. The thickness of the slides is usually less than 100 nm to achieve a good signal-to-noise ratio and sufficient transmission variation, and in TEM imaging it allows sufficient electron transmission through the sample to obtain a signal for imaging [104, 105].

1.12 Aims of the work

The aim of this work can be summarized as follows:

1- Synthesis of a novel nano co-polymer and characterized by FT-IR, ^{1}H-NMR, AFM, TEM, XRD and DSC techniques.

2- Synthesis two lines of a novel nano co-polymer-drugs through the reaction of the nano co-polymer with different drugs (Amoxicillin, Ampicillin, Ciprofloxacine, Cephalexin, Mefenamic acid, Theophylline and Pseudoephedrine), and characterized by FT-IR and ^{1}H-NMR techniques.

3- Studying some of properties of novel nano co-polymer-drugs, such as, solubility, release of drug.

4- Study the biological activity, by studying the possibility of using novel nano co-polymer-drugs known to be used to inhibit the speed of spread of breast cancer and treat it.

CHAPTER TWO

Experimental

2. Experimental Part

2.1 Chemical and Techniques

2.1.1 Chemicals

Table (2-1), show all solid and liquid chemical materials which are used in this work.

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

Materials	Company	Purities (%)
Malic anhydride	Fluka	95.5
Phthalic anhydride	ALPHA	99
Glycerol	BDH	99.5
Para xylene	MERCH	99
Ethanol absolute	BDH	99.9
Acetone	BDH	99.8
Hexane	BDH	99.7
Dimethyl sulphxide	BDH	98.9
Thionylchloride	Fluka	99.9
Trimethylamine	Fluka	99.5
Borax	BDH	99
KCl	BDH	99
4-amino anti pyrin	G. Com. Pharma. Ind. / Samarra / Iraq	99.9
Cephalexin	G. Com. Pharma. Ind. / Samarra / Iraq	99.9
Pseudoephedrine	G. Com. Pharma. Ind. / Samarra / Iraq	99.9

Theophylline	G. Com. Pharma. Ind. / Samarra / Iraq	99.9
Amoxicillin	G. Com. Pharma. Ind. / Samarra / Iraq	99.9
Ampicillin	G. Com. Pharma. Ind. / Samarra / Iraq	99.9
Ciprofloxacin	G. Com. Pharma. Ind. / Samarra / Iraq	99.9
Mefenamic acid	G. Com. Pharma. Ind. / Samarra / Iraq	99.9

2.1.2 Techniques

1- Fourier Transformer Infra-Red Spectroscopy (FT-IR) spectra in range 400-4000 cm^{-1} were obtained by using potassium bromide disc on FT-IR–instrument Bruker spectrophotometer /USA, Department of Chemistry/College of Sciences/ University of Babylon

2- ^{1}H-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.-Vis. Spectrometer, (Jenway Genova Plus), Department of Chemistry/College of Education for Pure Sciences/ University of Kerbala

4- Atomic Force Microscope (AFM), Oxford, USA / Department of Chemistry/ College of Sciences / Baghdad University.

5- Differential scanning calorimetry (DSC), Shimadzu, Japan / University of Babylon / College of Materials Engineering.

6- X-Ray Diffraction (XRD), Rigaku Ultima iv, Japan, Berta laboratory for laboratory investigations, Iran.

7- Transmission Electron Microscopy (TEM), Philips, CM30, Netherland, Berta laboratory for laboratory investigations, Iran.

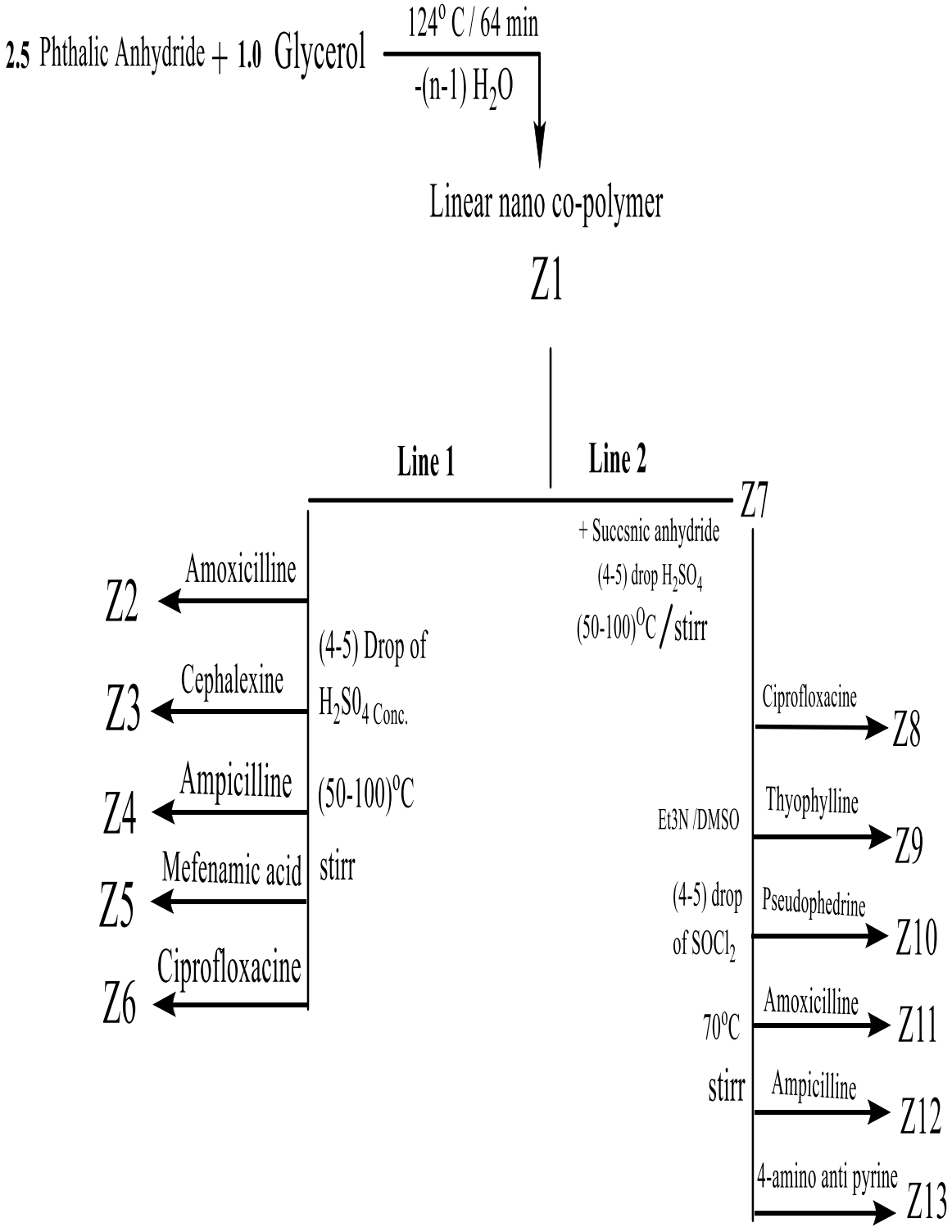
8- Melting points were determined using SMP30 melting point; College of Sciences, University of Babylon.

2.2 Synthesis of a novel Nano Co-polymer (Z1)

In 200 ml two-necked round bottom flask, (2.5 mole, 370 gm) of phthalic anhydride and (41ml) of DMSO, were mixed together. This flask was equipped with a thermometer. The mixture warmed carefully with a hot plate magnetic stirrer to100^{o}C until clear liquor is formed and added (1.0 mole, 92gm) of glycerol to the solution. The mixture warmed carefully to 110^{o}C, then about 12 ml of para xylene was added carefully to the reaction flask, in the form of batch (three drops in each batch), withdrawal of water formed as by-product in the esterification process, and the flask was gently heated. Heating was stopped after 64 min. at 124^{o}C, until no more water came off to prepare nano co-polymer, then add the cold distilled water, where the suspension solution is formed. Leave the suspension solution to precipitate, then filter and wash with distilled water and leave to dry in the room temperature.

Nano co-polymer which synthesis chractrization using FT-IR, ^{1}HNMR, DSC, AFM, XRD and TEM techniques.

The following scheme illustrates the steps of the reactions:



2.3 General Synthesis of (Line 1) [106,107]

In round bottom flask (0.5gm) of Z1 mixed with (0.5gm) of deffrent drugs (Amoxicillin, Cephalexin, Ampicillin, Mefenamic acid and Ciprofloxacin) respectively, placed in the heater and raise temperature gradually starting than 100°C with the addition of (4-5) drops of Conc. H_2SO_4 . Gradually with stirring continuous after melts mixture and leaves to cool and and filter the mixture via using acetone as a solvent. The nano co-polymer products codes are given (Z2, Z3, Z4, Z5 and Z6).

2.4 Synthesis of Nano co-polymer-drugs (Line 2)

2.4.1 Synthesis of Nano co-polymer (Z7) [106]

In round bottom flask, (5.0 gm) of Z1 mixed with (5.0gm) of Succinic anhydride placed in the heater and raise temperature gradually starting than 100°C with the addition of 5.0 drops of Conc. H_2SO_4.

Gradually with stirring continuous after melts mixture and leaves to cool and filter the mixture via using acetone as a solvent.

2.4.2 General Synthesis of Nano co-polymer-drugs [107-109]

In 50ml round bottom flask, adding 0.5 ml of Triethylamine to 5ml of Dimethylsulphoxide (DMSO), then put it on heater just for starring continuous by using magnetic starrer, add 0.5 gm of (Z7), add gradually 5.0 drops of Thionylchloride for 15Min., after that add 0.5 gm of (Ciprofloxacin, Theophylline, Pseudophedrine, Amoxicillin, Ampicillin, and 4-aminoantipyrine) respectively, for 30 Min. at 70^{o}C and left the mixture from the heater and starting filtration if the mixture appear as a precipitate but if the mixture don't appear the precipitate in this case used

separation technic by separation funnel by using Dichloromethan as asolvent.

2.5 Physical properties of the synthesis of Nano co-polymer-drugs

2.5.1 The characteristic of solubility [110,111]

Very small amounts (0.0001g) were taken from the synthesis nano co-polymers-drug (Z1-Z13) and were placed in test tubes in a number of solvents (H_2O, Ethanol, Methanol, DMSO, Hexane and Acetone) were used and measured the solubility of prepared monomers and polymers.

2.5.2 Swelling ratio [112]

The swelling ratio was determined by immersing the xerogel (0.05 gm) from nano co-polymers-drug, in 50 ml of different buffer solutions (pH=2.2, pH=7.0 and pH=8.0) and was allowed to soak for hours and days in constant temperatures at 310 K. After each 1 hr. and 24 hr., hydrogel removed from the water, blotted with filter paper to remove surface water weighted and the swelling ratio was calculated using equation:

$$\text{Swelling ratio}(\%) = \frac{(\text{wt. of hydrogel} - \text{wt. of xerogel})}{(\text{wt. of hydrogel})} \times 100$$

2.5.3 Perpared the Buffer solutions [113]

The Buffer solutions were prepared by the below methods:

1. **pH=2.2:**This solution was prepared, by mixing 500 ml of 0.2 M of KCl and 0.86 ml of 0.2 M of HCl.

2. **pH=8.0:**This solution was prepared, by mixing 500 ml of 0.025 M of Borax[$Na_2B_4O_7.10H_2O$] and 0.43 ml of 0.1 M of HCl.

2.6 Release of drug from Nano co-Polymer-drugs [114]

By using UV.-Vis. spectrophotometer, release the drug from the synthesis polymers were determined in three different buffer solutions (2.2, 7.0 and 8.0) at constant temperature 310 K. About (0.05 gm) for each nano co-polymer-drugs were put in the beaker (50 ml). Absorption (controlled drug release) was measured for some of consecutive hours and for some days was measured.

2.7 Preparation of standard calibration curve [115,116]

A standard calibration curve for albumin was determined by preparation solutions different concentrations from albumin in the range of (0.025- 0.225 %). The solutions were prepared, using deionized water as solvent. The absorbance of the resulting solutions was measured at λ_{max} 398.0 nm using deionized water as a blank on Shimadzu UV -1800PC spectrophotometer. Table (2-3), showed the λ_{max}.nm for all drug used .

Table (2-3): showed the λ_{max}.nm for all drug used .

Type of drug	**λ_{max}.nm**
Amoxcillin	274
Ampicillin	268
Cephalxine	212
Ciprofluxacine	276

Mefenamic acid	288
4-amino anti pyrine	298
Thyophyline	245
Pseudophdrine	256.5

2.8 Biological Activity Maesurments

2.8.1 Materials

Table (2-4): The materials, chemical methods and reagents used in biological activity

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 (2-5): The 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

2.8.2 Maintenance of cell cultures

MCF-7 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 [117].

2.8.3 Cytotoxicity Assays.

To determine the cytotoxic effect of (x- substances), the MTT cell viability assay was done using 96-well plates. Cell lines were seeded at 1×10^4 cells/well. After 24 hrs. or a confluent monolayer was achieved, cells were treated with tested compounds. Cell viability was measured after 72 hrs of treatment by removing the medium, adding 28 µL of 2 mg/mL solution of MTT and incubating the cells for 2.5 h at 37°C [118]. After removing the MTT solution, the crystals remaining in the wells were solubilized by the addition of 130 µL of DMSO (Dimethyl Sulphoxide) followed by 37°C incubation for 15 min with shaking. The absorbency was determined on a microplate reader at 492 nm (test wavelength); the assay was performed in triplicate. The inhibition rate of cell growth (the percentage of cytotoxicity) was calculated as the following equation [119, 120]:-

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

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

2.8.4 Statistical Analysis

The obtained data were statically analyzed using an unpaired t-test with GraphPad Prism 6. The values were presented as the mean ± SEM of triplicate measurements [121].

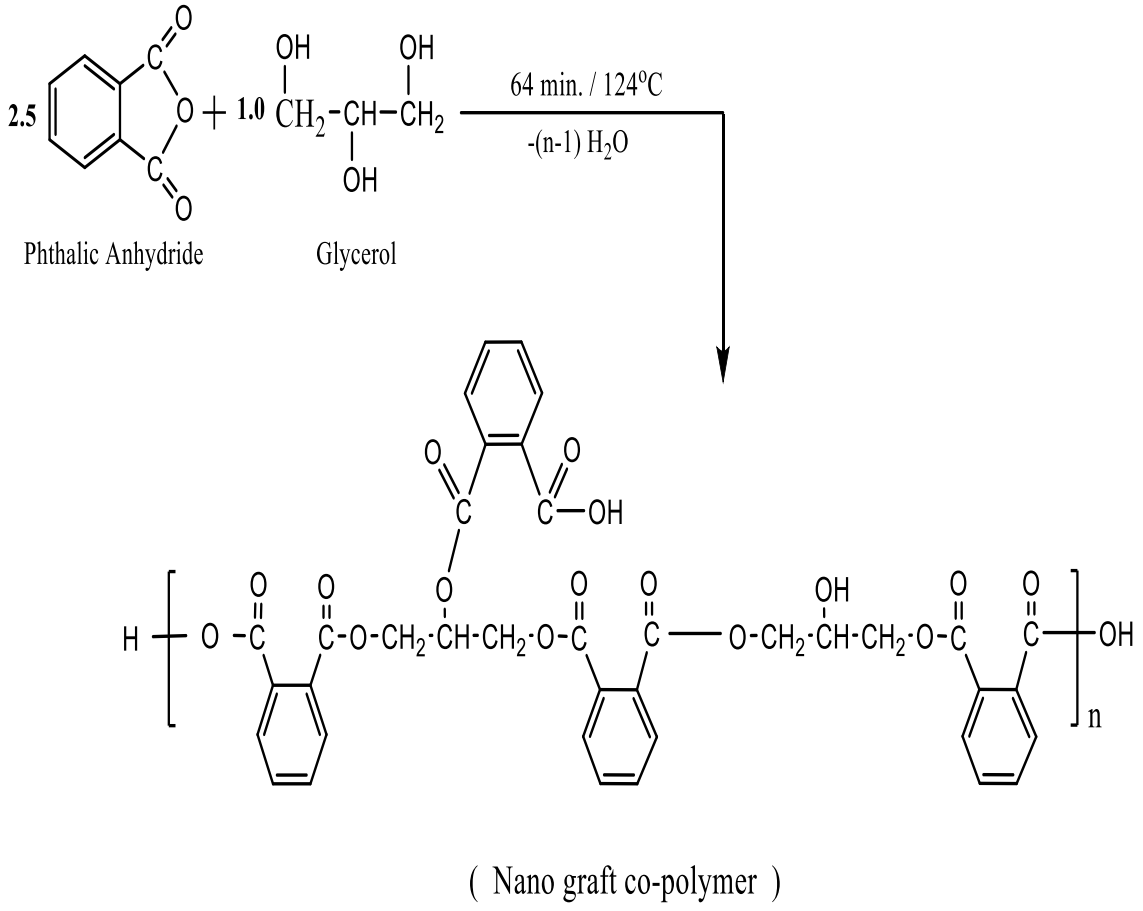
CHAPTER THREE

Results & Discussion

3. Results & Discussion

3.1 Synthesis of nano co-polymers (Z1)

The nano particle graft co-polymer was synthesized using solubilization process by condensation polymerization from the reaction of one mole of glycerol with 2.5 mole of phthalic anhydride at 124°C and 64 min. with releasing of water as by-product, as showed in Equations (3-1).



Equation (3-1): Reaction of synthesis of nano graft co-polymer

This nano co-polymer was characterized with techniques (FT-IR, ^{1}H-NMR, DSC, AFM, XRD and TEM).

Figure (3-1) showed the FT-IR spectrum which appear a weak broad band at (3073 cm^{-1}) attributed to the bond (O-H) carboxylic and H-bond, also showed a stretching band at (3003 cm^{-1}) attributed to the bond (C-H) aromatic, and shows a stretching bands at the (2810, 2884 cm^{-1}) attributed to the symmetric and asymmetric (C-H) aliphatic bond, and a strong stretching band at (1670 cm^{-1}) attributed to the (C=O) ester, and stretching bands at (1400, 1493 and 1584 cm^{-1}) attributed to (C=C) aromatic, and showed a peak at (1069 cm^{-1}) attributed to the (C-O) ester, and shows bands at (734 and 898 cm^{-1}) attributed to di substitution of aromatic ring.

Figure (3-2) shows the ^{1}H-NMR spectrum, which explain the singlet signal at 13.12 ppm of characteristic proton in the carboxylic acid group. Moreover, the multiplet in the region 7.57-7.79 ppm attributed to all protons in the aromatic ring, the signals at 4.25-4.28 ppm for four methylene protons in the co-polymer structure, and multiple at 4.17 ppm of methyl protons, but aliphatic alcohol signal has disappeared indicating the formation of a graft co-polymer.

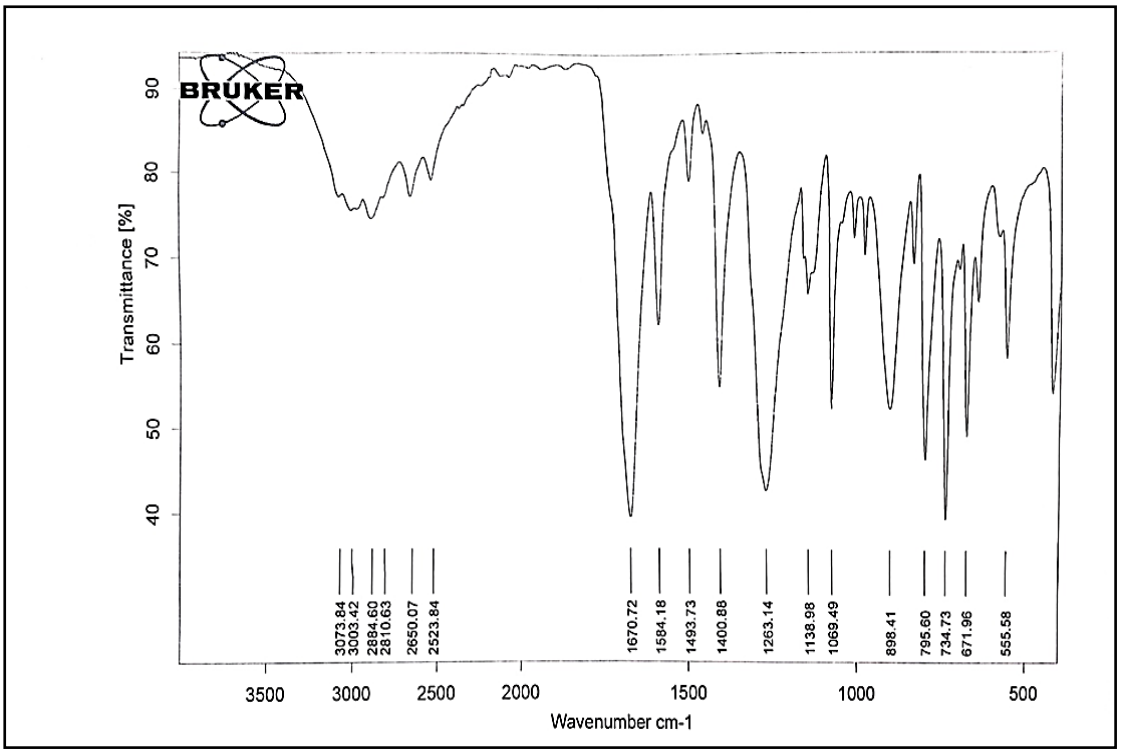


Figure (3-1): FT-IR of nano co-polymer

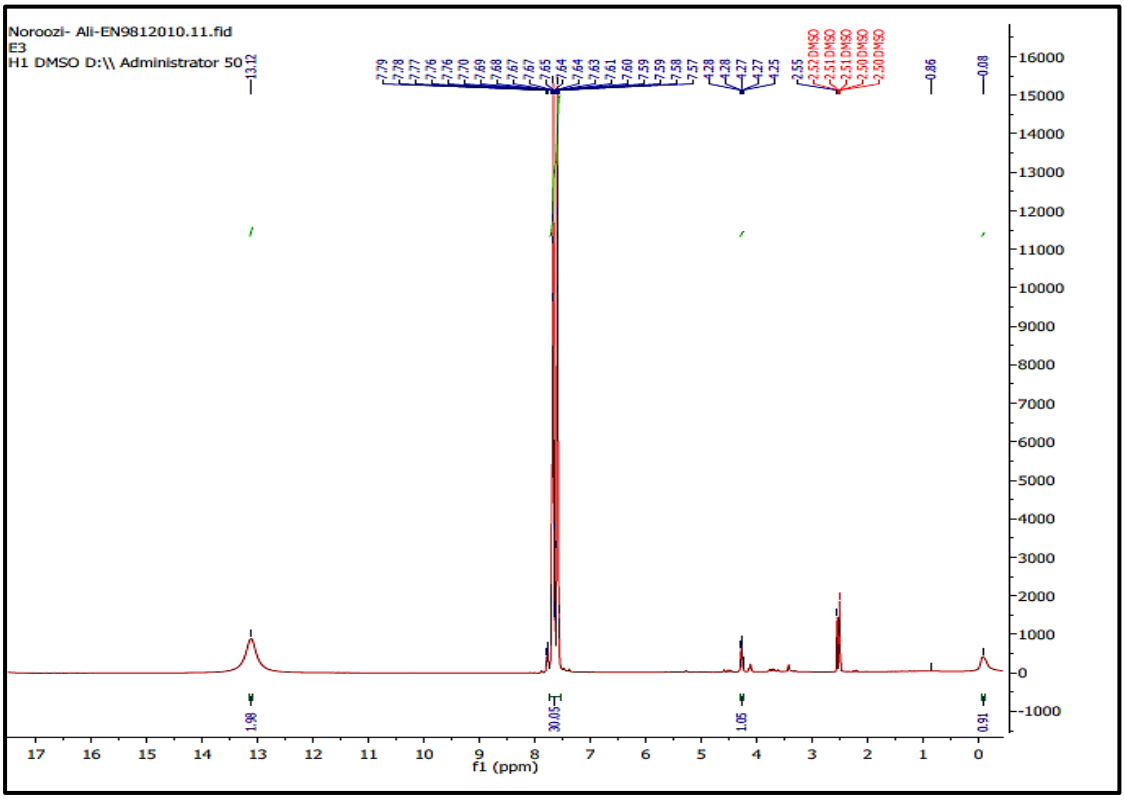


Figure (3-2): The ^{1}H-NMR spectrum of nano co-polymer

Figure (3-3 a, b and c) showed the outer surface of the nanoparticles of co-polymer. The roughness coefficient of co-polymer surface was 0.993 nm and the square root square was equal to 1.15 nm. This indicates that the bold size of the nanoparticles plays an important role in the roughness of the surface, its uniform crystalline system, and the surface homogeneity. Also, the average of height of the particles was equal to 3.89 nm, as observed in Figure (3-3 a). Table (3-1) represents the total rate of the particle sizes of the common nanoparticle and the different proportions of these volumes; the results indicate that the molecular size of the co-polymer nanoparticle was 91.26 nm and Figure (3-4) represents the distribution of the different proportions of particle sizes of the co-polymer nanoparticle.

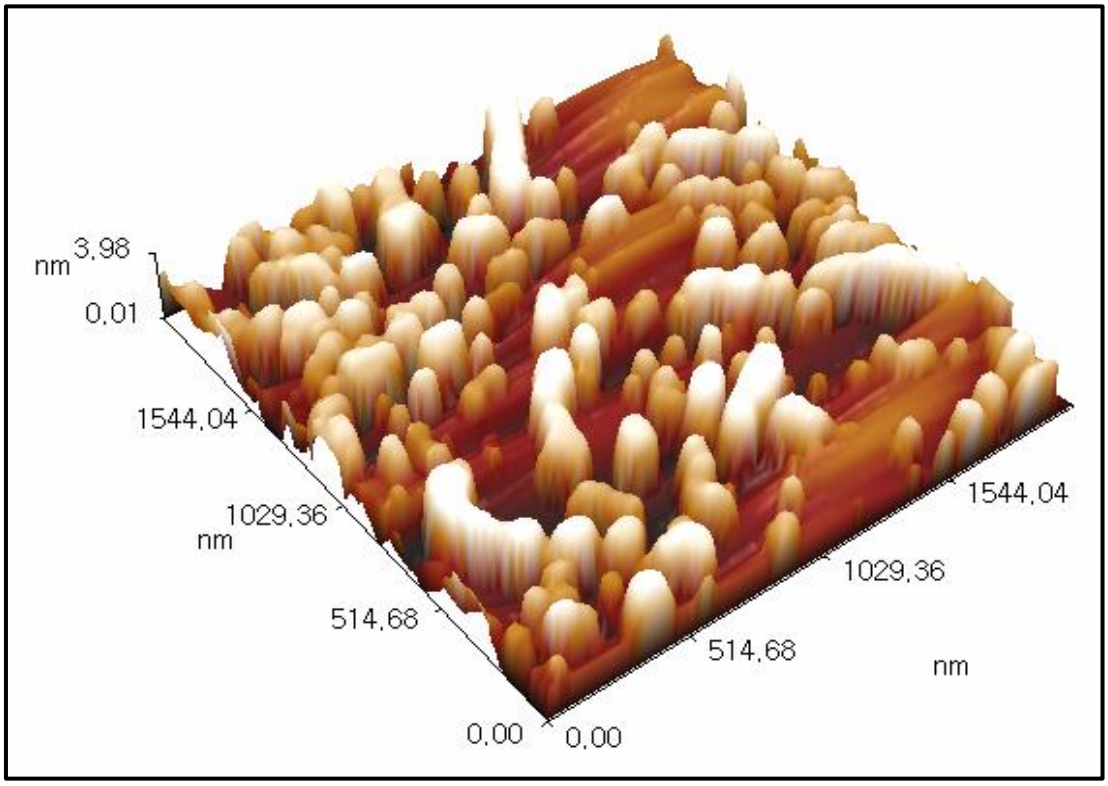


Figure (3-3 a): Image of Atomic Force Microscope for nanoco-polymer shows 3D Image

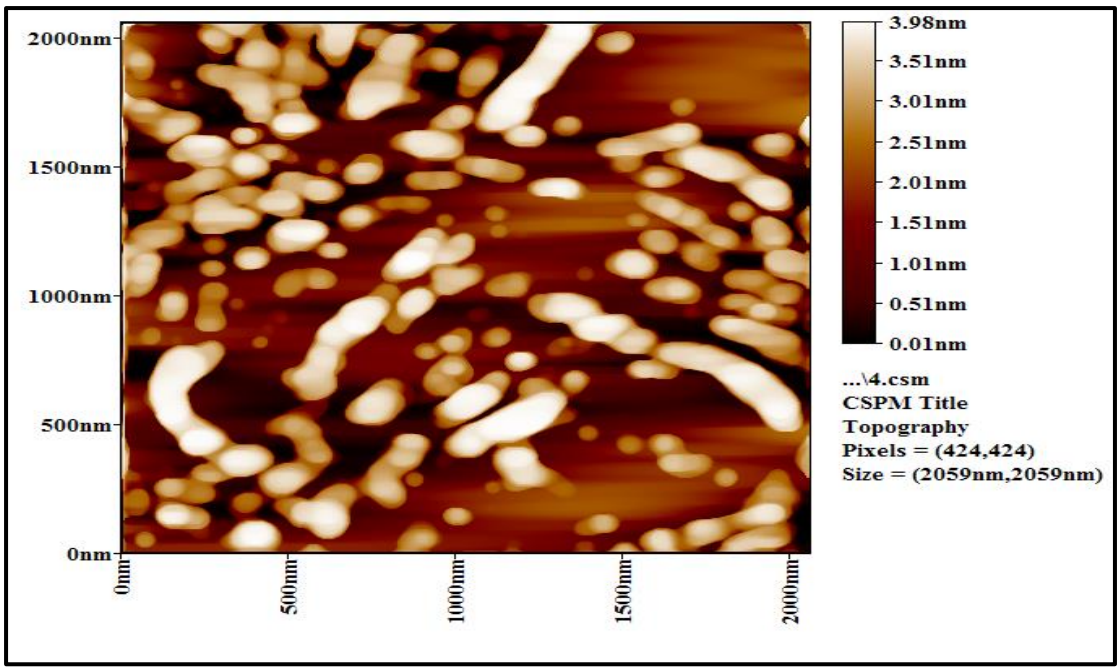


Figure (3-3 b): Image of Atomic Force Microscope for nano co-polymer shows 2D Image

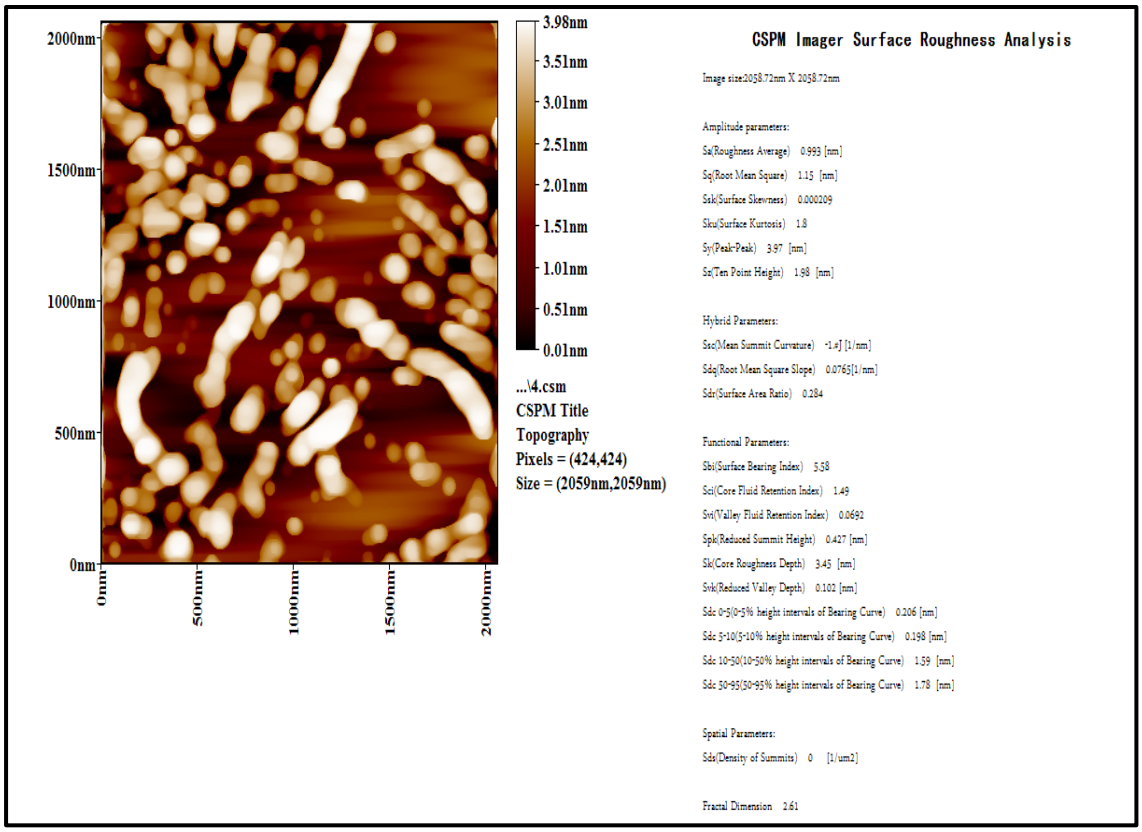


Figure (3-3 c): Image of Atomic Force Microscope for nano co-polymer shows 2D Image and showing all details of particles

Table (3-1): The total rate of the particle sizes of the nano co-polymer nanoparticle and the different proportions of these volumes

Sample: 4	**Code:** Sample Code
Line No.:lineno	**Grain No.:** 90
Instrument: CSPM	**Date:** 2020-09-24

Avg. Diameter: 91.26 nm	**<=10% Diameter: 55.00 nm**
<=50% Diameter: 90.00 nm	**<=90% Diameter: 115.00 nm**

Diameter (nm)<	Volume (%)	Cumulation (%)	Diameter (nm)<	Volume (%)	Cumulation (%)	Diameter (nm)<	Volume (%)	Cumulation (%)
45.00	4.44	4.44	85.00	7.78	37.78	115.00	10.00	86.67
55.00	3.33	7.78	90.00	10.00	47.78	120.00	7.78	94.44
65.00	3.33	11.11	95.00	8.89	56.67	125.00	3.33	97.78
70.00	5.56	16.67	100.00	2.22	58.89	130.00	2.22	100.00
75.00	4.44	21.11	105.00	8.89	67.78			
80.00	8.89	30.00	110.00	8.89	76.67			

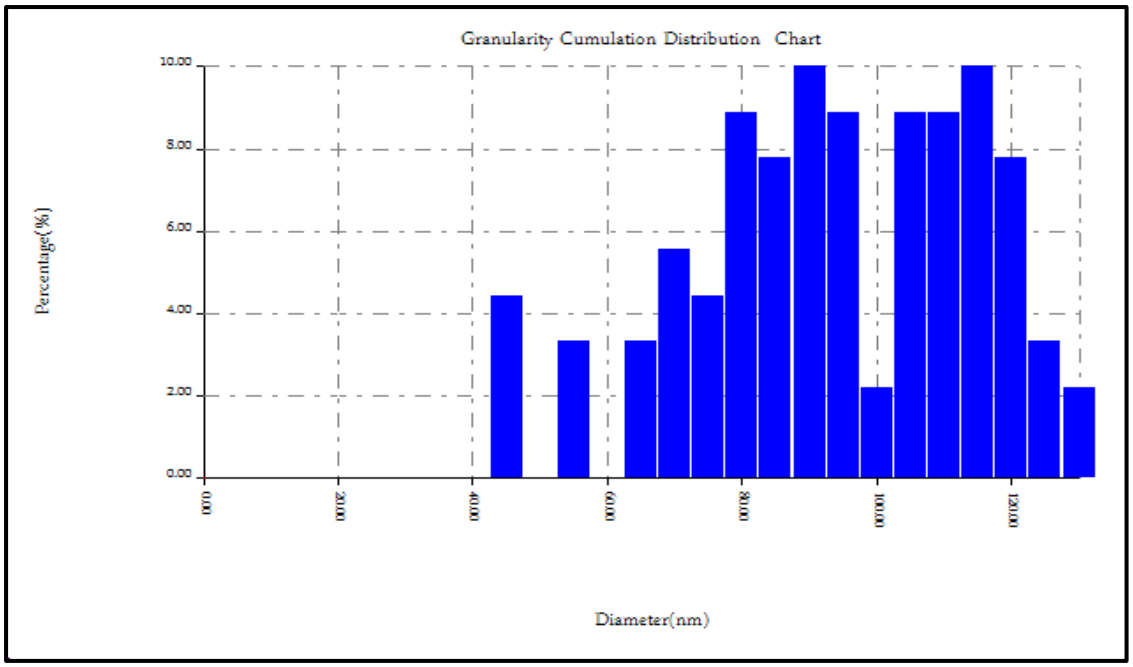


Figure (3-4): Distribution of the different proportions of particle sizes of the nano co-polymer

The x-ray diffraction (XRD) in the nanoparticles co-polymer, Figure (3-5), shows peaks at 2θ values of (15.4°, 18.6°, 21.2°, 22.3°, 27.0°, 30.6°). These peaks indicated that the new co-polymer has been formed as a crystalline compound with less of amorphous carbon atoms . By using origin software the average inter planer spacing between atoms (d_{hkl}) was 0.414 nm according to Bragg's Law:

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

The total average crystallites size were 91.24 nm relative to Scherrer's equation:

$$D = \frac{k\lambda}{\beta cos\theta} \ldots\ldots\ldots\ldots \text{Scherrer's equation}$$

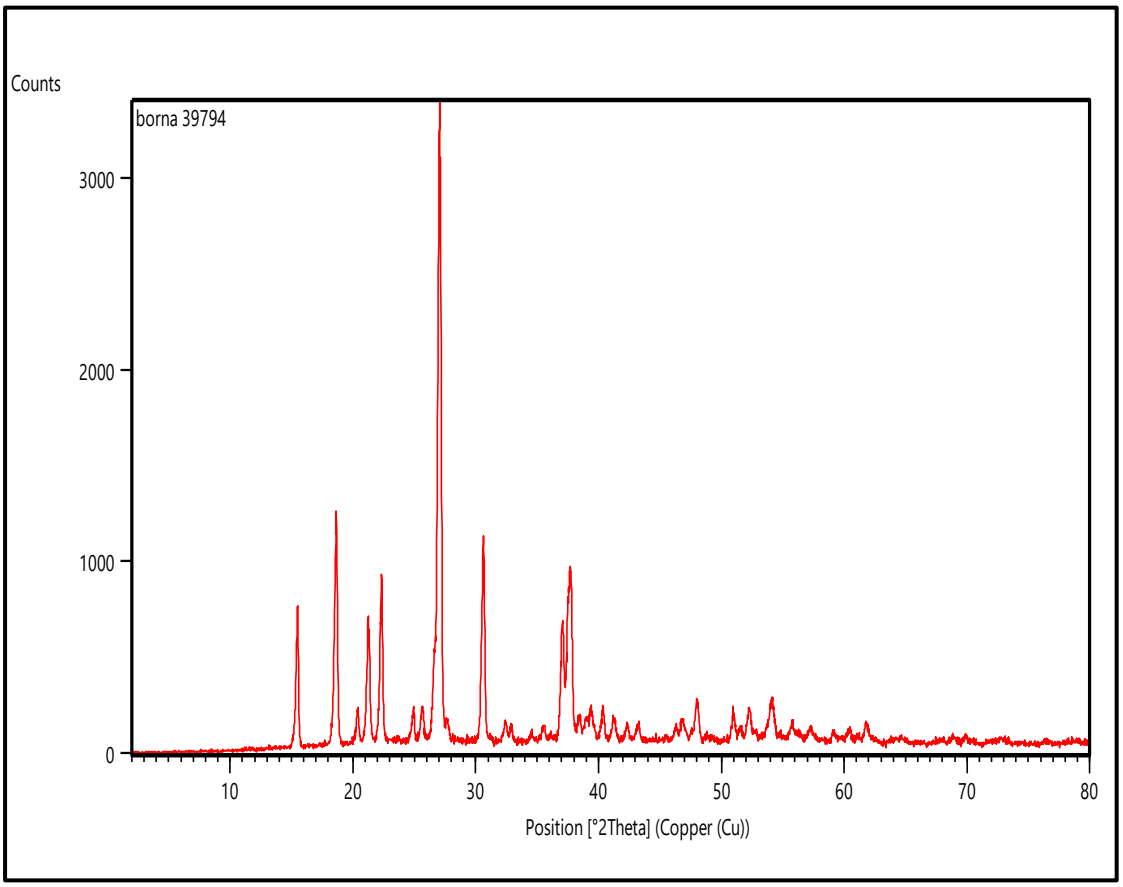


Figure (3-5): The x-ray diffraction in the nanoparticles co-polymer

Table (3-2) the proportions crystallites sizes and the distances between atoms (d-spacing) in the nano co-polymer

2 θ	**θ**	**FWHM**	**D nm**	**d_{hkl} nm**	**D (Av.) nm**	**d_{hkl} (Av.) nm**
15.47788	7.73894	0.069784	114.8882	0.572035	**91.2386**	**0.4141**
18.62578	9.31289	0.09057	88.88545	0.476006		
21.26164	10.63082	0.092711	87.18472	0.417552		
22.32109	11.16055	0.086459	93.65619	0.397967		
27.04898	13.52449	0.107085	76.30245	0.329384		
30.61175	15.30588	0.0956	86.15515	0.291811		

Figure (3-6) showed, the TEM micrographs for the nanoparticles co-polymer containing irregular particles in the form of layers with different sizes and shapes in the form of semi-spherical. An average particle size of the co-polymer nanoparticle was found to be 91.2386 nm. Table (3-3) shows the proportions diameters, angels and standard deviations of the nano co-polymer using image-j software and Figure (3-7) represents the histogram for distribution of the different proportions of particle sizes of the nano co-polymer.

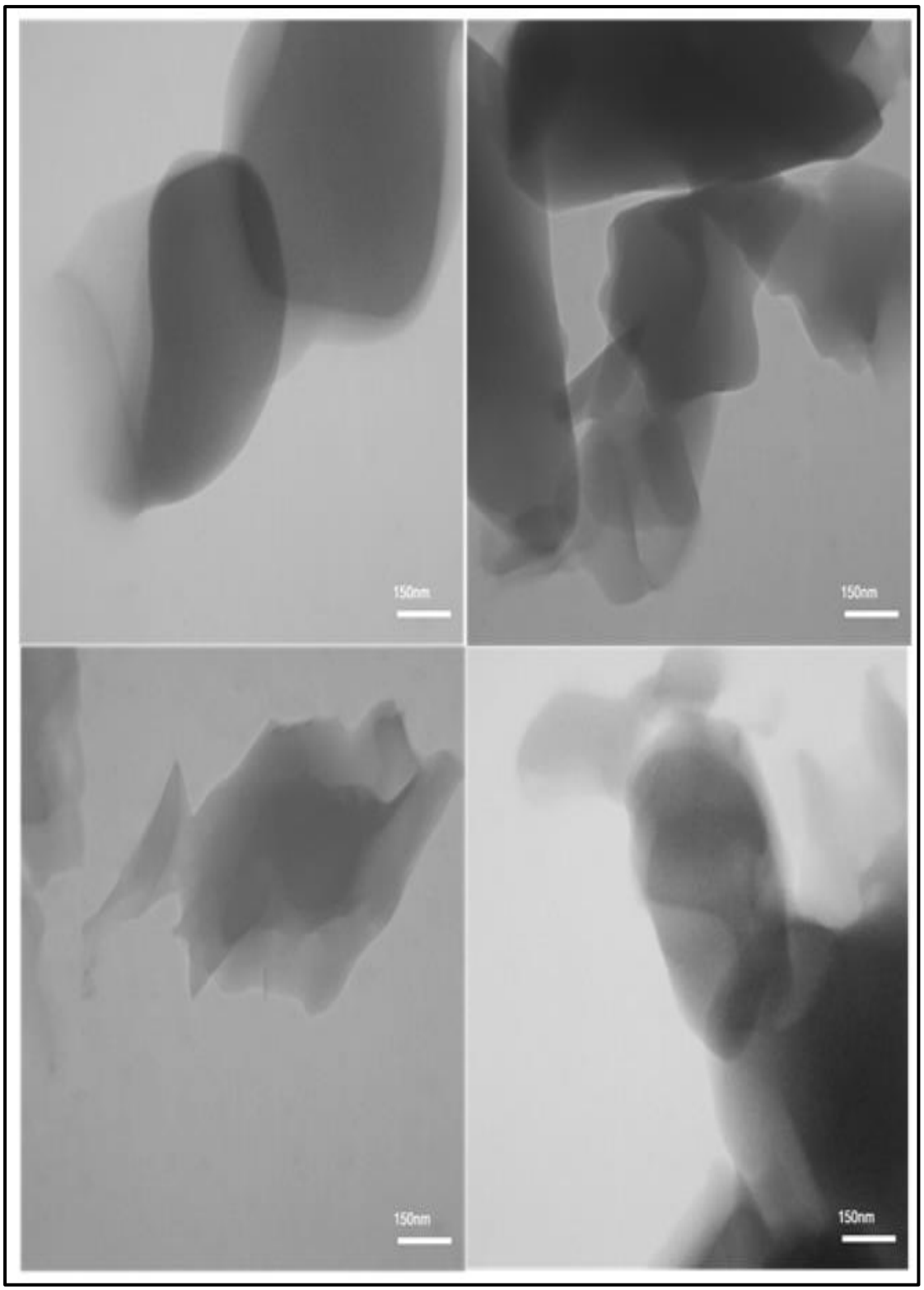


Figure (3-6): TEM micrographs for the nanoparticles co-polymer

Table (3-3): The proportions diameters, angels and Standard deviations of the nano co-polymer

Area	StdDev	Angle	Diameter nm	D (av.) nm
38.586	8.672	-80.5	65.367	**90.621**
42.106	13.003	-138	66.894	
46.53	10.497	122.6	68.621	
68.461	4.433	-158	71.73	
43.651	7.3	-165	79.344	
50.991	8.795	-90	82.041	
69.745	3.024	132.9	87.497	
64.511	10.233	81.67	89.016	
71.377	6.062	-177	92.192	
87.944	21.573	-23.8	92.388	
59.876	4.934	-65.4	95.675	
60.262	8.7	180	96.958	
65.284	8.496	56.69	104.12	
67.215	7.186	18.85	107.709	
69.919	22.035	-57.7	111.736	
70.692	8.624	140.4	113.001	
78.031	8.581	-149	124.925	

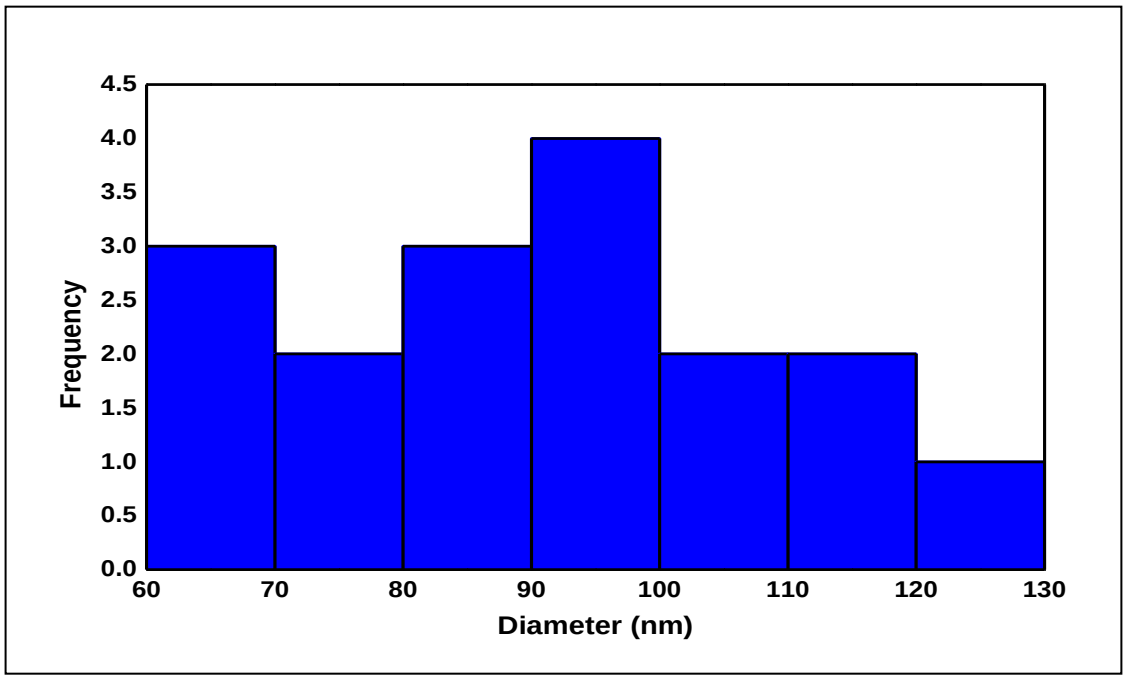


Figure (3-7): Histogram for distribution of the different proportions of particle sizes of the nano co-polymer

Figure (3-8) showed the DSC thermo grams for the nano co-polymer, the first thermal transition at the peak (86.21^{o}C) represents the glass transition temperature (T_g), and the second transition at the peak (226.85 ^{o}C) represents the crystallization temperature (T_c), and the third and fourth transitions at the peaks (247.62 and 293.47 ^{o}C) represents the melting temperature (T_{m1} andT_{m2}) respectively for the nano co-polymer.

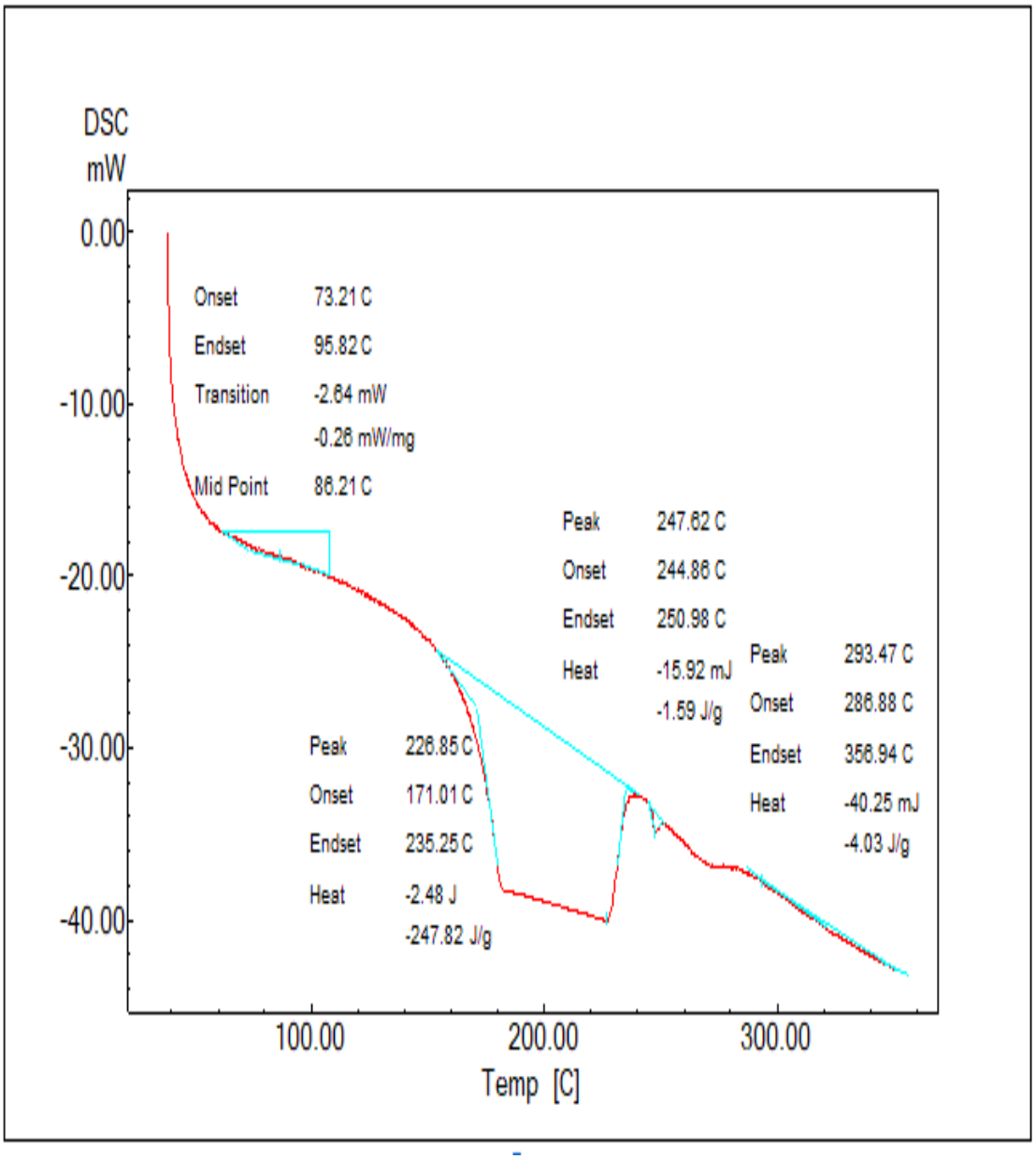


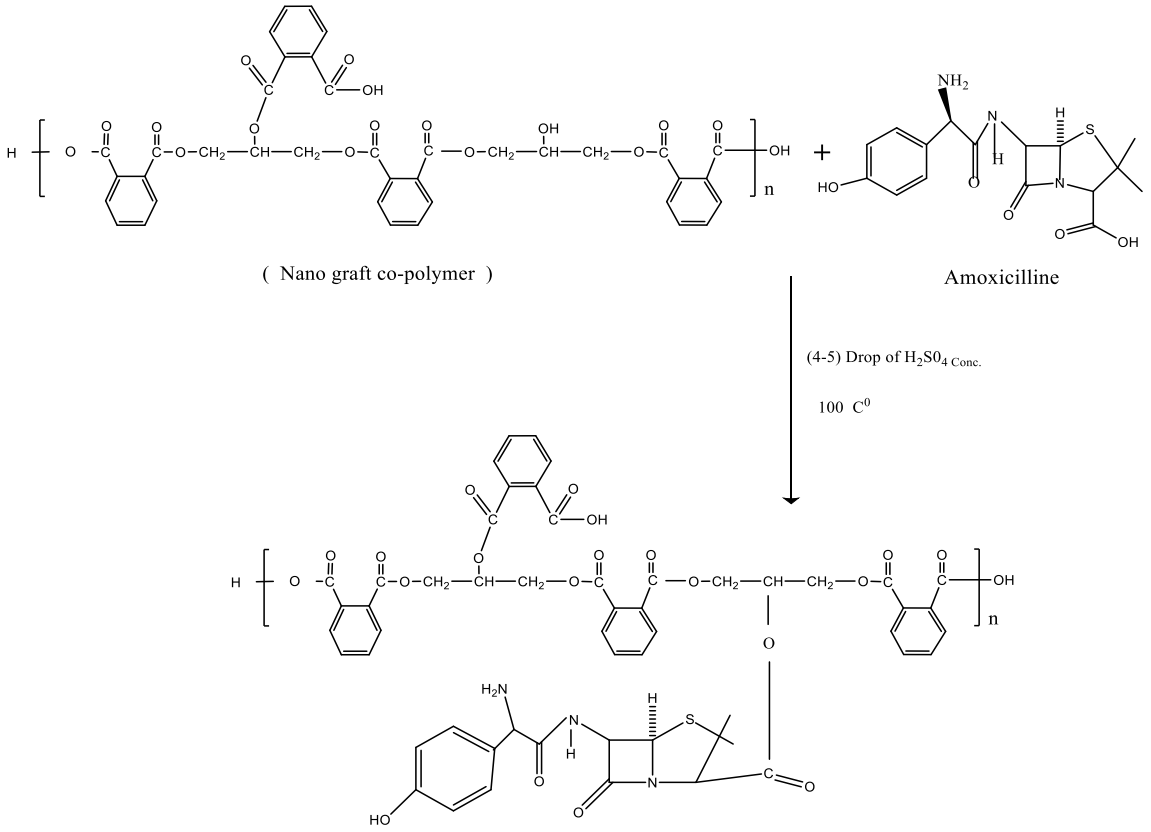
Figure (3-8): DSC thermo grams of nano co-polymer

3.2 Synthesis of the nano co-polymer-drug

3.2.1 Synthesis of graft nano co-polymer-Drug (Line 1)

3.2.1.1 Synthesis of compound (Z2)

Amount of compound (Z1) reacted with Amoxicillin and mixed to gather add to the mixture (3-4) drops of H_2SO_4 Conc. at 100^oC. Equation (3-2) represents synthesis the compound (Z2).



Equation (3-2): Synthesis the nano co-polymer-drug (Z2)

The FT-IR, shows the spectrum of compound (Z2), Figure (3-9), shows appearance absorption band appear a weak broad band at (3029.56 cm^{-1}) attributed to the bond (O-H) alcoholic and appearance of absorption band of C=C-H_{amide} at (3060.72) cm^{-1} and absorption band of C-C-H_{aliph} at (2923.35) cm^{-1} and absorption band at (1718.52) cm^{-1} of C=O ester and absorption band of at C-N-C (1651.02) cm^{-1} , and absorption band of C=C

at (1533) cm^{-1}, and absorption band of C-O at (1379.07) cm^{-1}, and absorption band of C-N at (1215.72) cm^{-1} and appear absorption bond Di substation aromatic ring at 741.66 cm^{-1}. The ^{1}H-NMR spectrum of compound (C4), Figure (3-10), shows disappearance a single signal at 13ppm for $(OH)_{acid}$, and appearance signal at 3.38ppm for $(C=C-H)_{amid}$, and appearance signal at 3ppm for $(C-H_3)$.

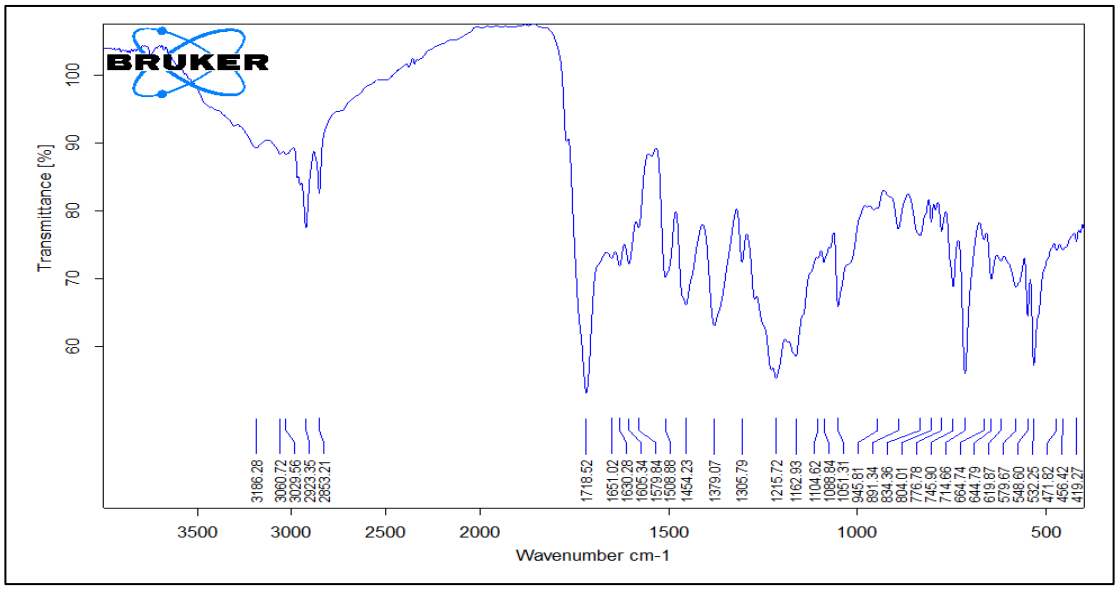


Figure (3-9): The FT-IR spectrum of nano co-polymer-drug (Z2)

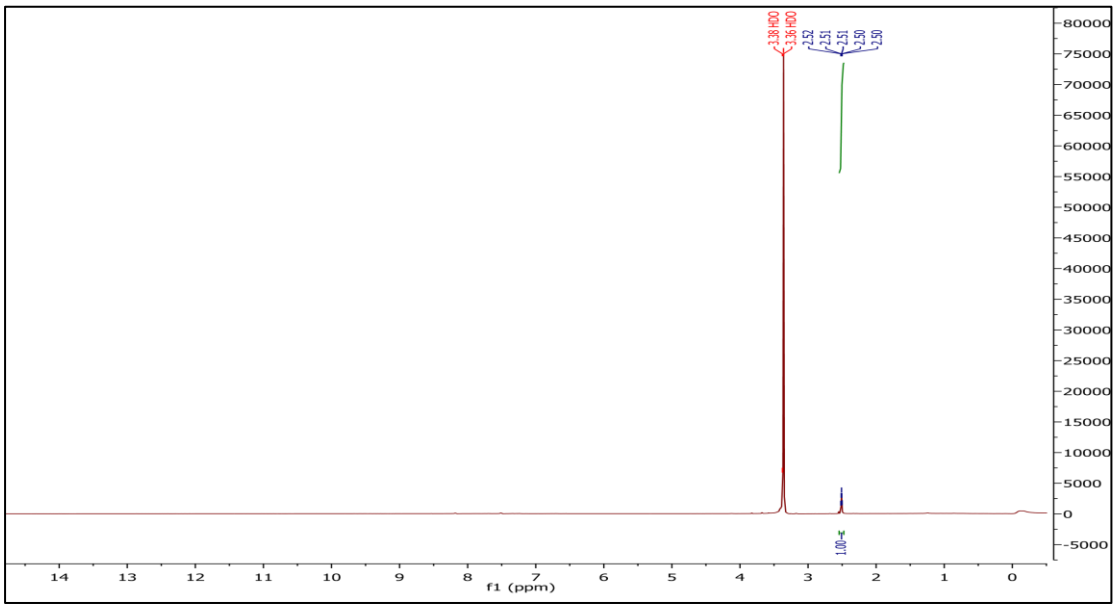
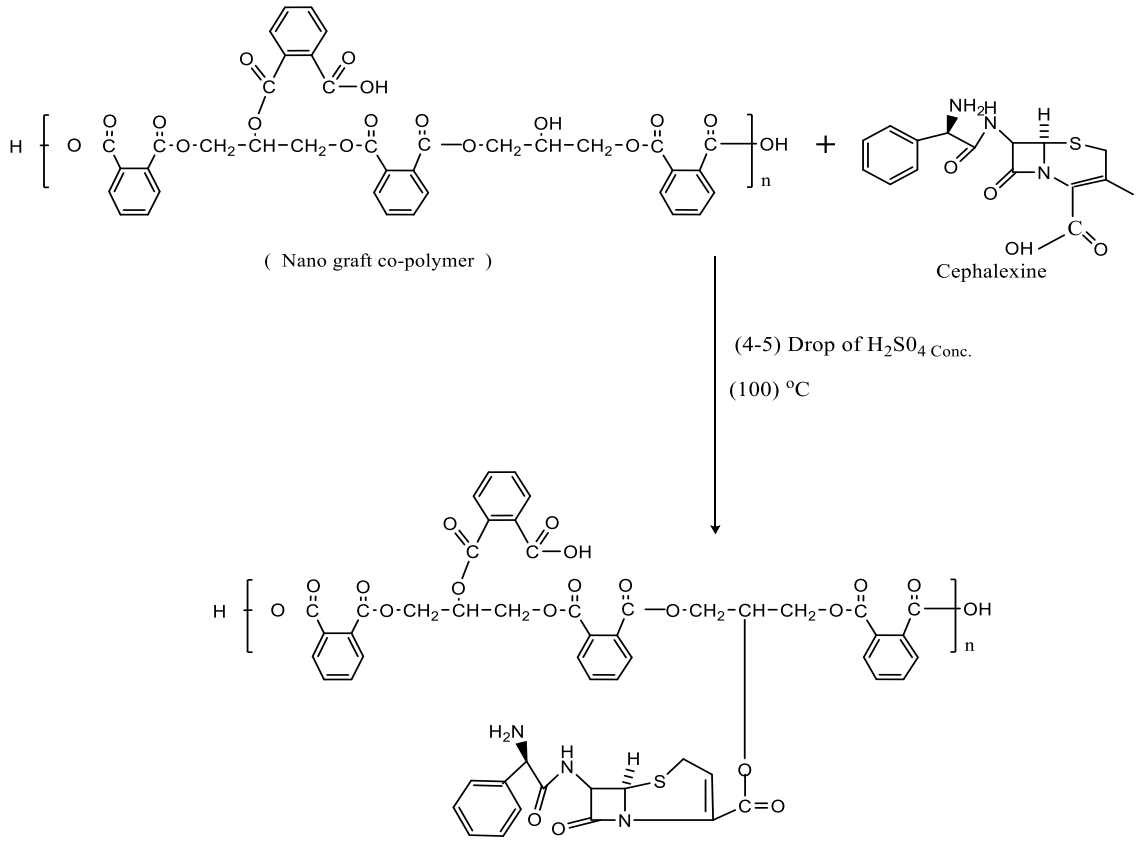


Figure (3-10): The ^{1}HNMR spectrum of nano co-polymer-drug (Z2)

3.2.1.2 Synthesis of compound (Z3)

Amount of compound (Z1) reacted with Cephalexine drug and mixed to gather add to the mixture (3-4) drops of H_2SO_4 Conc. in 100^oC, Equation (3-3) represent synthesis the polymer (Z3).



Equation (3-3): Synthesis the nano co-polymer-drug (Z3)

The FT-I.R spectrum of compound (Z3), Figure (3-11), shows appearance absorption band appear a weak broad band at (3069.93 cm^{-1}) attributed to the bond (O-H) alcoholic and appearance of absorption band of C=C-H_{amide} at (3004.93) cm^{-1} and absorption band of C-C-H_{aliph} at (2970.22) cm^{-1} and absorption band at (1671.77) cm^{-1} of C=O ester , and absorption band of C=C ph at (1402.47) cm^{-1} , and absorption band of C-O at (1070.42) cm^{-1}, and absorption band of C-N at (1277.68) cm^{-1} , and appear absorption bond Di substation aromatic ring at 736.49 cm^{-1}. The ^{1}H-NMR spectrum for compound (Z3), Figure (3-12), shows disappearance a

single signal at 13 for $(OH)_{acid}$, and appearance signal at 7.58 for $(C=C-H)_{ph}$, and appearance signal at 5.70 for $(C=C-H)_{amid}$,and appear singl at 9.52 for (CHO),and appear signal at 2.5 (C=O) ester and appearance signal at 3 for $(C-H_3)$.

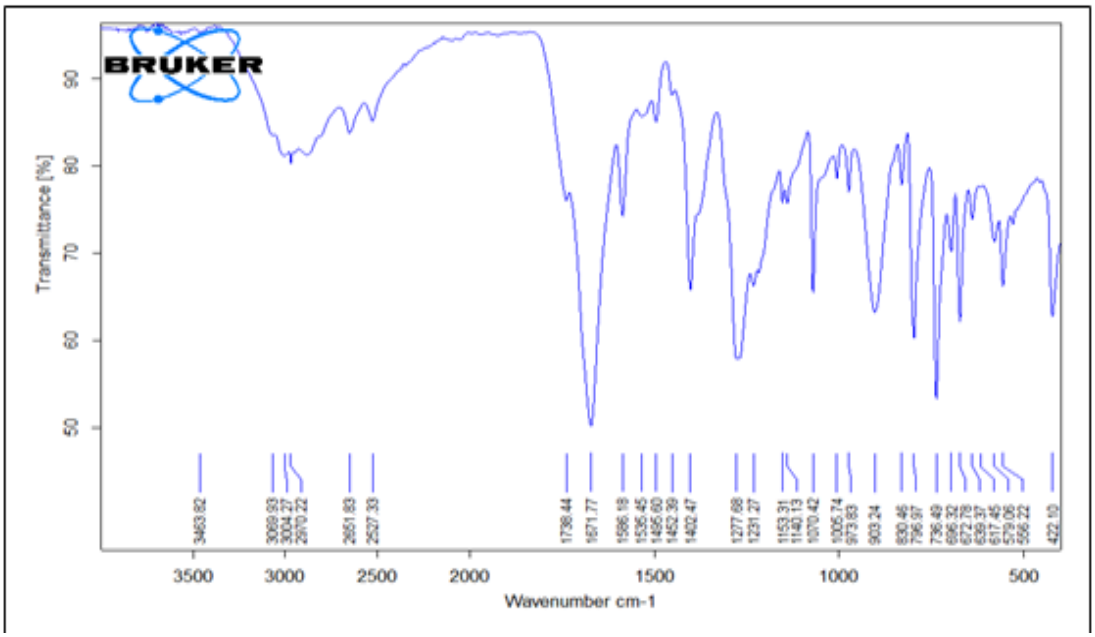


Figure (3-11): The FT-IR spectrum of nano co-polymer-drug (Z3)

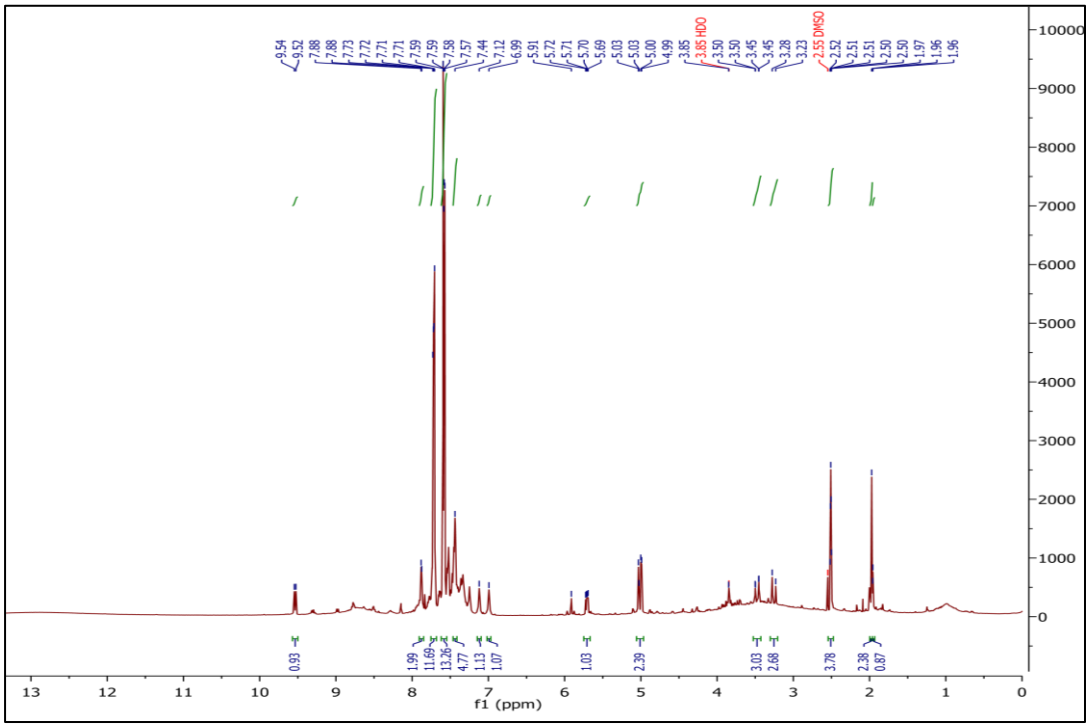
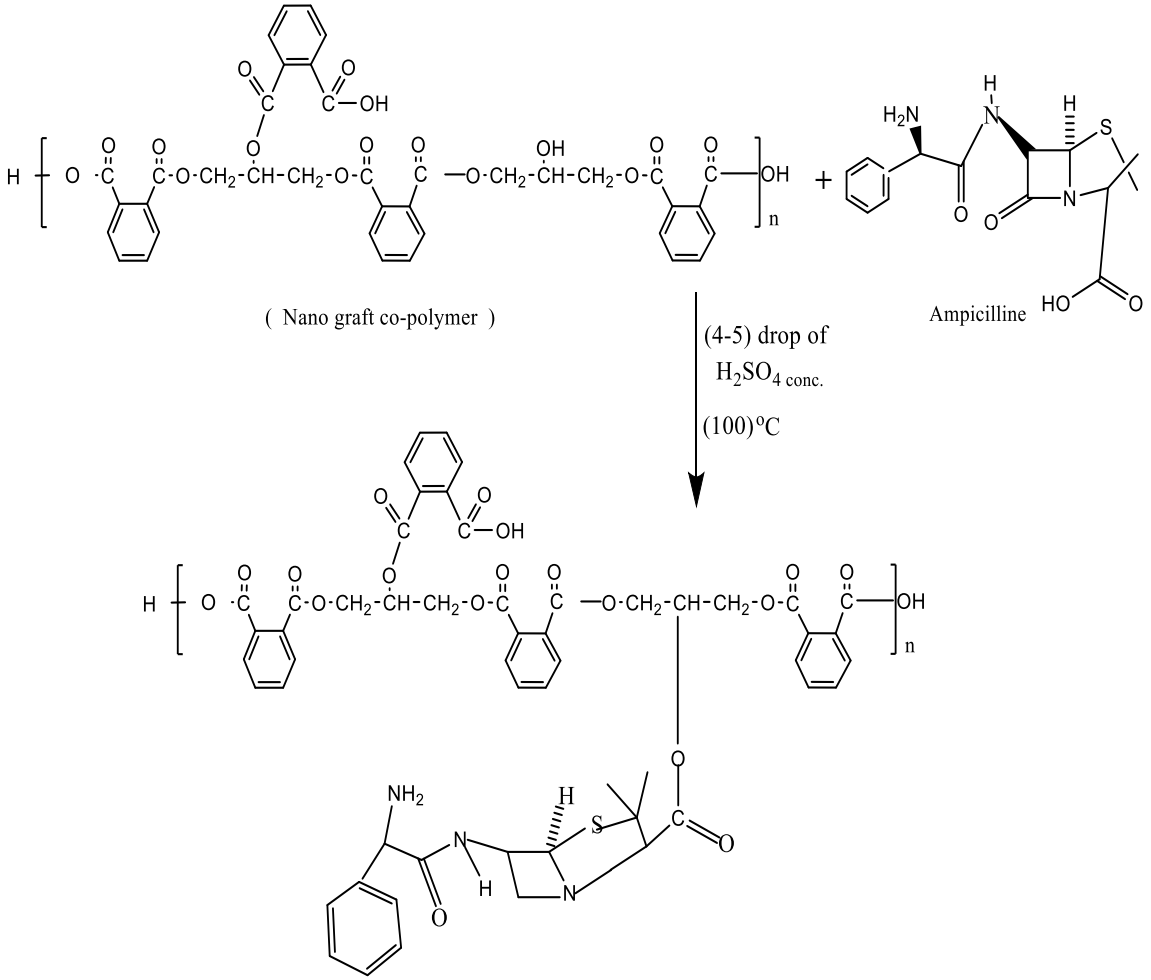


Figure (3-12): The ^{1}HNMR spectrum of nano co-polymer-drug (Z3)

3.2.1.3 Synthesis of compound (Z4)

Amount of compound (Z1) reacted with Ampicillin drug and mixed to gather add to the mixture (3-4) drops of H_2SO_4 Conc. at 100°C, Equation (3-4) represent synthesis the polymer (Z4).



Equation (3-4): Synthesis the nano co-polymer-drug (Z4)

The FT-I.R spectrum of compound (Z4), Figure (3-13), shows appearance absorption band appear a weak broad band at (3060.92 cm^{-1}) attributed to the bond (O-H) alcoholic and appearance of absorption band of C=C-H_{amide} at (3004.37) cm^{-1} and absorption band of C-C-H_{aliph} at (2970.24) cm^{-1} and absorption band at (1738.50) cm^{-1} of C=O ester , and absorption band of C=C ph at (1402.09) cm^{-1} , and absorption band of C-O at (1070.78) cm^{-1}, and absorption band of C-N at (1139.01) cm^{-1} , and appear absorption bond Di substation aromatic ring at 736.98 cm^{-1}. The ^{1}H-

NMR spectrum for compound (Z4), Figure (3-14), shows disappearance a single signal at 13 for $(OH)_{acid}$, and appearance signal at 8.7 for $(C=C-H)_{ph}$, and appearance signal at 7 for $(C=C-H)_{amid}$.

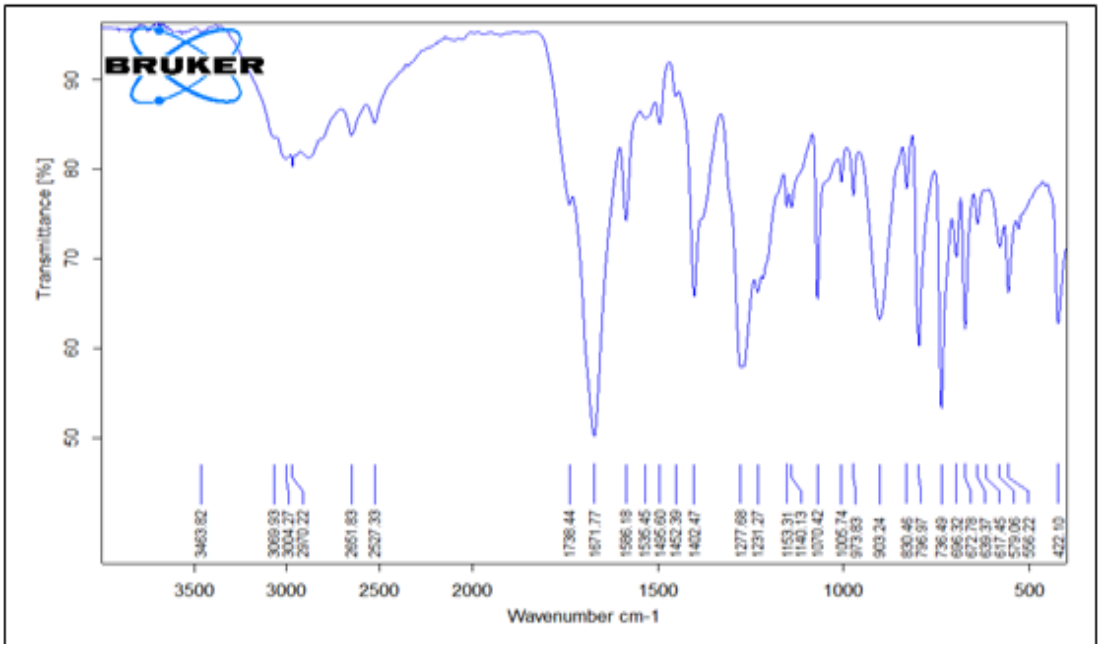


Figure (3-13): The FT-IR spectrum of nano co-polymer-drug (Z4)

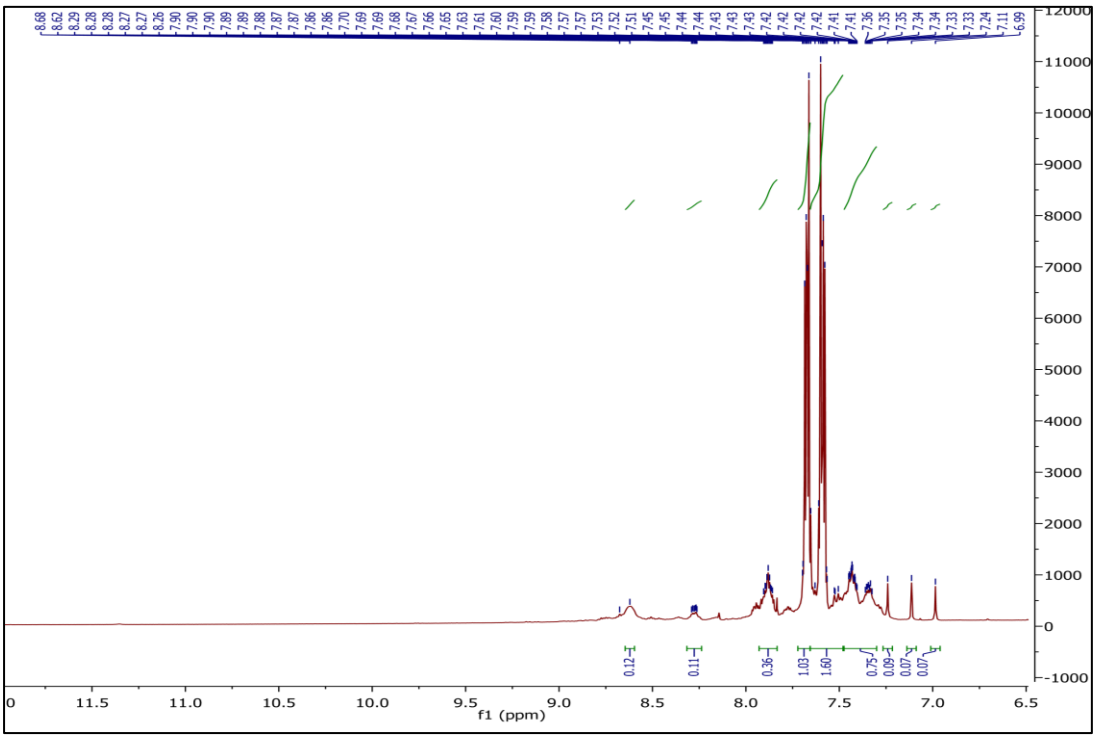
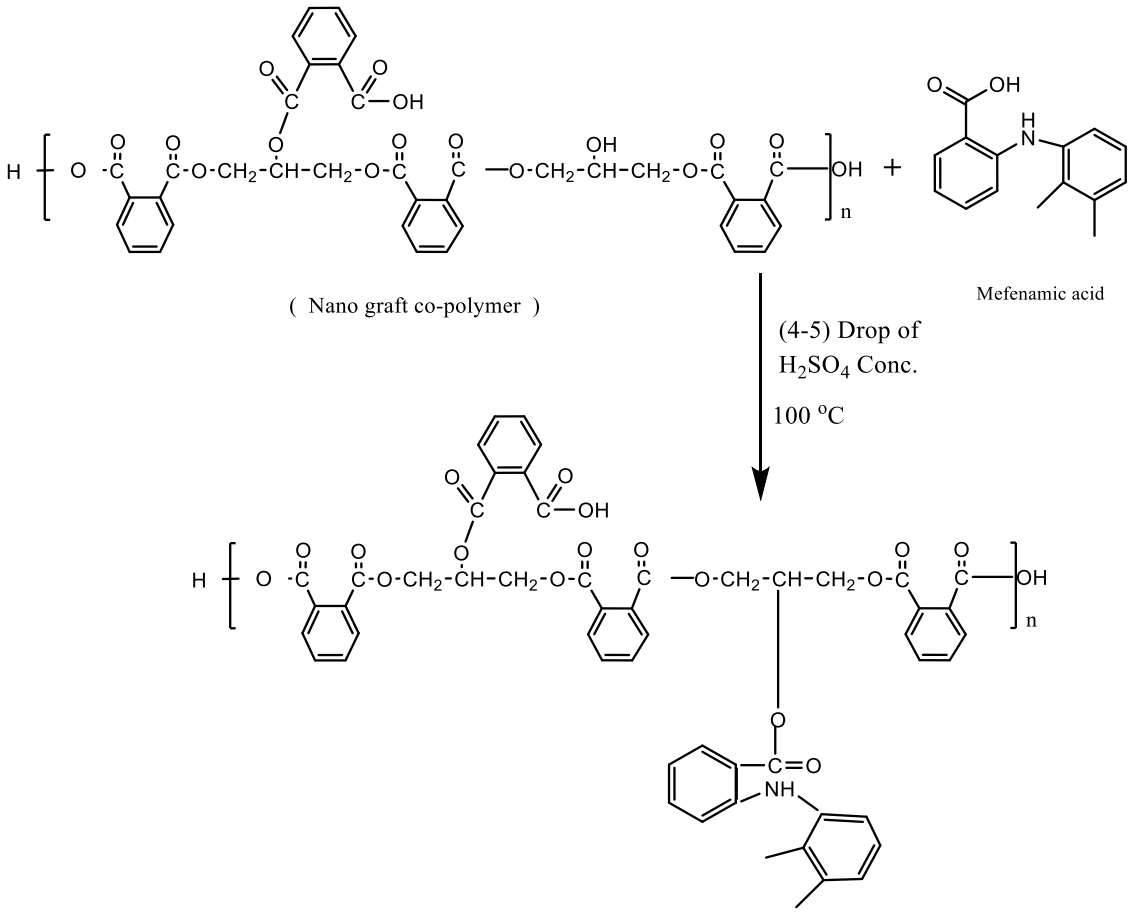


Figure (3-14): The ^{1}HNMR spectrum of nano co-polymer-drug (Z4)

3.2.1.4 Synthesis of compound (Z5)

Amount of compound (Z1) reacted with Mefenamic acid drug and mixed to gather add to the mixture (3-4) drops of H_2SO_4 Conc. in 100^oC, Equation (3-5) represent synthesis the polymer (Z5).



Equation (3-5): synthesis the nano co-polymer-drug (Z5)

The FT-I.R spectrum of compound (Z5), Figure (3-15), shows appearance absorption band appear a weak broad band at (3343.71 cm^{-1}) attributed to the bond (O-H) alcoholic and appearance of absorption band of $C=C-H_{amide}$ at (3009.81) cm^{-1} and absorption band of $C-C-H_{aliph}$ at (2970.47) cm^{-1} and absorption band at (1658.98) cm^{-1} of C=O ester , and absorption band of C=C ph at (1400.43) cm^{-1} , and absorption band of C-O at (1068.48) cm^{-1}, and absorption band of C-N at (1138.23) cm^{-1} , and appear absorption bond Di substation aromatic ring at 733.13cm^{-1}. The ^{1}H-

NMR spectrum for compound (Z5), Figure (3-16), shows appearance a single signal at 10.5ppm for $(OH)_{acid}$, and appearance signal at 7.8ppm for $(C=C-H)_{ph}$, and appearance signal at 6.5ppm for $(C=C-H)_{amid}$ and appear at (2-2.5)ppm (C=O) ester, and appearance signal at 3ppm for $(C-H_3)$.

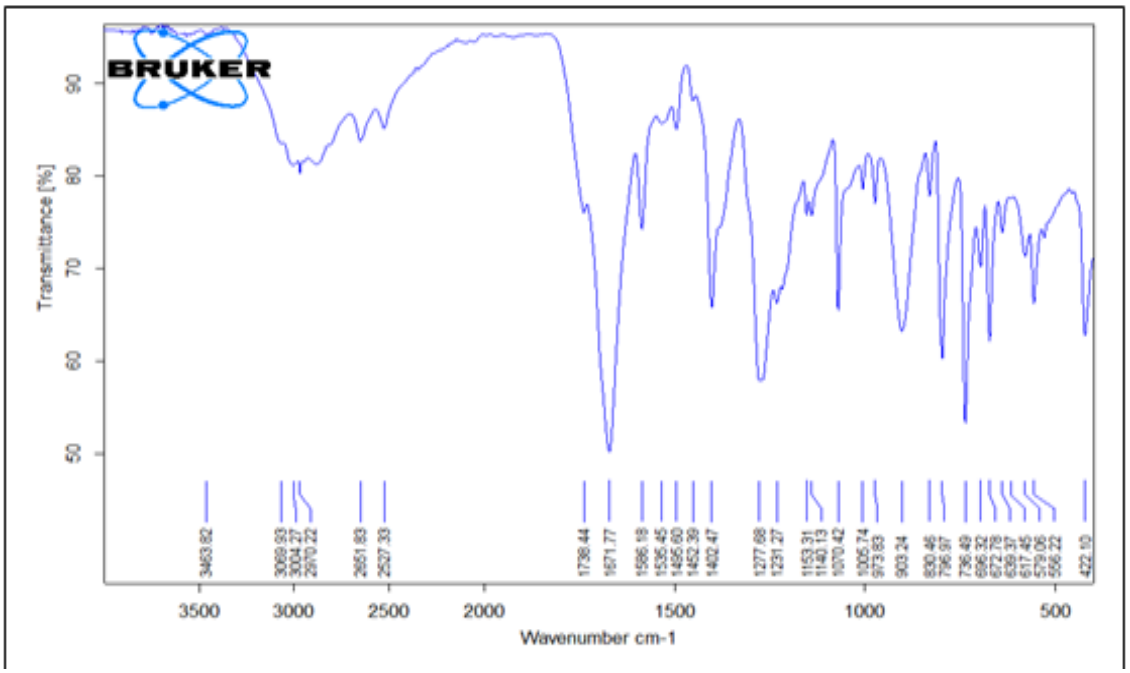


Figure (3-15): The FT-IR spectrum of nano co-polymer-drug (Z5)

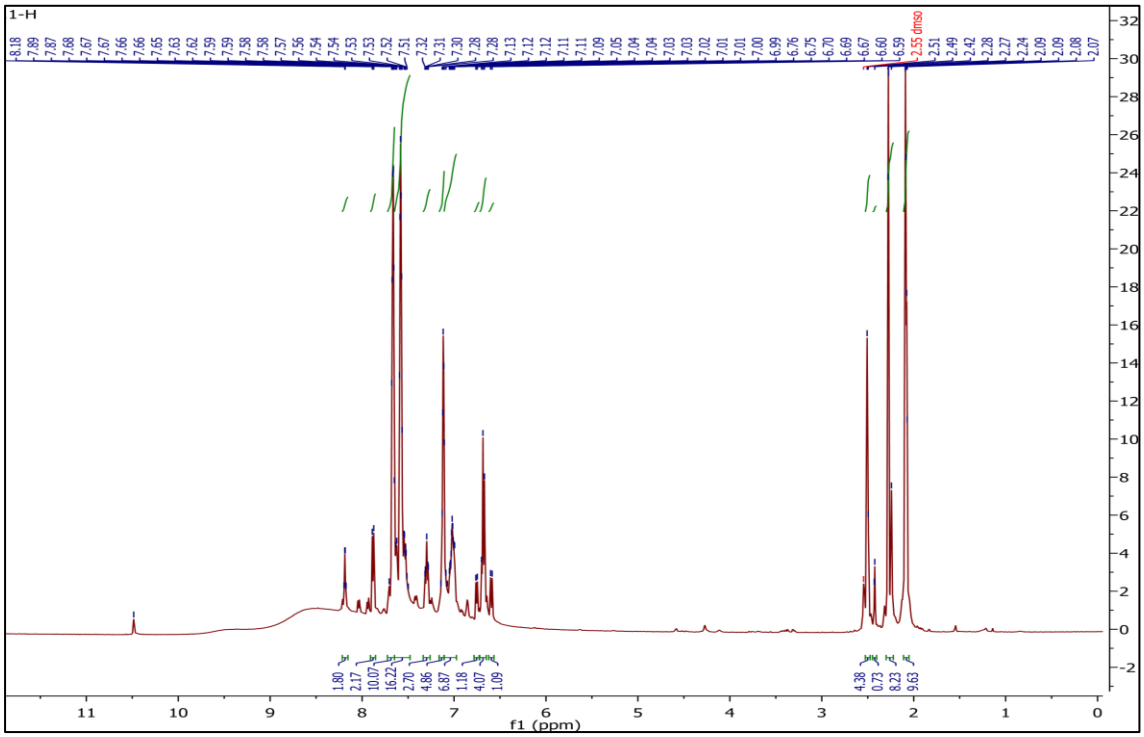
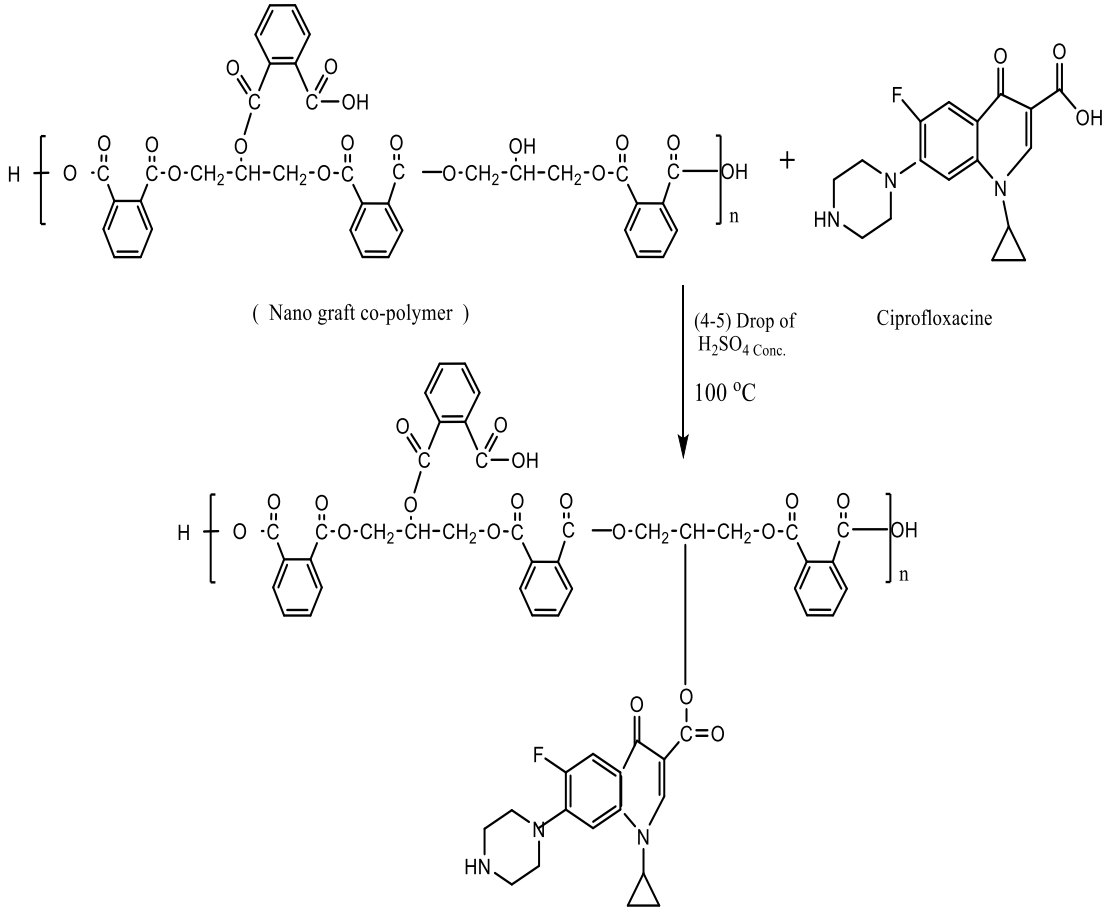


Figure (3-16): The ^{1}HNMR spectrum of nano co-polymer-drug (Z5)

3.2.1.5 Synthesis of compound (Z6)

Amount of compound (Z1) reacted with Ciprofloxacin drug and mixed to gather add to the mixture (3-4) drops of H_2SO_4 Conc. at 100^oC, Equation (3-6) represent synthesis the polymer (Z6).



Equation (3-6): Synthesis the nano co-polymer-drug (Z6)

The FT-I.R spectrum of compound (Z6), Figure (3-17), shows appearance absorption band appear a weak broad band at (3432.08 cm^{-1}) attributed to the bond (O-H) alcoholic and appearance of absorption band of C=C-H_{amide} at (3014.68) cm^{-1} and absorption band of C-C-H_{aliph} at (2837.93) cm^{-1} and absorption band at (1720.25) cm^{-1} of C=O ester , and absorption band of C=C ph. at (1500.6) cm^{-1}, and absorption band of C-O at (1272.18) cm^{-1}, and absorption band of C-N at (1164.00) cm^{-1}, and appear absorption bond Di substation aromatic ring at 745.71 cm^{-1}.

The ^{1}H-NMR spectrum for compound (Z6), Figure (3-18), shows disappearance a single signal at 13 for $(OH)_{acid}$, and appearance signal at 8 for $(C=C-H)_{ph}$, and appearance signal 3.5 (C=O)ester, and appearance signal at 2.5 for $(C-H_3)$.

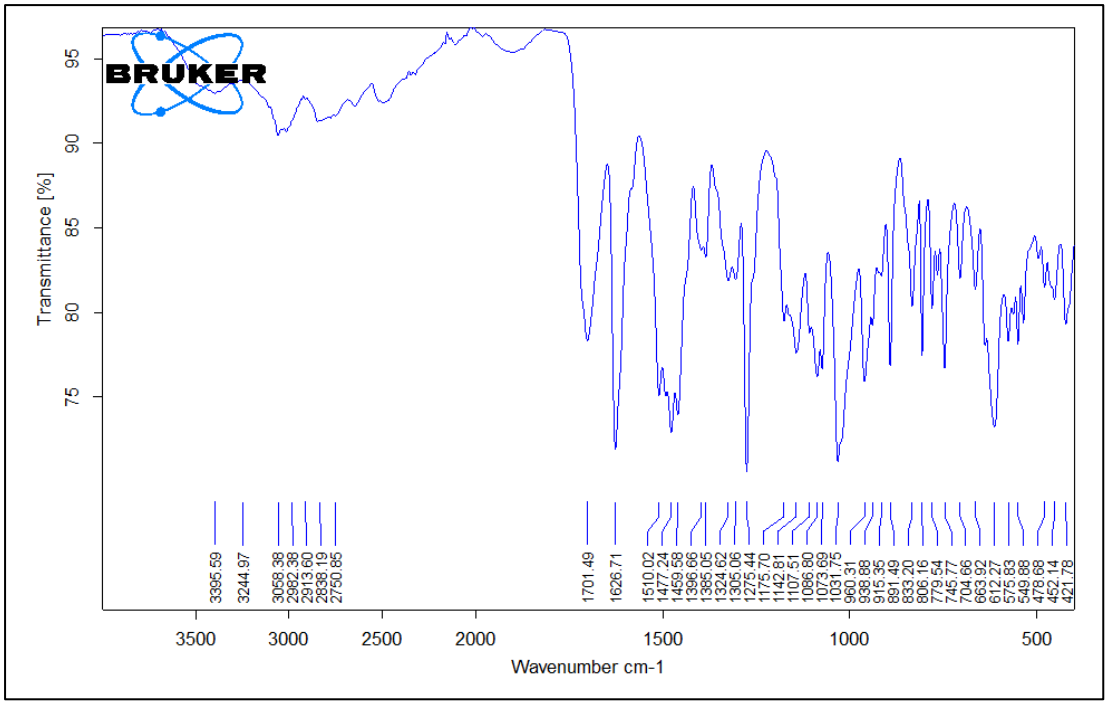


Figure (3-17): The FT-IR spectrum of nano co-polymer-drug (Z6)

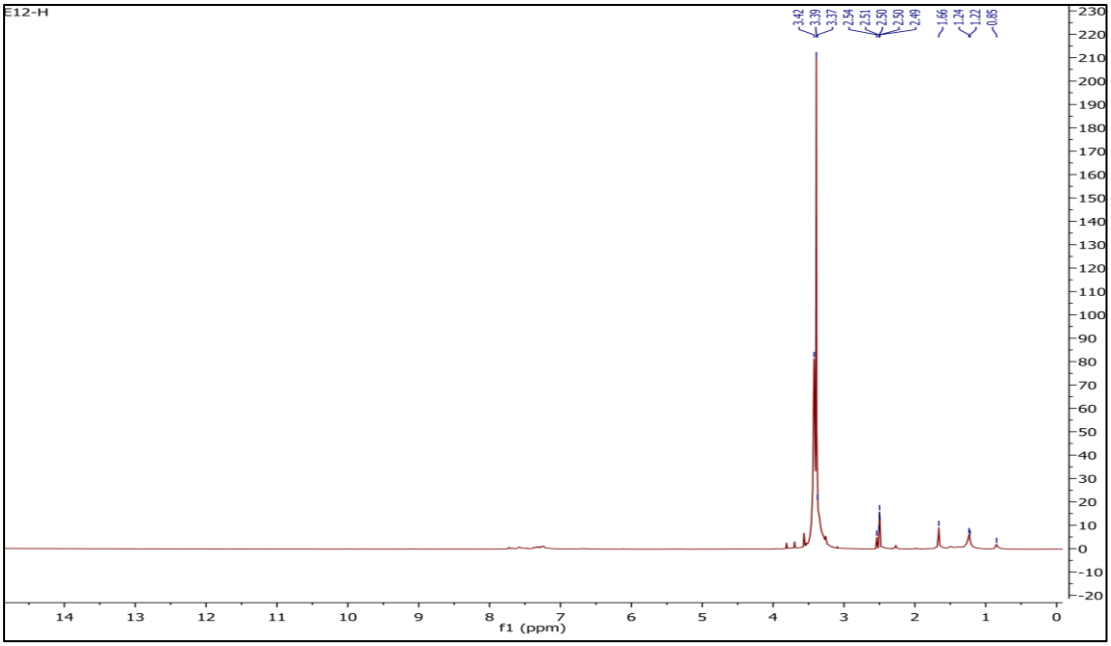
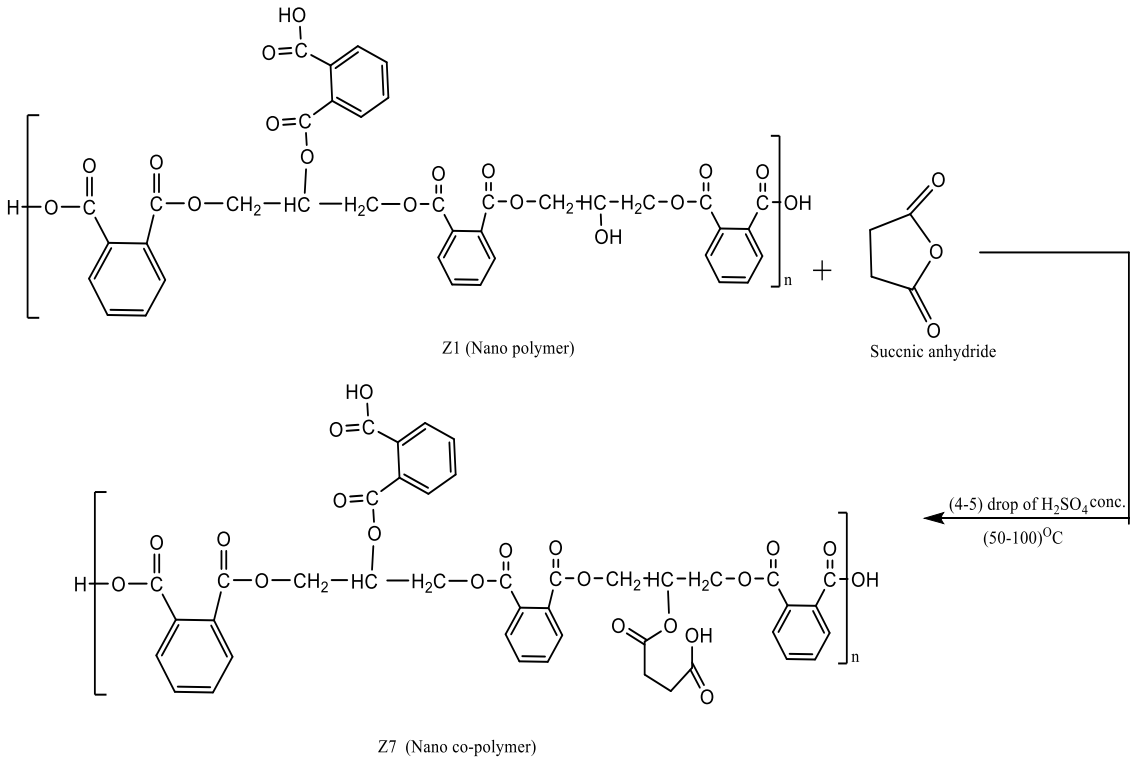


Figure (3-18): The ^{1}HNMR spectrum of nano co-polymer-drug (Z6)

3.2.2 Synthesis of nano co-polymer-Drug (Line 2)

3.2.2.1 Synthesis of polymer (Z7)

Amount of compound (Z1) reacted with Succsnic anhydride and mixed to gather add to the mixture (3-4) drops of H_2SO_4 Conc. in (50-100^oC); Equation (3-7) represent synthesis the co-polymer (Z7).



Equation (3-7): Synthesis the nano co-polymer-drug (Z7)

The FT-IR spectrum of compound (Z7), Figure (3-19), shows appearance absorption band appear a weak broad band at (3063 cm^{-1}) attributed to the bond (O-H) alcoholic, and absorption band of C-C-H_{aliph} at (2970.21) cm^{-1} and absorption band at (1671) cm^{-1} of C=O ester and absorption band of C=$C_{ph.}$ at (1402.84) cm^{-1} and absorption band of C-O at (1069) cm^{-1} and appear absorption bond di-substation aromatic ring at 797 cm^{-1}.

Figure (3-20), shows the ^{1}H-NMR spectrum of compound (Z7), disappearance a single signal at 13ppm for $(OH)_{acid}$, and appearance signal at 7.5 ppm for $(C=C-H)_{ph.}$, and appearance signal at 3ppm for $(C-H_3)$.

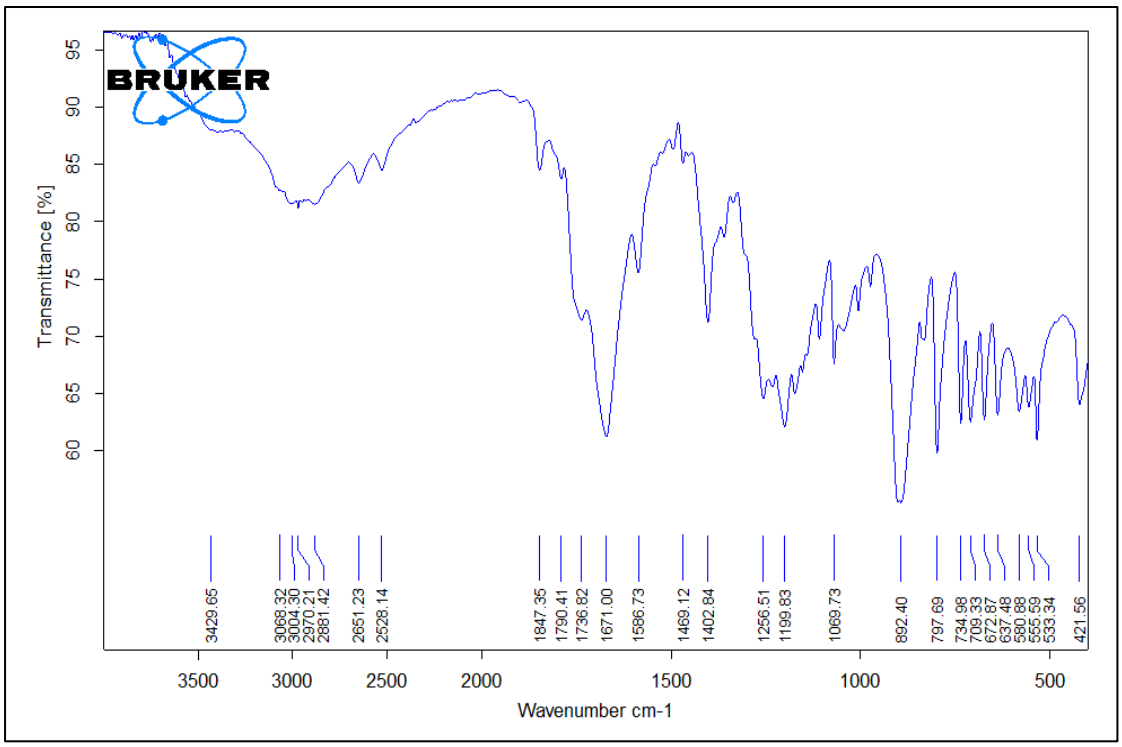


Figure (3-19): FT-IR spectrum of nano co-polymer-drug (Z7)

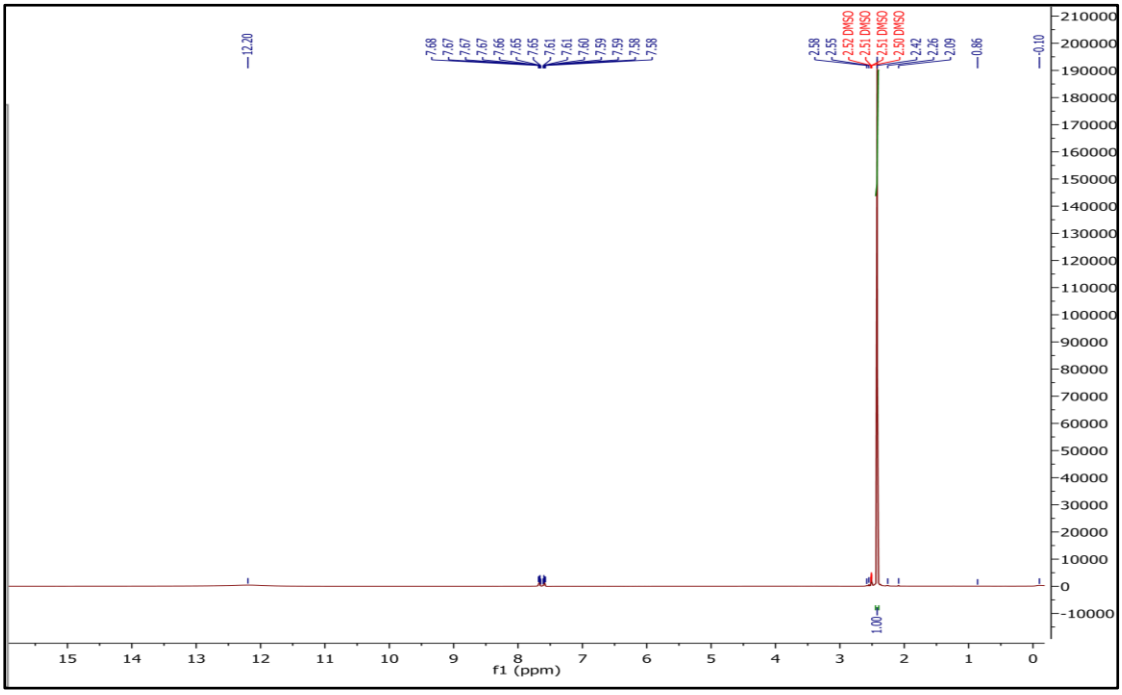
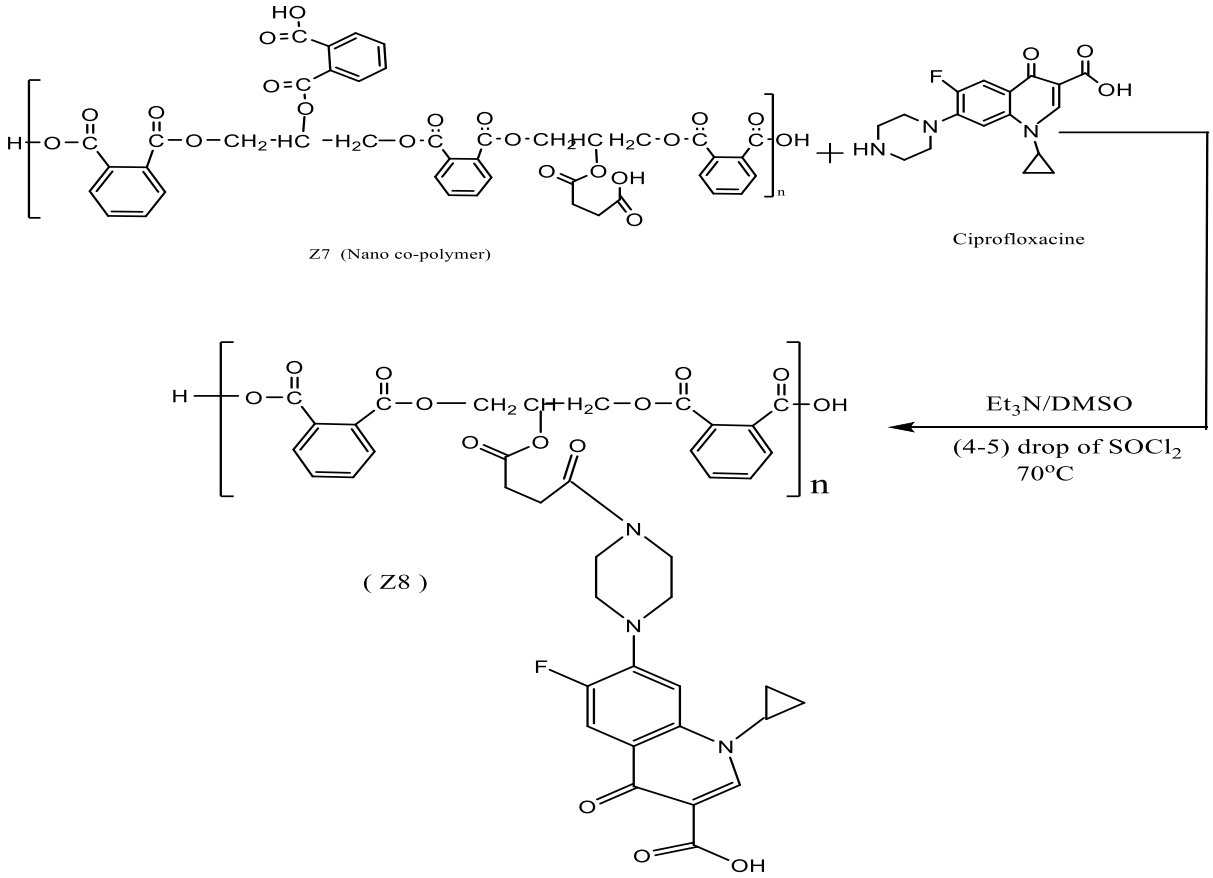


Figure (3-20): ^{1}HNMR spectrum of nano co-polymer-drug (Z7)

3.2.2.2 Synthesis of polymer (Z8)

Amount of compound (Z7) and added dimethylsulfoxide (DMSO) then add thionylchloride ($SOCl_2$), were mixed together and heating at 20°C, and then added trimethylamine, after 15 Min., add the drug of Ciprofloxacin at 70°C and 30 Min., Equation (3-8) represent synthesis the polymer (Z8).



Equation (3-8): Synthesis the nano co-polymer-drug (Z8)

The FT-I.R spectrum of compound (Z8), Figure (3-21), shows appearance of absorption band of C=C-H_{amide} at (3057.10) cm^{-1} and absorption band of C-C-H_{aliph} at (2846.21) cm^{-1} and absorption band at (1697.32) cm^{-1} of C=O amide and absorption band of C=C ph. at (1459.12) cm^{-1}, and absorption band of C-O at (1029.85) cm^{-1}, and absorption band of C-N at (1174.51) cm^{-1} and appear absorption bond di substation aromatic ring at (745.49) cm^{-1} . The ^{1}H-NMR spectrum for compound (Z8), Figure

(3-22), shows disappearance a single signal at 13ppm for $(OH)_{acid}$, and appearance signal at 8ppm for $(C=C-H)_{ph}$, and appearance signal at 7.5ppm for $(C=C-H)_{amid}$, and appear signal at 2.5ppm for (CH_3).

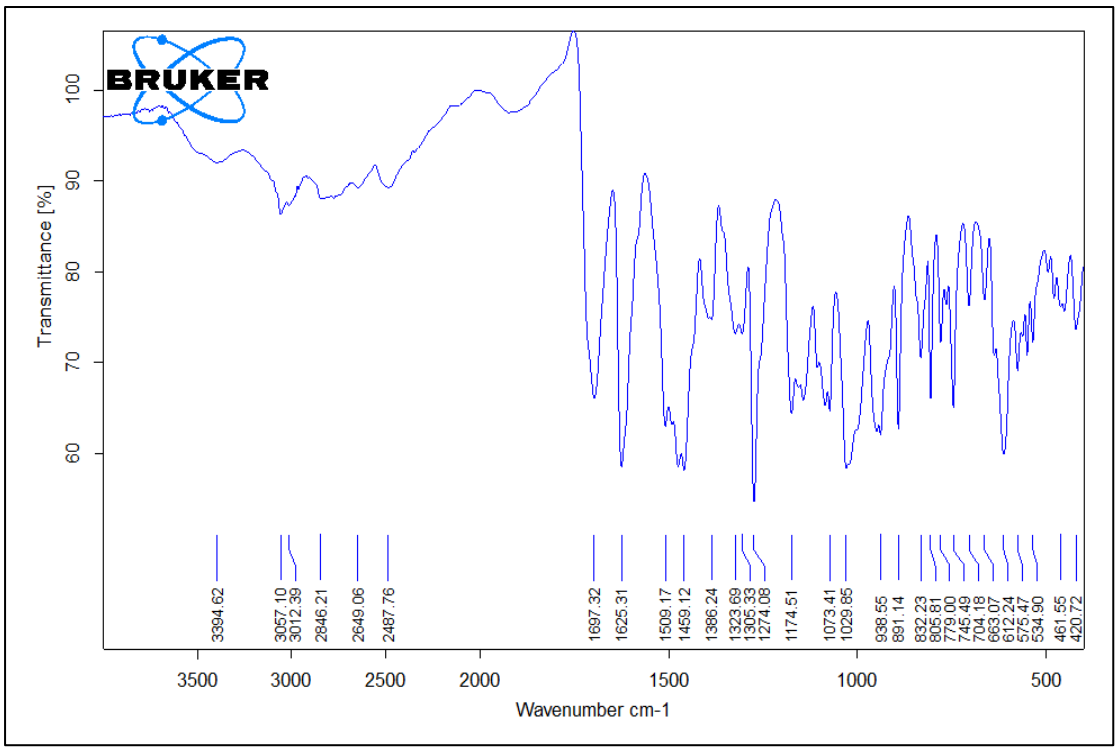


Figure (3-21): FT-IR spectrum of nano co-polymer-drug (Z8)

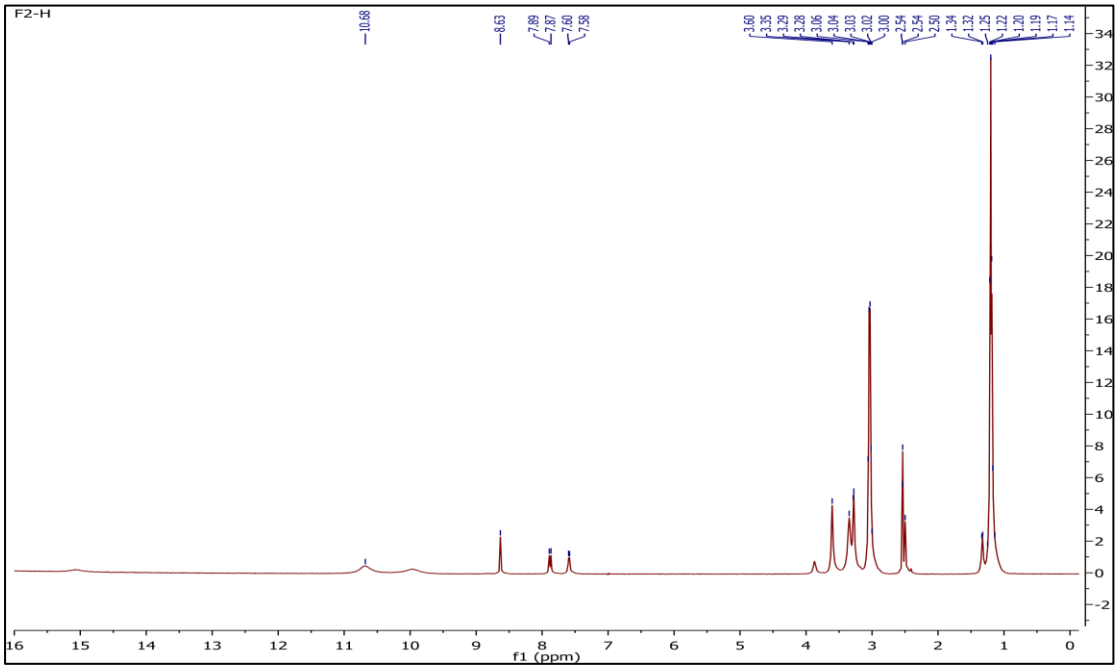
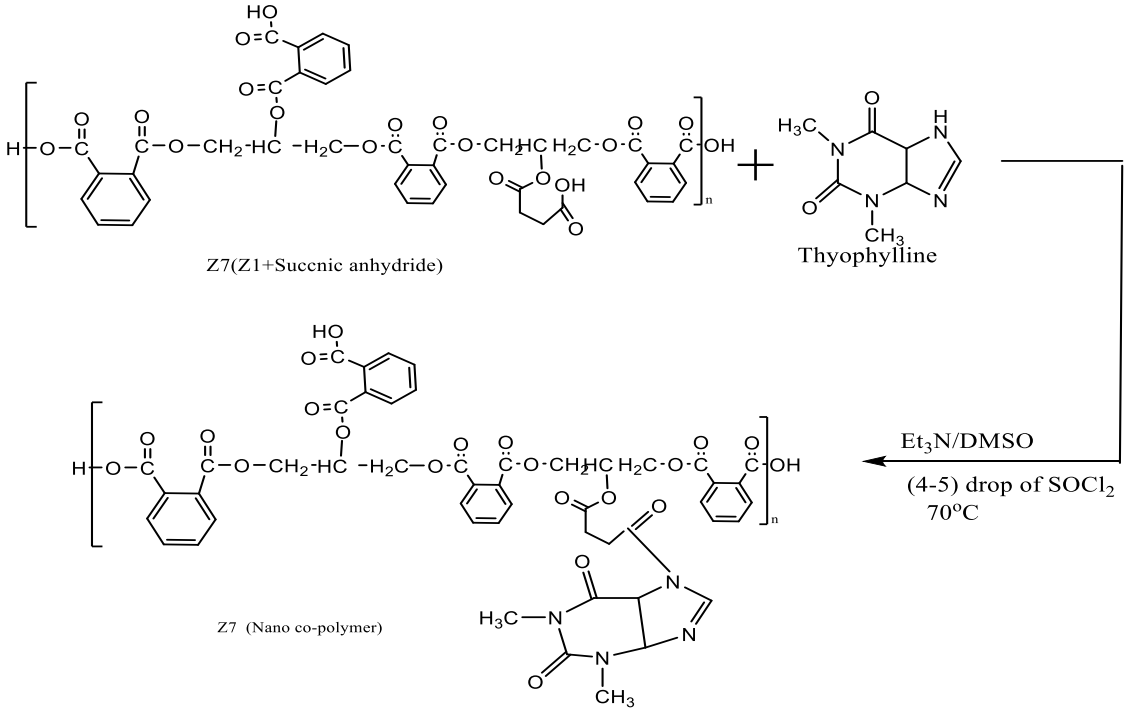


Figure (3-22) The ^{1}HNMR spectrum of nano co-polymer-drug (Z8)

3.2.2.3 Synthesis of nano co-polymer-drug (Z9)

Amount of compound (Z7) and added dimethylsulfoxide (DMSO) then add thionylchloride($SOCl_2$), were mixed together and heating at 20°C, and then added trimethylamine, after 15 Min., add the drug of Theophylline at 70°C and 30 Min., Equation (3-8) represent synthesis the polymer (Z9).

The FT-IR spectrum of compound (Z9), Figure (3-23), shows appearance of absorption band of $C=C-H_{amide}$ at (3055.07) cm^{-1} and absorption band of $C-C-H_{aliph}$ at (2981.35) cm^{-1} and absorption band at (1660.74) cm^{-1} of C=O amide, and absorption band of C=C ph. at (1441.81) cm^{-1}, and absorption band of C-O at (1047.82) $cm^{-1}$and absorption band of C-N at (1187.20) cm^{-1}, and appear absorption bond Di substation aromatic ring at (741.54) cm^{-1}. The ^{1}H-NMR spectrum for compound (Z9), Figure (3-24), shows appearance a single signal at 13ppm for $(OH)_{acid}$, and appearance signal at 8ppm for $(C=C-H)_{ph}$, and appearance signal at (3-4)ppm for $(C=C-H)_{amid}$.



Equation (3-8): synthesis the nano co-polymer-drug (Z9)

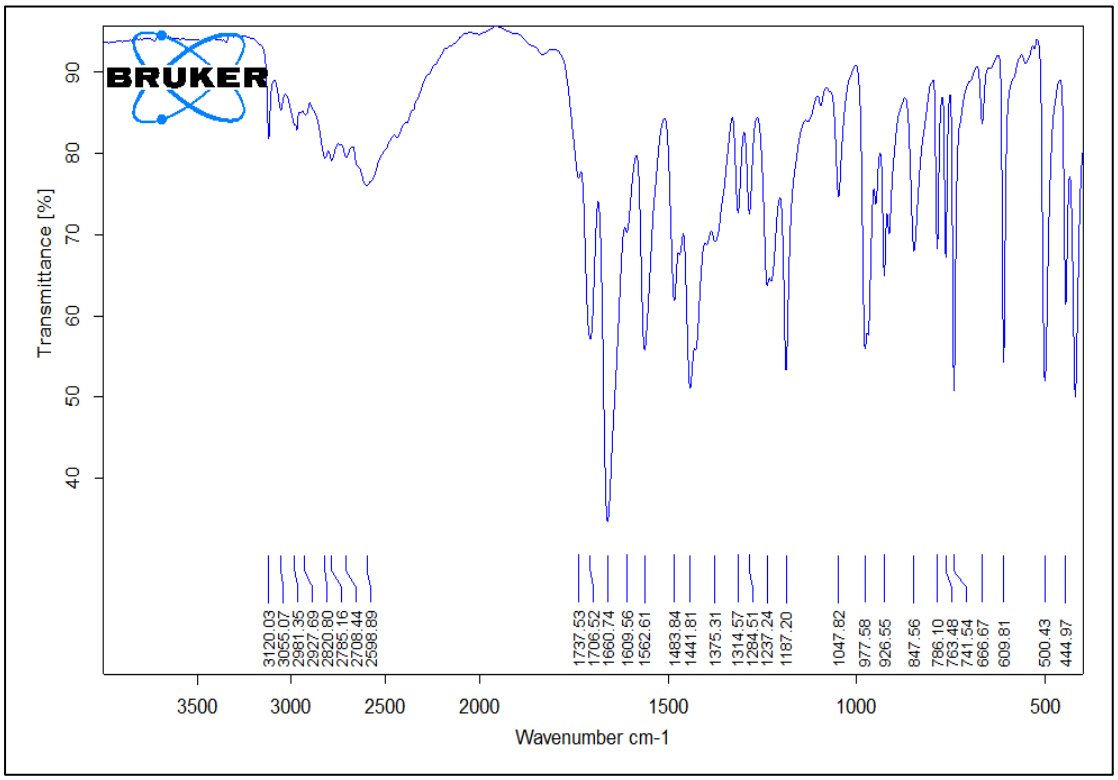


Figure (3-21): The FT-IR spectrum of nano co-polymer-drug (Z9)

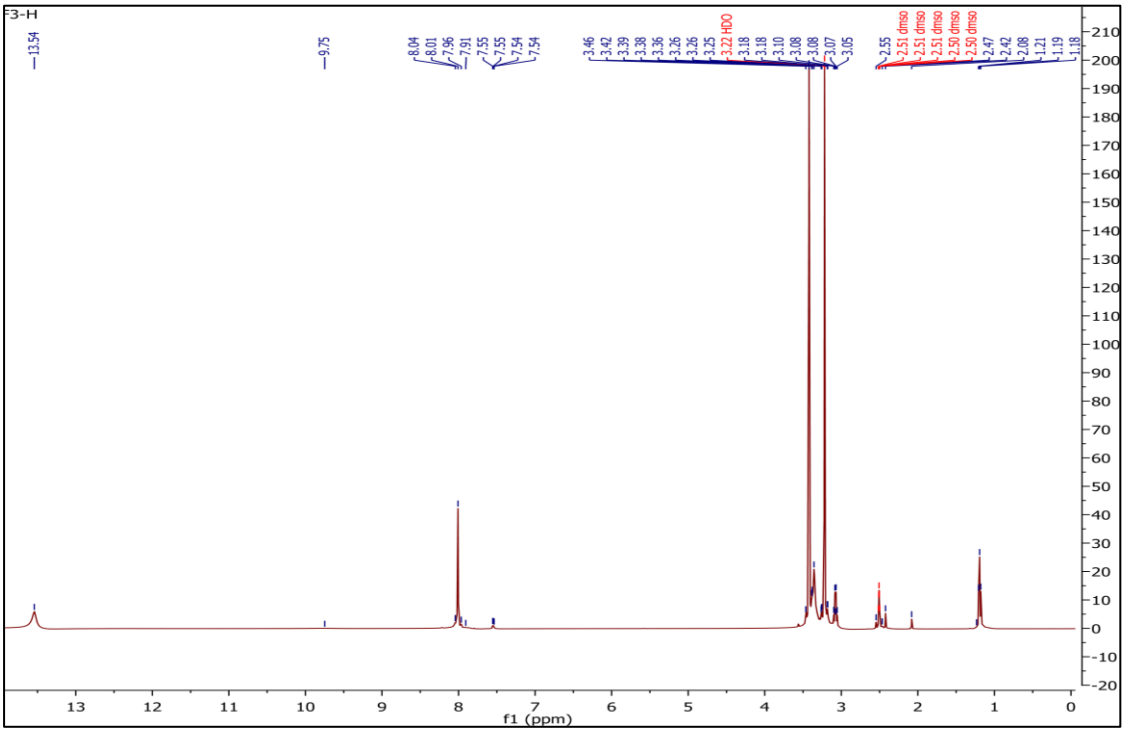
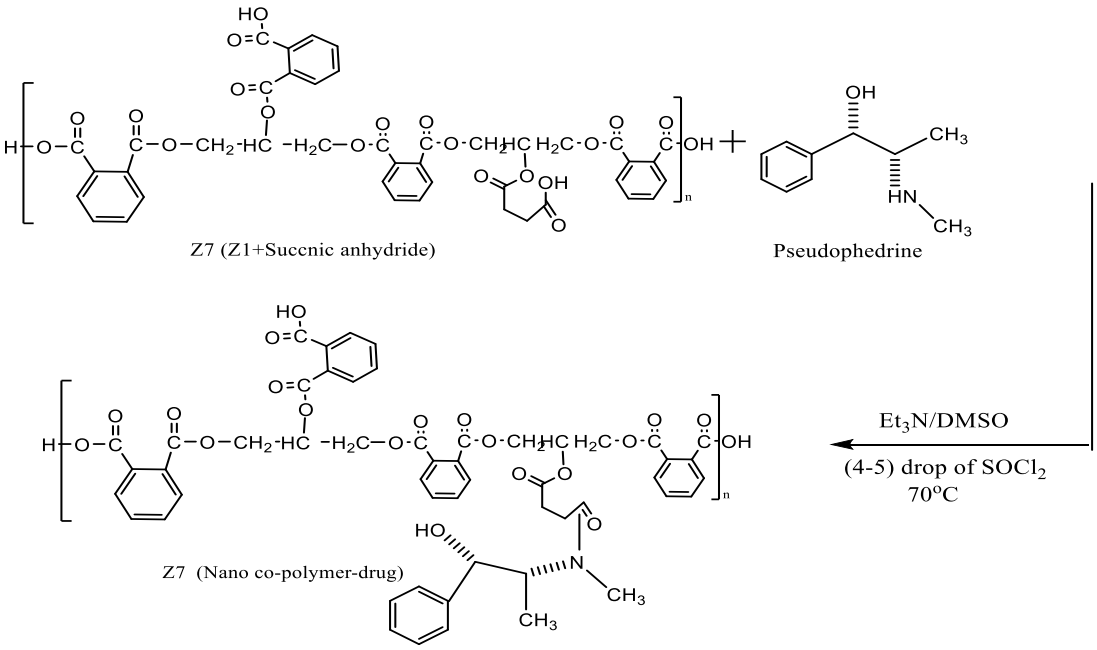


Figure (3-22) The ^{1}HNMR spectrum of nano co-polymer-drug (Z9)

3.2.2.3 Synthesis of polymer (Z10)

Amount of compound (Z7) and added dimethyl sulfoxide (DMSO) then add thionylchloride($SOCl_2$), were mixed together and heating at 20°C, and then added trimethylamine, after 15 Min., add the drug of Pseudoephedrine at 70°C and 30 Min., Equation (3-7) represent synthesis the polymer (Z10).

The FT-IR spectrum of compound (Z10), Figure (3-23), shows appearance of absorption band of C=C-Hamide at (3010) cm^{-1} and absorption band of C-C-Haliph at (2921.07) cm^{-1} and absorption band at (1674.38) cm^{-1} of C=O amide, and absorption band of C=C ph. at (1401.49) cm^{-1}, and absorption band of C-O at (1069.20) cm^{-1}, and absorption band of C-N at (1257.28) cm^{-1}, and appear absorption bond Di substation aromatic ring at (735.47) cm^{-1}. The 1H-NMR spectrum for compound (Z10), Figure (3-24), shows appearance a single signal at 13ppm for (OH)acid, and appearance signal at 8 ppm for (C=C-H) ph, and appearance signal at 4 ppm for (C=C-H)amid.



Equation (3-7): Synthesis of the nano co-polymer-drug (Z10)

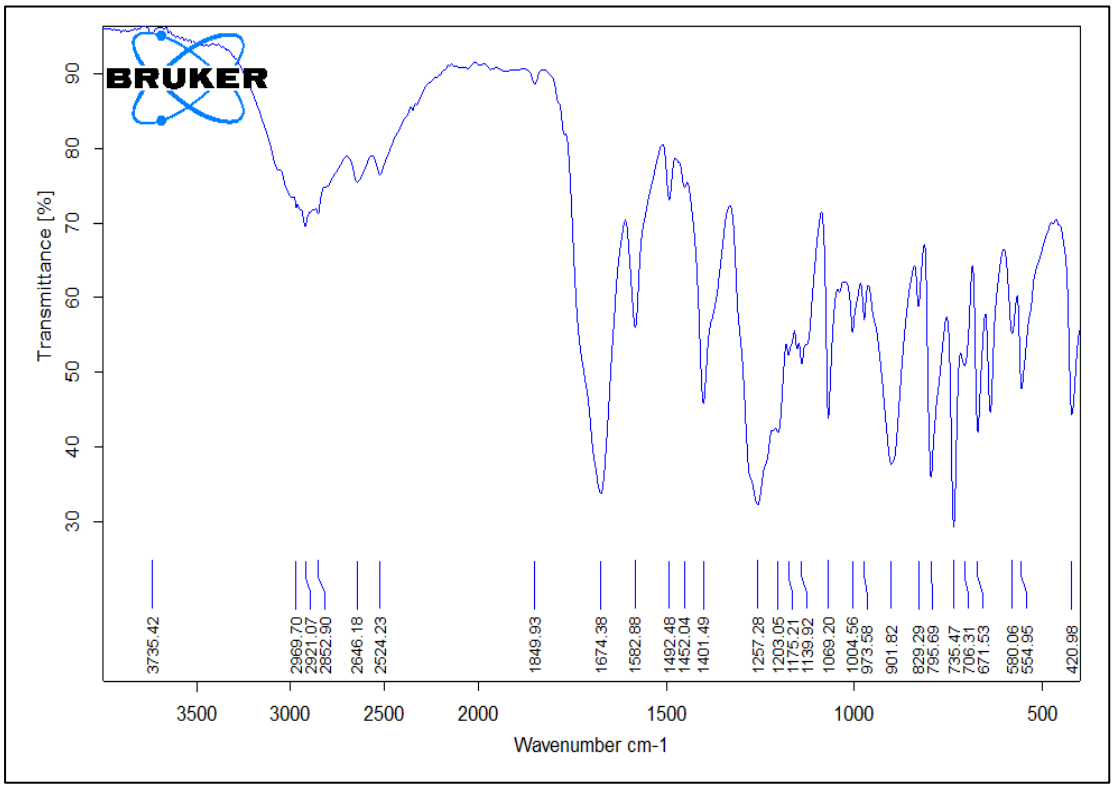


Figure (3-23): The FT-IR spectrum of nano co-polymer-drug (Z10)

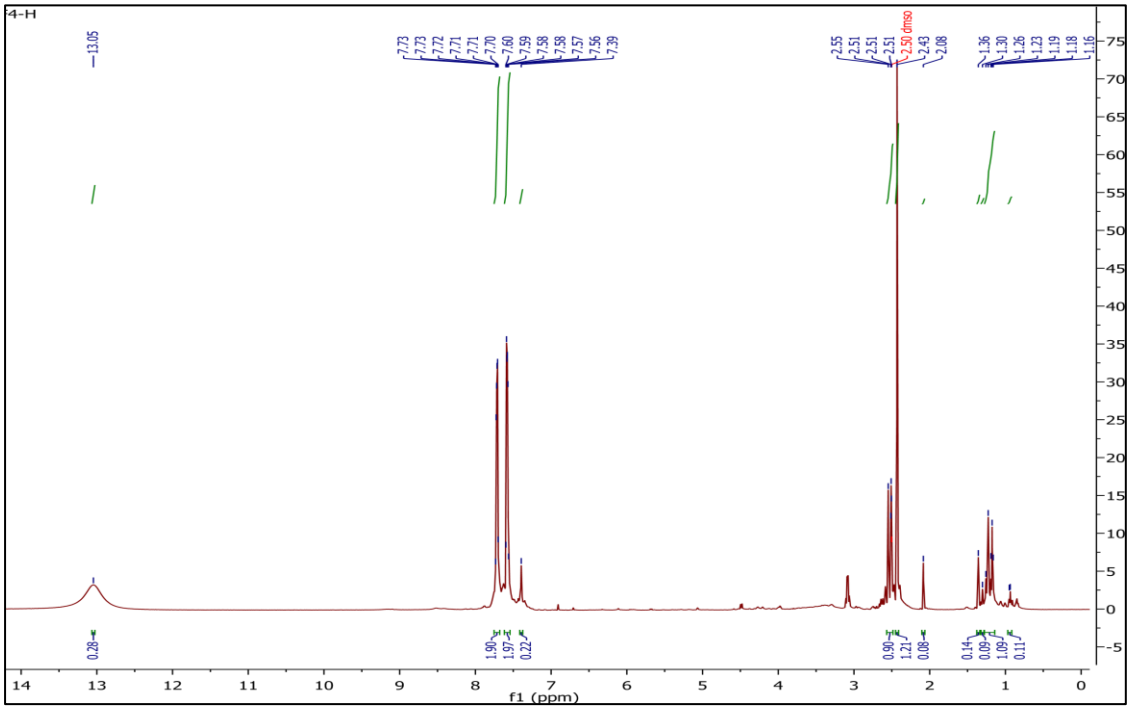
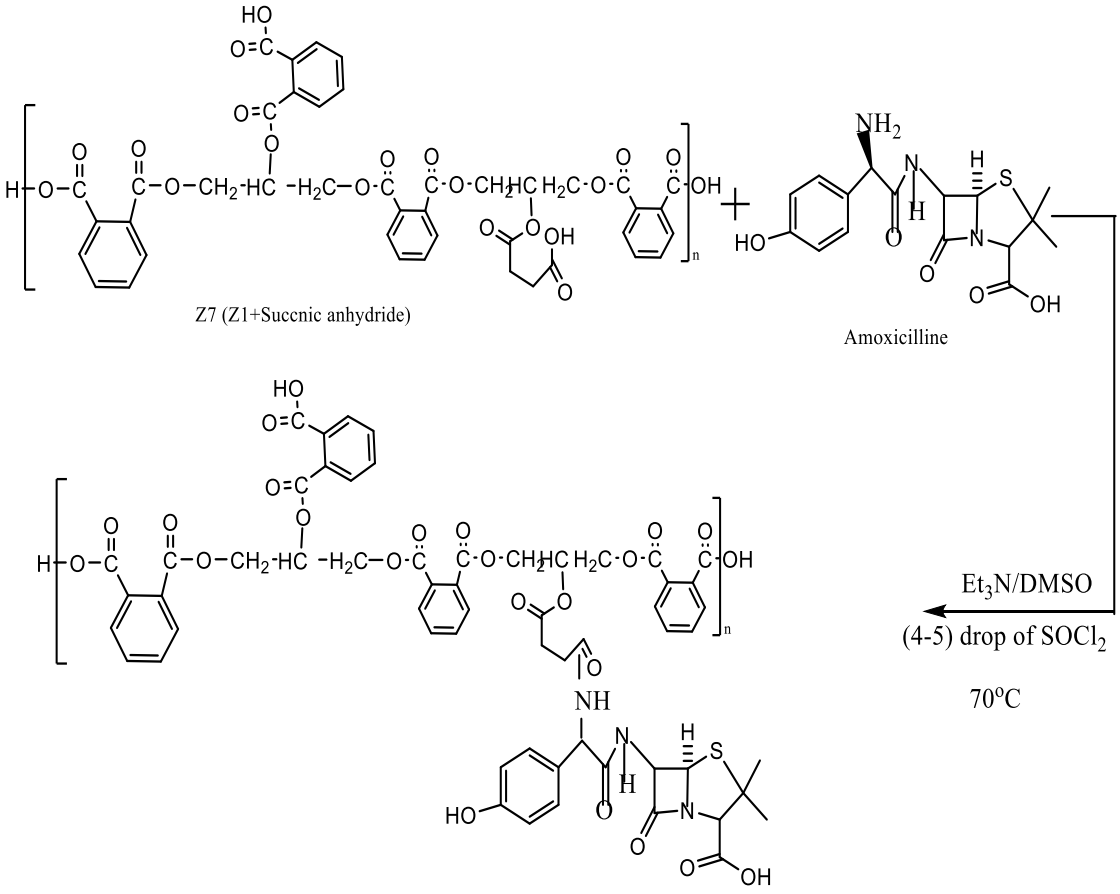


Figure (3-24): ^{1}HNMR spectrum of the nano co-polymer-drug (Z10)

3.2.2.4 Synthesis of polymer (Z11)

Compound (Z7), dimethyl sulfoxide (DMSO) and thionylchloride ($SOCl_2$), were mixed and heating at 20°C, and trimethylamine was added, after 15 min., the Amoxicillin drug was added at 70°C and heft for 30 min., Equation (3-8) represent the synthesis of polymer (Z11).



Equation (3-8): Synthesis of the nano co-polymer-drug (Z11)

The FT-IR spectrum of compound (Z11), Figure (3-25), shows appearance of absorption band of C=C-H_{amide} at (3010) cm^{-1} and absorption band of C-C-H $_{aliph}$ at (2982.73) cm^{-1} and absorption band at (1715.80) cm^{-1} of $C=O_{amide}$ and absorption band of $C=C_{ph.}$ at (1069.19) cm^{-1}, and absorption band of C-O at (1377.05) cm^{-1}, and absorption band of C-N at (1251.35) cm^{-1}, and appear absorption bond disubstation aromatic ring at (738.75) cm^{-1}. The ^{1}H-NMR spectrum for compound (Z7), Figure (3-26),

shows disappearance a single signal at 13ppm for $(OH)_{acid}$ and appearance signal at 8 ppm for $(C=C-H)_{ph}$ and appearance signal at (3-4)ppm for $(C=C-H)_{amid}$.

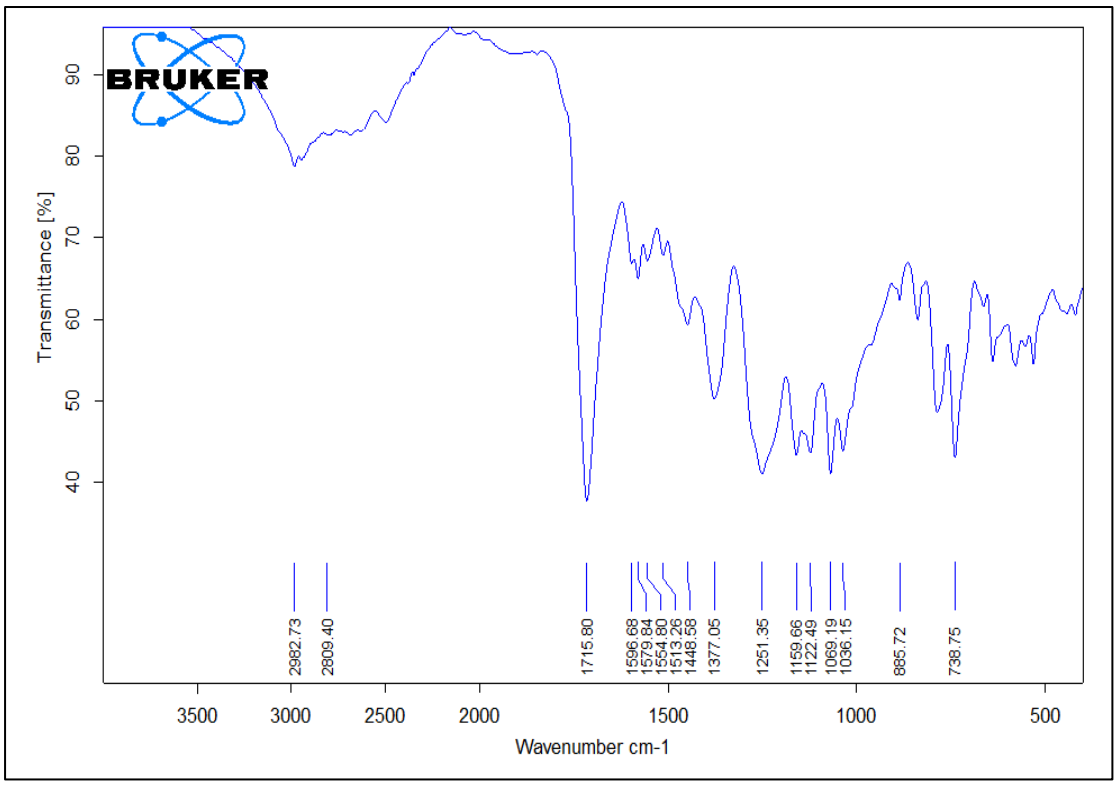


Figure (3-25): FT-IR spectrum of nano co-polymer-drug (Z11)

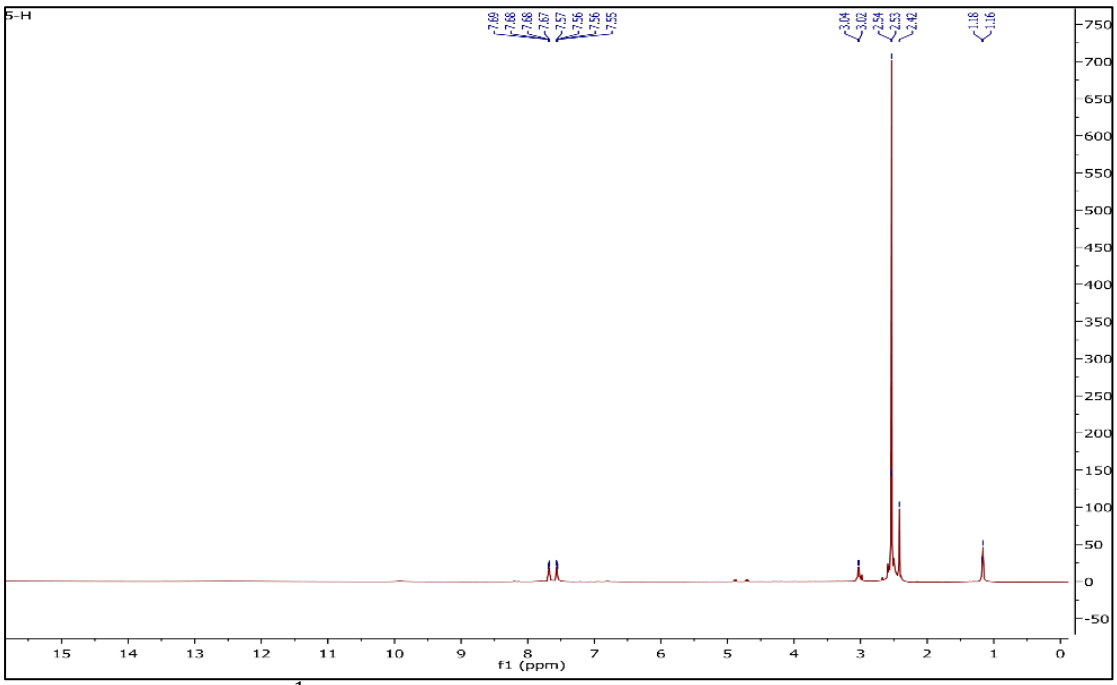
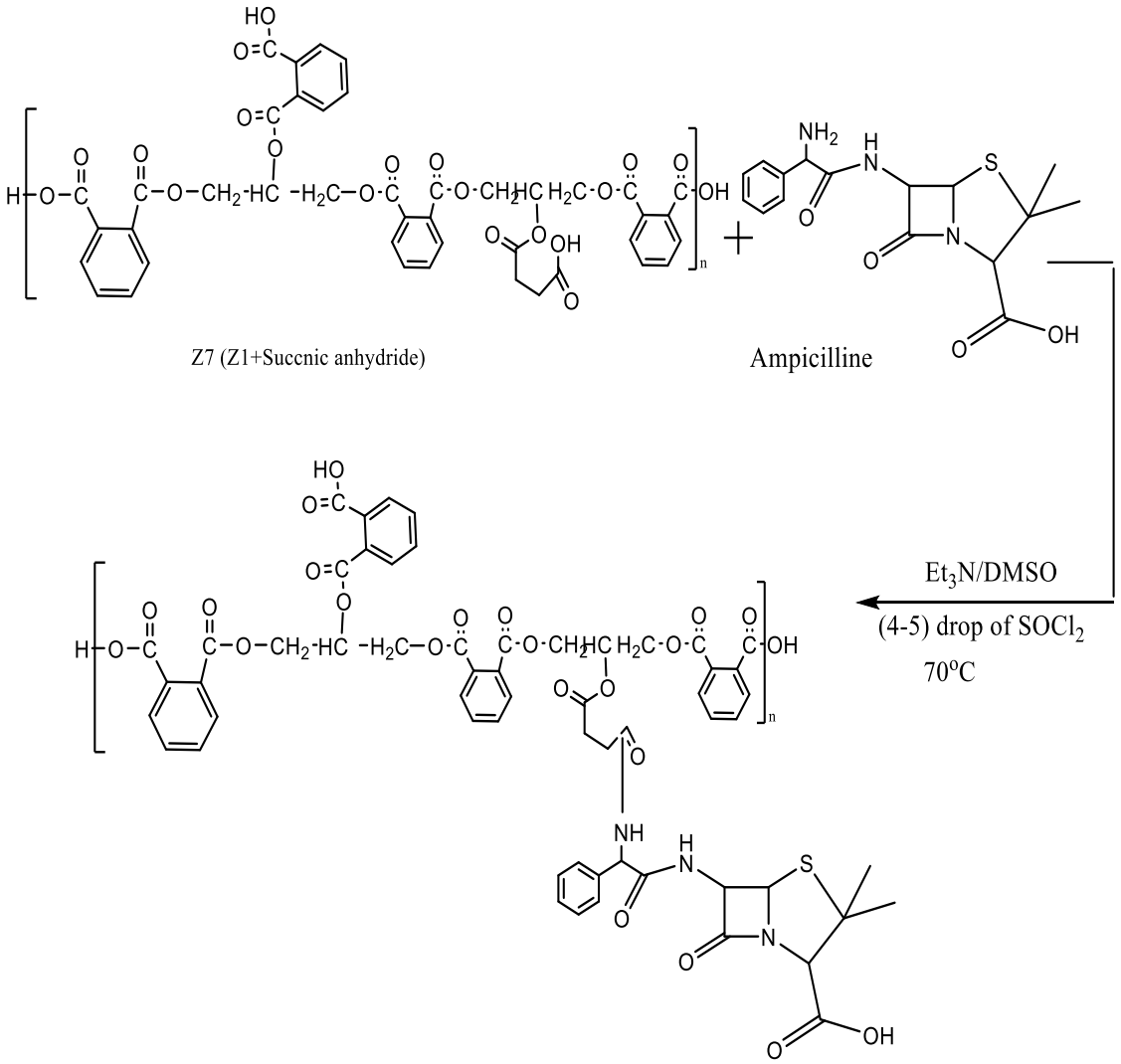


Figure (3-26): ^{1}HNMR spectrum of nano co-polymer-drug (Z11)

3.2.2.5 Synthesis of nano co-polymer-drug (Z12):

Amount of compound (Z7) and added dimethyl sulfoxide (DMSO) then add thionylchloride($SOCl_2$), were mixed together and heating at 20^{o}C, and then added trimethylamine, after 15 Min., add the drug of Ampicillin at 70°C and 30 Min., Equation (3-27) represent synthesis the polymer (Z12).



Equation (3-19): synthesis the nano co-polymer-drug (Z12)

The FT-I.R spectrum of compound (Z12), Figure (3-37), shows appearance of absorption band of C=C-H_{amide} at (3010) cm^{-1} and absorption band of C-C-H_{aliph} at (2980.98) cm^{-1} and absorption band at (1713.21) cm^{-1}

of C=O amide , and absorption band of C=C ph. at (1379.56) cm^{-1}, and absorption band of C-O at (1071.22) cm^{-1}, and absorption band of C-N at (1253.19) cm^{-1}, and appear absorption bond Di substation aromatic ring at (715.86). The ^{1}H-NMR spectrum for compound (Z12), Figure (3-38), shows appearance a single signal at 13ppm for $(OH)_{acid}$, and appearance signal at 8ppm for $(C=C-H)_{ph}$, and appearance signal at 4ppm for $(C=C-H)_{amid}$.

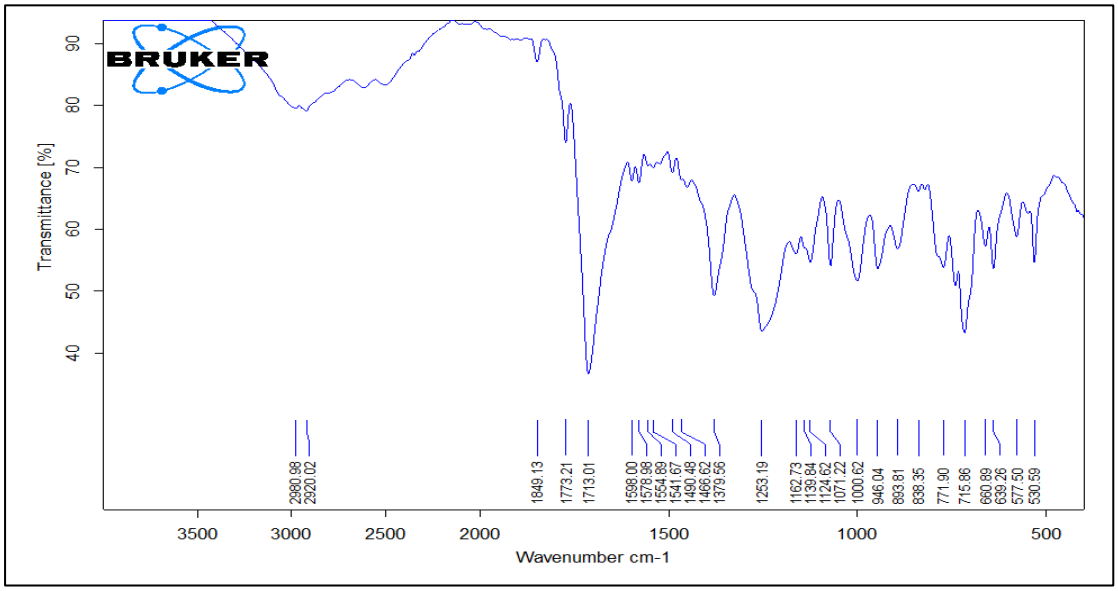


Figure (3-27): FT-IR spectrum of nano co-polymer-drug (Z12)

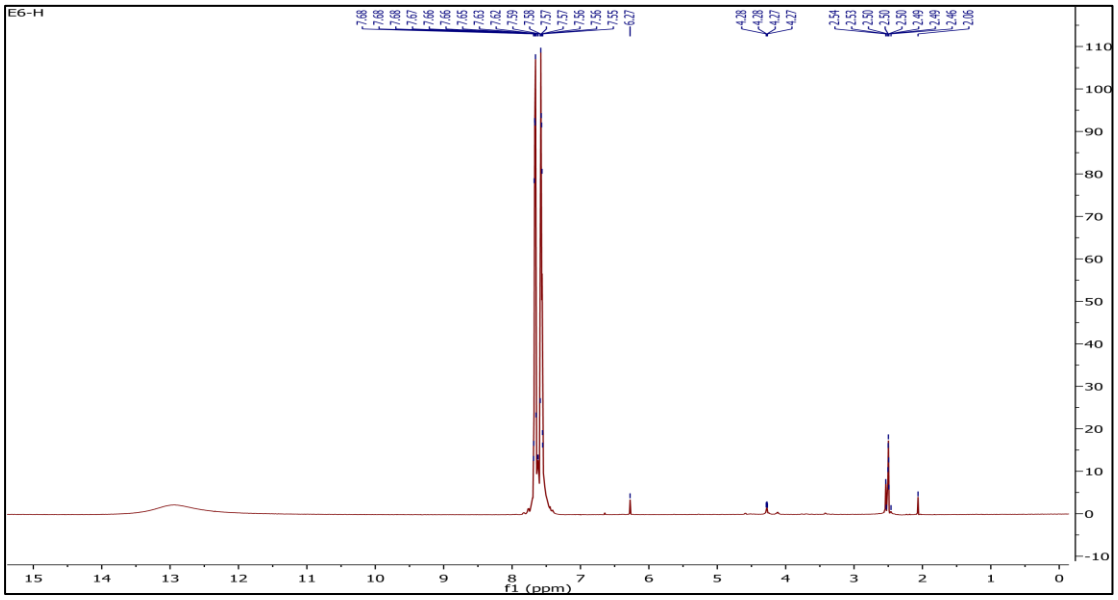
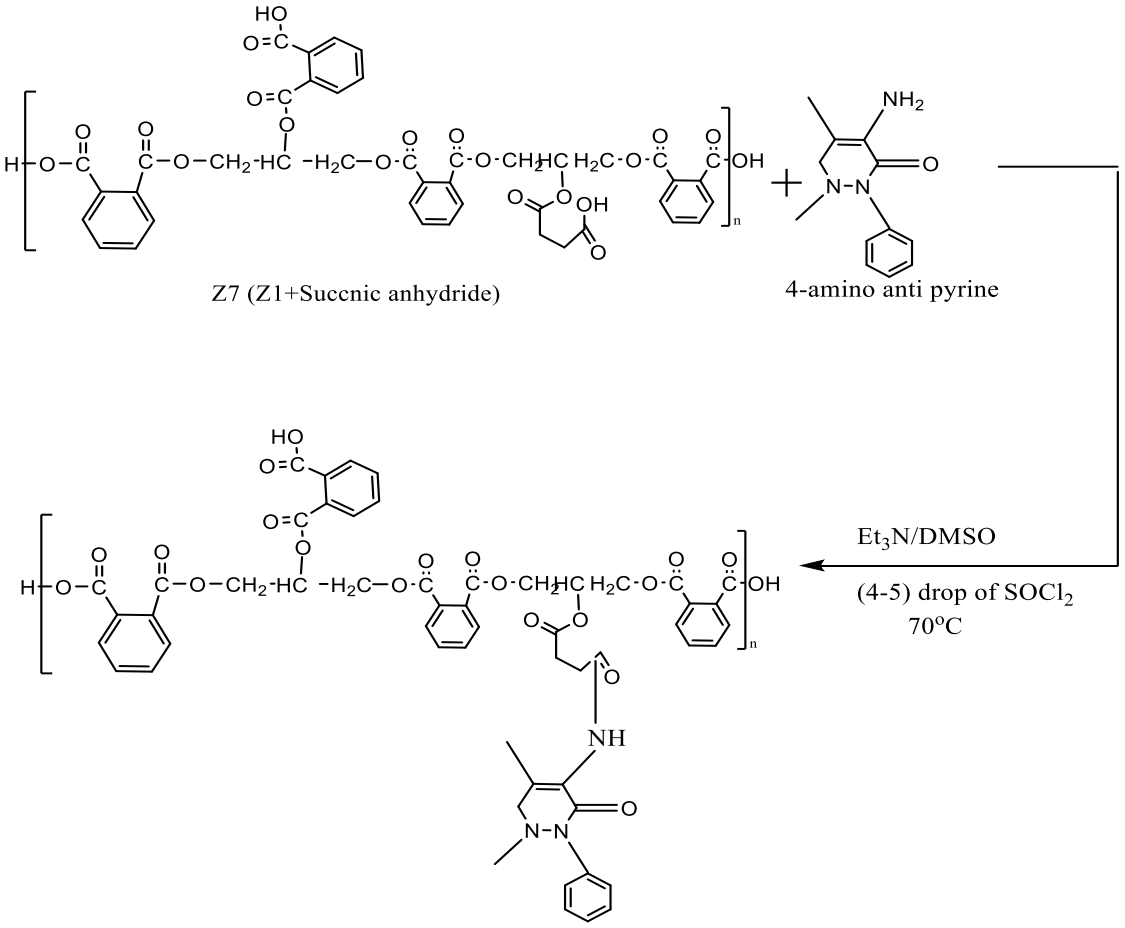


Figure (3-28): ^{1}HNMR spectrum of nano co-polymer-drug (Z12)

3.2.2.6 Synthesis of nano co-polymer-drug (Z13)

Amount of compound (Z7) and added dimethyl sulfoxide (DMSO) then add thionylchloride($SOCl_2$), were mixed together and heating at 20°C, and then added trimethylamine, after 15 Min., add the drug of 4-aminoantipyrine at 70°C and 30 Min., Equation (3-20) represent synthesis the polymer (Z13).



Equation (3-20): Synthesis of the nano co-polymer-drug (Z13)

The FT-IR spectrum of compound (Z13), Figure (3-29), shows appearance of absorption band of C=C-H_{amide} at (3010) cm^{-1} and absorption band of C-C-H_{aliph} at (2921.64) cm^{-1} and absorption band at (1713.24) cm^{-1} of C=O amid, and absorption band of C=C ph. at (1577.96) cm^{-1}, and absorption band of C-O at (1383.65) cm^{-1}, and absorption band of C-N at (1246.77) cm^{-1} and appear absorption bond disubstation aromatic ring at

(741.12) cm^{-1} . The ^{1}H-NMR spectrum for compound (Z13), Figure (3-30), shows disappearance a single signal at 13ppm for $(OH)_{acid}$ and appearance signal at 8ppm for $(C=C-H)_{ph}$ and appearance signal at (2-4)ppm for $(C=C-H)_{amid}$.

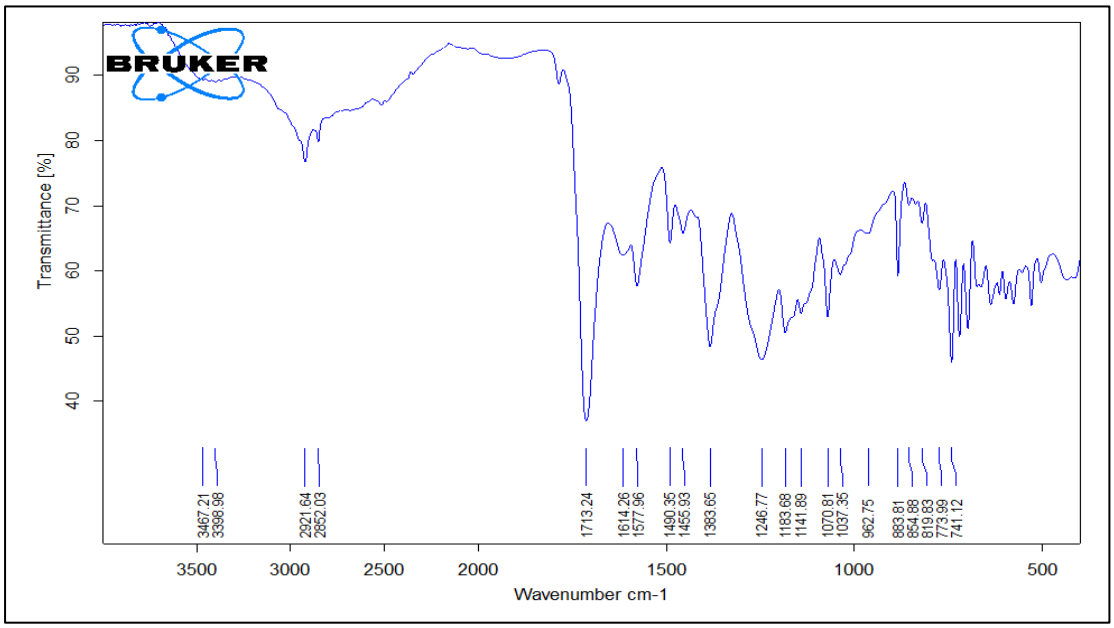


Figure (3-29): FT-IR spectrum of nano co-polymer-drug (Z13)

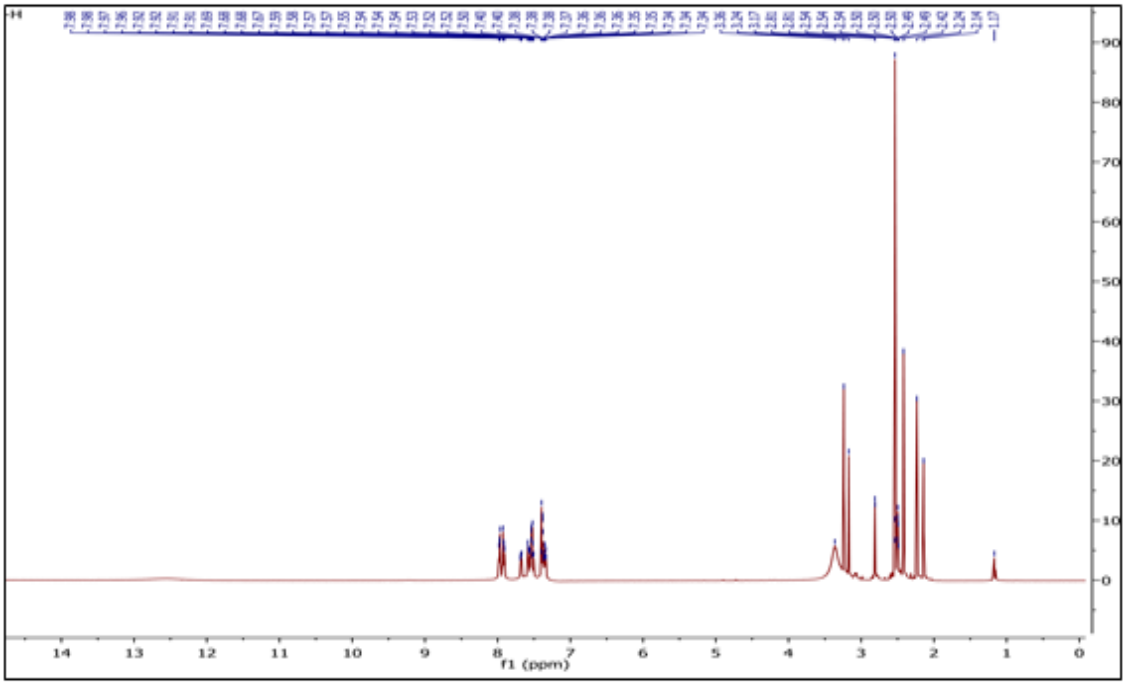


Figure (3-30): ^{1}HNMR spectrum of nano co-polymer-drug (Z13)

3.3 Characteristic of Solubility

The solubility properties of prepared polymers, in different solvents (H_2O, Ethanol, Methanol, DMSO, Hexane and Acetone) were studied.

The solubility of these polymers was observed, some of which were completely dissolved (+) and some of them solids partially dissolved (partial), the other andissolved (-), as shown in Tables (3-4) for synthesis of the nano co-polymers-drug.

Table (3-4): The solubility of synthesis polymers

Nano co-polymer-drugs	H_2O	EtOH	MeOH	DMSO	Hexane	Acetone
Z1	Partial	partial	partial	+	_	+
Z2	Partial	+	+	+	_	+
Z3	Partial	+	+	+	_	+
Z4	Partial	+	+	+	_	+
Z5	Partial	+	+	+	_	+
Z6	Partial	_	+	+	_	+
Z7	Partial	+	+	+	_	+
Z8	Partial	_	partial	+	_	partial
Z9	+	+	+	+	_	+
Z10	Partial	+	+	+	_	_
Z11	Partial	_	_	+	_	+
Z12	+	+	+	+	_	+
Z13	+	+	+	+	_	+

3.4 Swelling ratio

Tables (3-5) to (3-7) and Figures (3-31) to (3-36) represent the swelling ratio and the behavior curves of swelling in different time (hour and day) of prepared nano co-polymer-drugs **(Line 1)**.

Table (3-5): Swelling ratio per time (hour and day) of nano co-polymer-drugs in pH=2.2 at 310 K **(Line 1)**

Time	**Swelling Ratio %**				
(Hour)	**Types of polymers**				
	Z2	**Z3**	**Z4**	**Z5**	**Z6**
1	1.155	0.626	0.823	0.179	0.402
2	1.348	0.823	1.002	0.243	0.626
3	1.568	1.005	1.199	0.402	0.823
4	1.885	1.219	1.502	0.434	1.002
5	1.955	1.347	1.822	0.476	1.228
(Day)					
1	2.723	2.223	2.113	0.526	1.933
2	2.922	2.333	2.166	0.544	2.00
3	3.122	2.524	2.244	0.566	2.075
4	3.277	2.723	2.331	0.586	2.205
5	3.505	2.996	2.664	0.622	2.455
6	3.846	3.474	3.100	0.642	2.956
7	4.030	3.660	3.121	0.661	3.007

Table (3-6): Swelling ratio per time (hour and day) of nano co-polymer-drugs in pH=7.0 at 310 K **(Line 1)**

Time	**Swelling Ratio %**				
(Hour)	**Types of polymers**				
	Z2	**Z3**	**Z4**	**Z5**	**Z6**
1	1.386	0.793	0.992	0.378	0.626
2	1.663	0.999	1.223	0.586	0.793
3	1.966	1.221	1.442	0.773	0.992
4	2.339	1.388	1.677	0.993	1.187
5	2.553	1.926	2.210	1.116	1.768
(Day)					
1	2.922	2.522	2.723	1.961	2.142
2	3.102	2.623	2.932	2.152	2.343
3	3.362	2.773	3.111	2.206	2.446
4	3.642	3.107	3.394	2.378	2.706
5	4.003	3.553	3.801	2.398	3.009
6	4.114	3.746	3.927	2.522	3.256
7	4.223	3.756	4.030	2.597	3.556

Table (3-7): Swelling ratio per time (hour and day) of nano co-polymer-drugs in pH=8.0 at 310 K **(Line 1)**

Time	**Swelling Ratio %**				
(Hour)	**Types of polymers**				
	Z2	**Z3**	**Z4**	**Z5**	**Z6**
1	1.798	0.992	1.382	0.585	0.7646
2	1.990	1.189	1.579	0.873	0.9925
3	2.162	1.543	1.884	1.224	1.3726
4	2.344	1.793	2.133	1.565	1.6626
5	2.740	1.998	2.305	1.599	1.7662
6	2.901	2.432	2.537	1.728	1.849
(Day)					
1	3.003	2.733	2.883	2.142	2.343
2	3.209	2.962	3.110	2.223	2.534
3	3.299	3.114	3.221	2.537	2.884
4	3.662	3.488	3.553	2.733	3.155
5	4.123	3.845	3.993	3.102	3.603
6	4.443	4.099	4.334	3.552	3.852
7	4.562	4.334	4.443	3.693	4.107
8	4.803	4.672	4.848	3.905	4.361

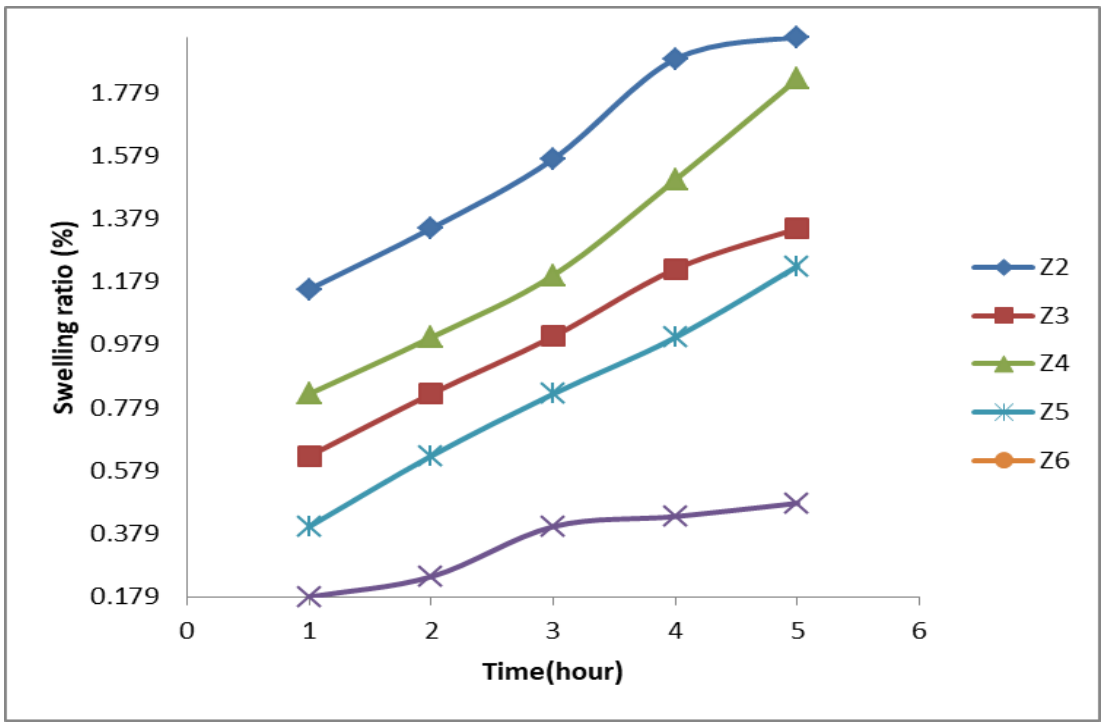


Figure (3-31): Swelling ratio per time (hour) of nano co-polymer-drugs in pH=2.2 at 310 K **(Line 1)**

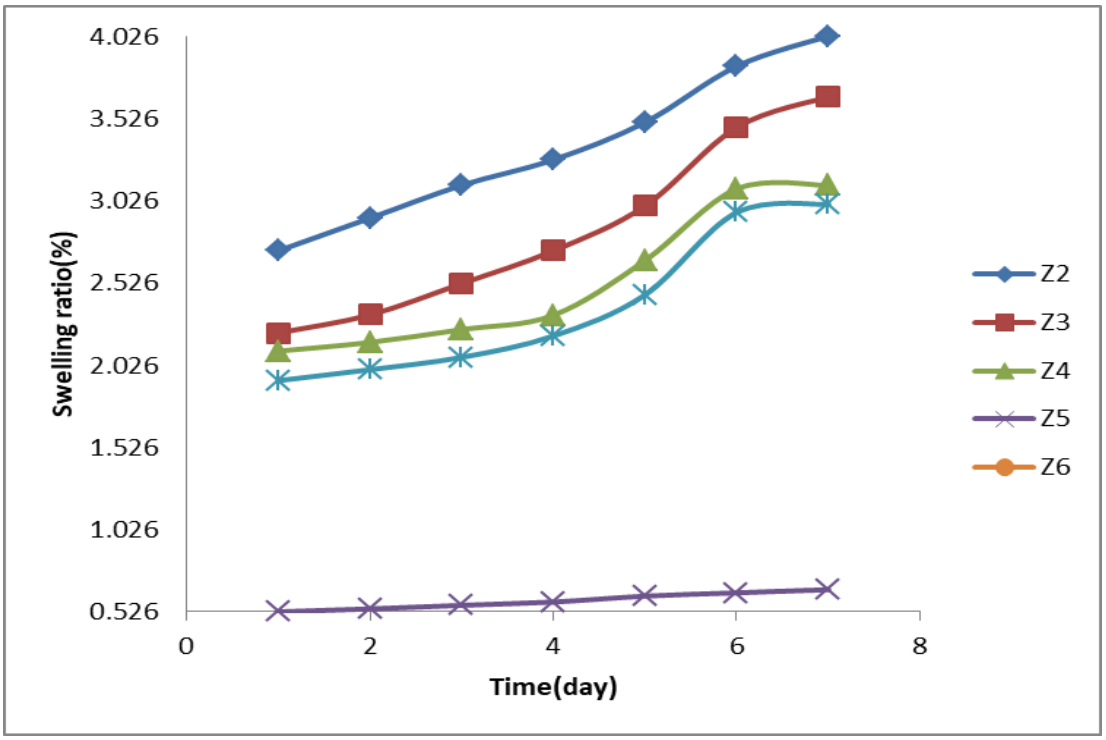


Figure (3-32): Swelling ratio per time (day) of nano co-polymer-drugs in pH=2.2 at 310 K **(Line 1)**

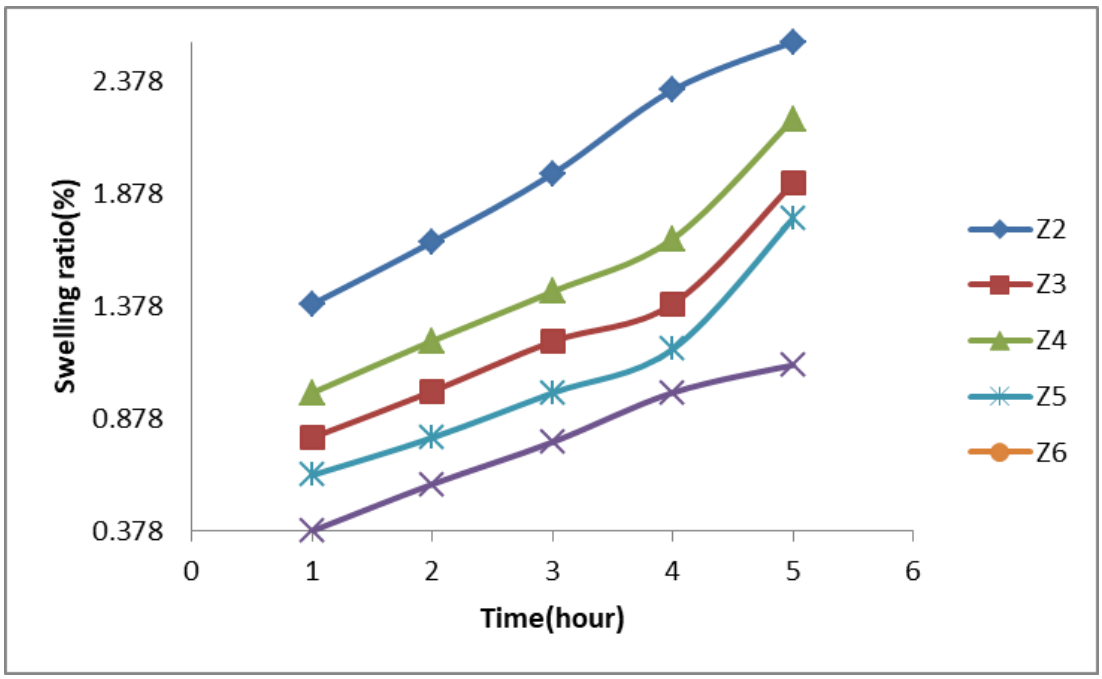


Figure (3-33): Swelling ratio per time (hour) of nano co-polymer-drugs in pH=7.0 at 310 K **(Line 1)**

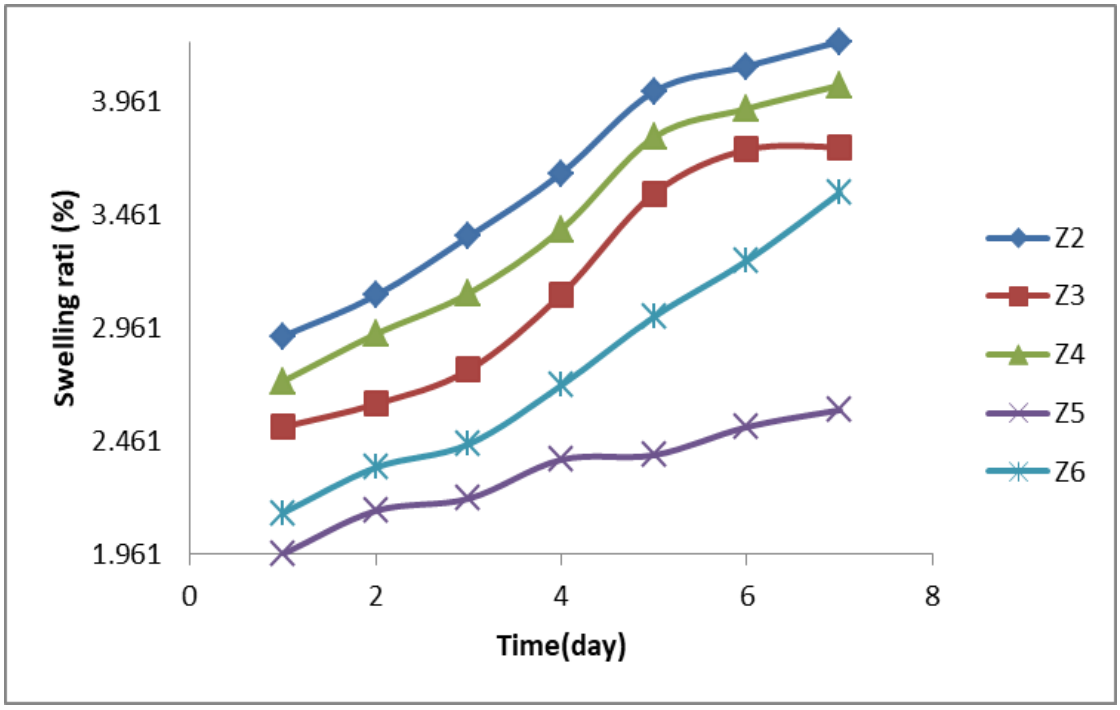


Figure (3-34): Swelling ratio per time (day) of nano co-polymer-drugs in pH=7.0 at 310 K **(Line 1)**

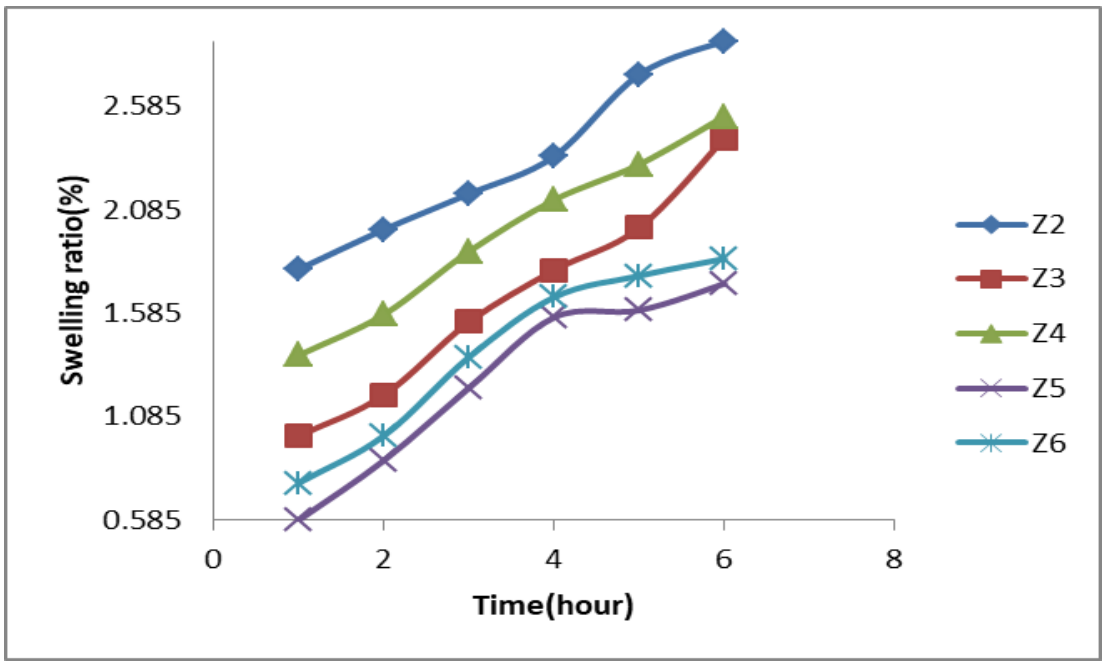


Figure (3-35): Swelling ratio per time (hour) of nano co-polymer-drugs in pH=8.0 at 310 K **(Line 1)**

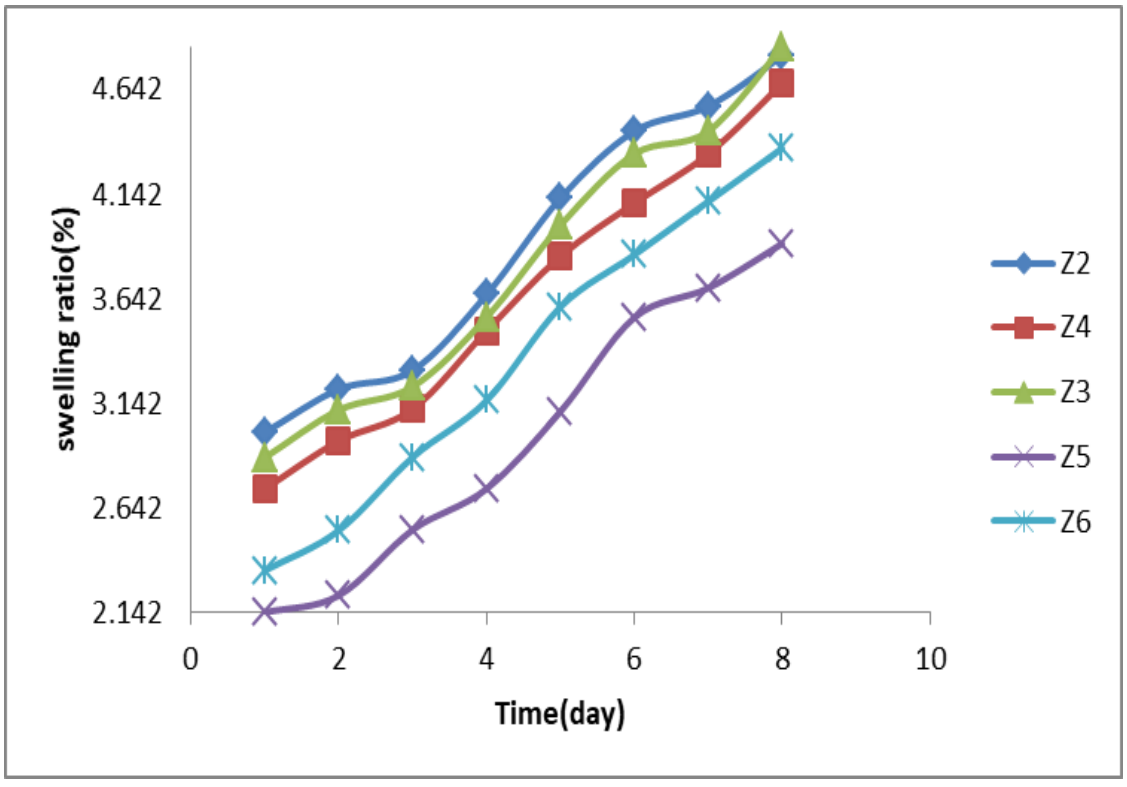


Figure (3-36): Swelling ratio per time (day) of nano co-polymer-drugs in pH=8.0 at 310 K **(Line 1)**

Tables (3-8) to (3-10) and Figures (3-37) to (3-42) represent the swelling ratio (%) and the behavior curves of swelling in different time (hour and day) of prepared nano co-polymer-drug **(Line 2)**.

Table (3-8): Swelling ratio per time (hour and day) of nano co-polymer-drugs in pH=2.2 at 310 K **(Line 2)**

Time	**Swelling Ratio %**					
(Hour)	**Types of polymers**					
	Z8	**Z9**	**Z10**	**Z11**	**Z12**	**Z13**
1	1.3866	1.4255	1.3055	1.4674	1.5049	1.3455
2	1.4275	1.4665	1.3566	1.5079	1.5468	1.3891
3	1.4679	1.5069	1.3972	1.5482	1.5874	1.4295
4	1.5082	1.5574	1.4382	1.5891	1.6276	1.4672
5	1.5469	1.5981	1.4789	1.6286	1.6521	1.5092
6	1.5469	1.5981	1.4789	1.6286	1.6521	1.5092
(Day)						
1	1.5971	1.6433	1.5233	1.6734	1.7121	1.5543
2	1.6344	1.6834	1.5642	1.7142	1.7522	1.5942
3	1.6734	1.7244	1.6042	1.7532	1.7932	1.6342
4	1.7144	1.7634	1.6432	1.7942	1.8344	1.6734
5	1.7534	1.8043	1.6824	1.8344	1.8742	1.7124
6	1.7942	1.8443	1.7245	1.8733	1.9142	1.7541
7	1.8354	1.8852	1.7643	1.9142	1.9524	1.7952
8	1.8354	1.8852	1.7643	1.9142	1.9524	1.7952

Table (3-9): Swelling ratio per time (hour and day) of nano co-polymer-drugs in pH=7.0 at 310 K **(Line 2)**

Time (Hour)	Swelling Ratio %					
	Types of polymers					
	Z8	Z9	Z10	Z11	Z12	Z13
1	1.5177	1.4655	1.3666	1.5667	1.6182	1.4165
2	1.5582	1.5065	1.4069	1.6085	1.6579	1.4489
3	1.5986	1.5474	1.4484	1.6492	1.6969	1.4892
4	1.6376	1.5876	1.4869	1.6889	1.7311	1.5295
5	1.6782	1.6285	1.5289	1.7294	1.7553	1.5682
6	1.6782	1.6285	1.5289	1.7294	1.7553	1.5682
(Day)						
1	1.8167	1.6781	1.5775	1.7782	1.8554	1.6175
2	1.8672	1.7279	1.6281	1.8265	1.9553	1.6682
3	1.9186	1.7782	1.6765	1.8765	1.9942	1.7195
4	1.9682	1.8276	1.7282	1.9269	2.1009	1.7682
5	2.1008	1.8782	1.7792	1.9772	2.1443	1.8193
6	2.1233	1.9276	1.8289	2.0003	2.1663	1.8691
7	2.1442	1.9785	1.8769	2.0331	2.1994	1.9156
8	2.1442	1.9785	1.8769	2.0331	2.1994	1.9156

Table (3-10): Swelling ratio per time (hour and day) of nano co-polymer-drugs in pH=8.0 at 310 K **(Line 2)**

Time	**Swelling Ratio %**					
(Hour)	**Types of polymers**					
	Z8	**Z9**	**Z10**	**Z11**	**Z12**	**Z13**
1	1.6455	1.5782	1.4366	1.7184	1.7892	1.5069
2	1.6882	1.6179	1.4772	1.7582	1.8286	1.5472
3	1.7266	1.6582	1.5166	1.7972	1.8665	1.5892
4	1.7656	1.6972	1.5592	1.8346	1.9056	1.6269
5	1.8022	1.7368	1.5982	1.8766	1.9221	1.6682
6	1.9852	1.8931	1.7340	1.9630	2.1070	1.7940
(Day)						
1	2.0331	1.9241	1.9824	2.2624	2.8345	2.0542
2	2.1052	1.9752	2.1362	2.28162	2.8841	2.2044
3	2.2187	2.0265	2.1875	2.3675	2.9392	2.2563
4	2.1420	2.0719	2.2369	2.3965	2.9864	2.3056
5	2.1921	2.1262	2.2872	2.4662	3.0332	2.3573
6	2.3813	2.1775	2.3324	2.4442	3.1074	2.4075
7	2.4067	2.2282	2.3864	2.4663	3.1322	2.4546
8	2.4067	2.3282	2.3864	2.4663	3.1322	2.4546

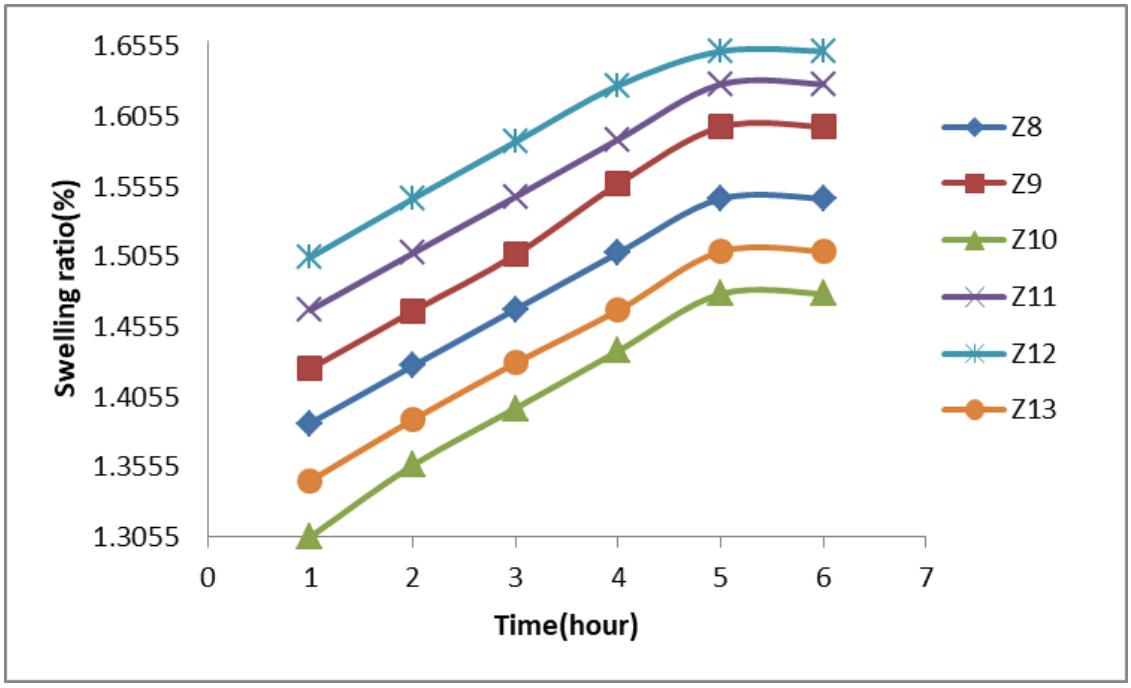


Figure (3-37): Swelling ratio per time (hour) of nano co-polymer-drugs in pH=2.2 at 310 K **(Line 2)**

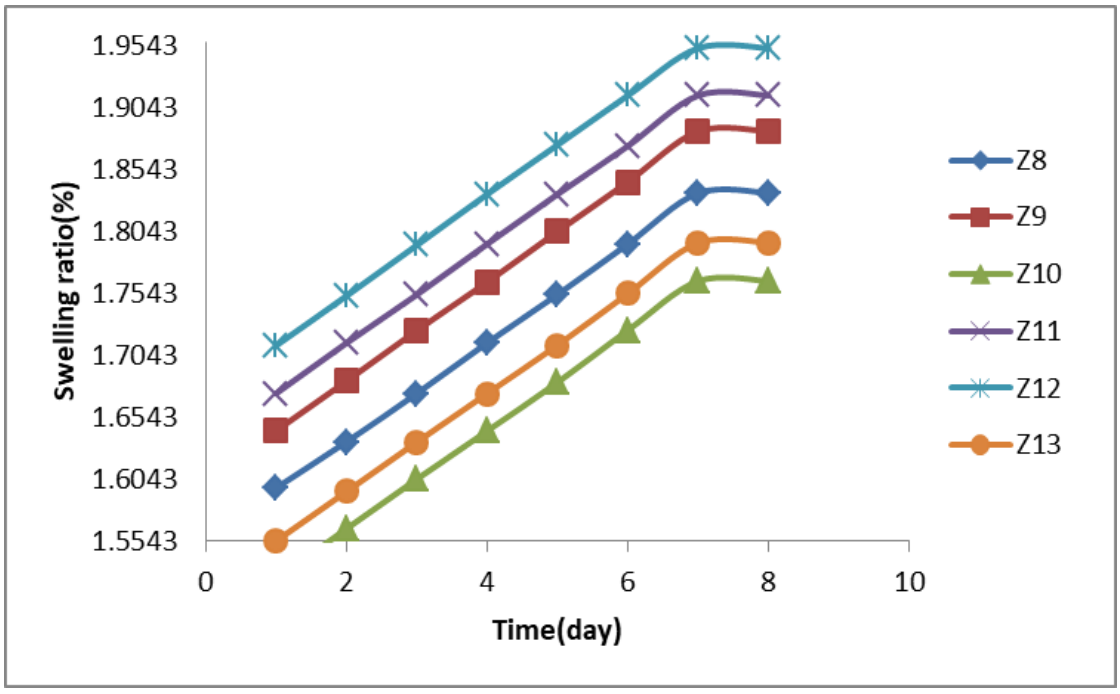


Figure (3-38): Swelling ratio per time (day) of nano co-polymer-drugs in pH=2.2 at 310 K **(Line 2)**

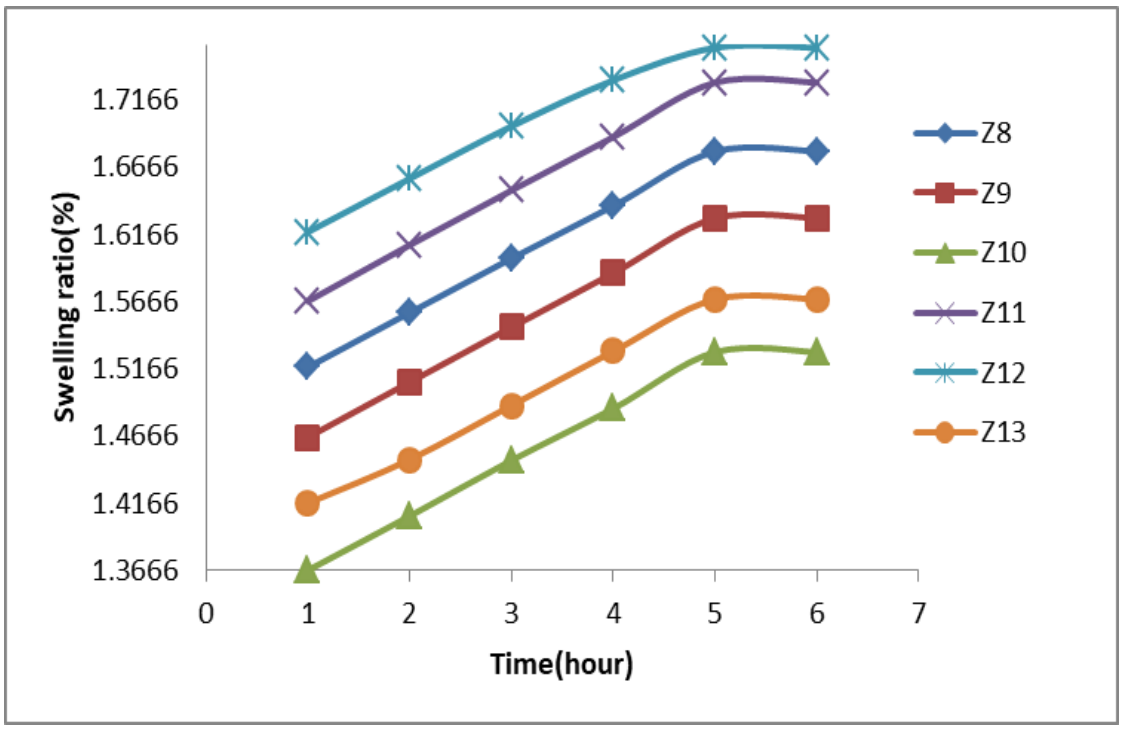


Figure (3-39): Swelling ratio per time (hour) of nano co-polymer-drugs in pH=7.0 at 310 K **(Line 2)**

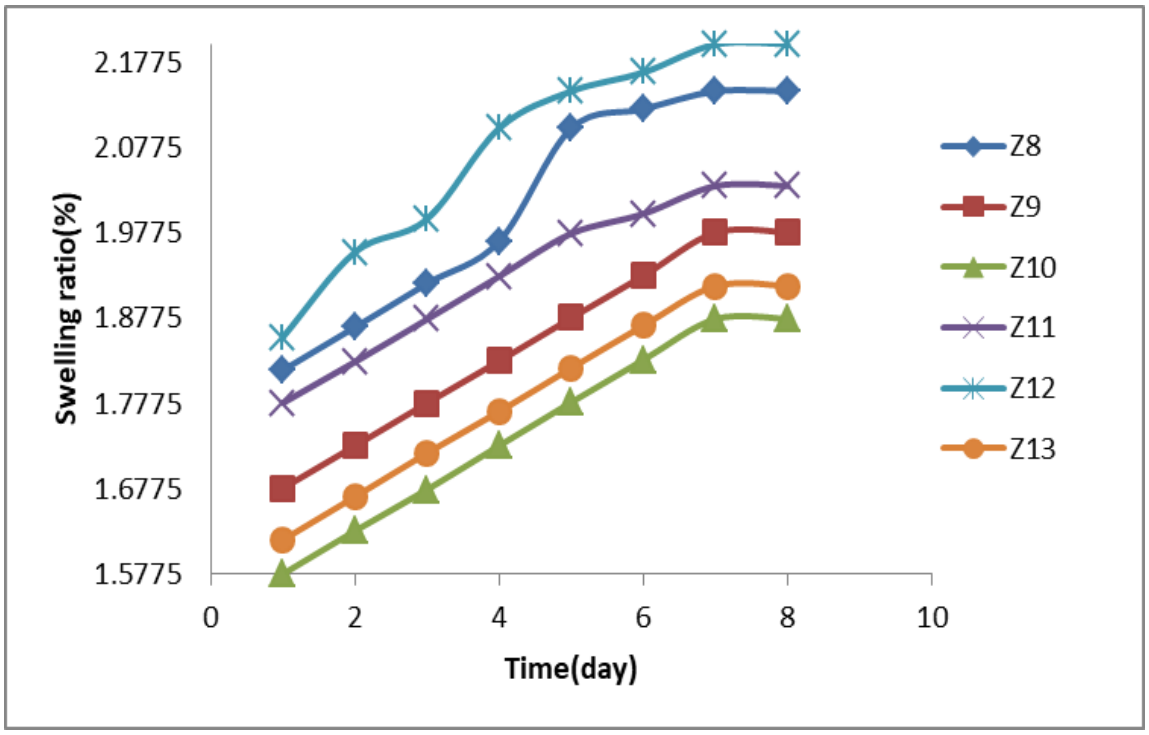


Figure (3-40): Swelling ratio per time (day) of nano co-polymer-drugs in pH=7.0 at 310 K **(Line 2)**

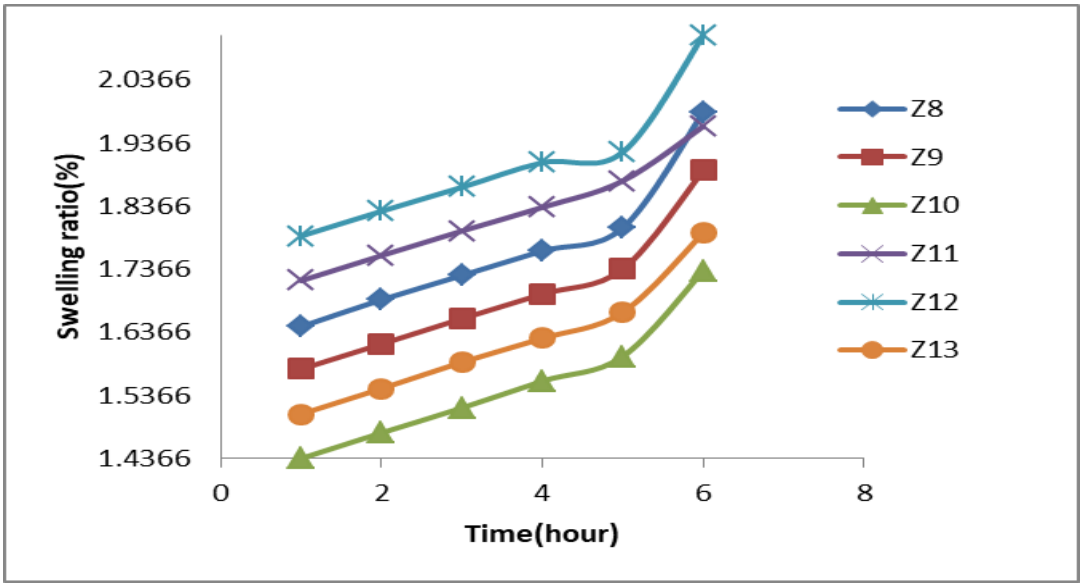


Figure (3-41): Swelling ratio per time (hour) of nano co-polymer-drugs in pH=8.0 at 310 K **(Line 2)**

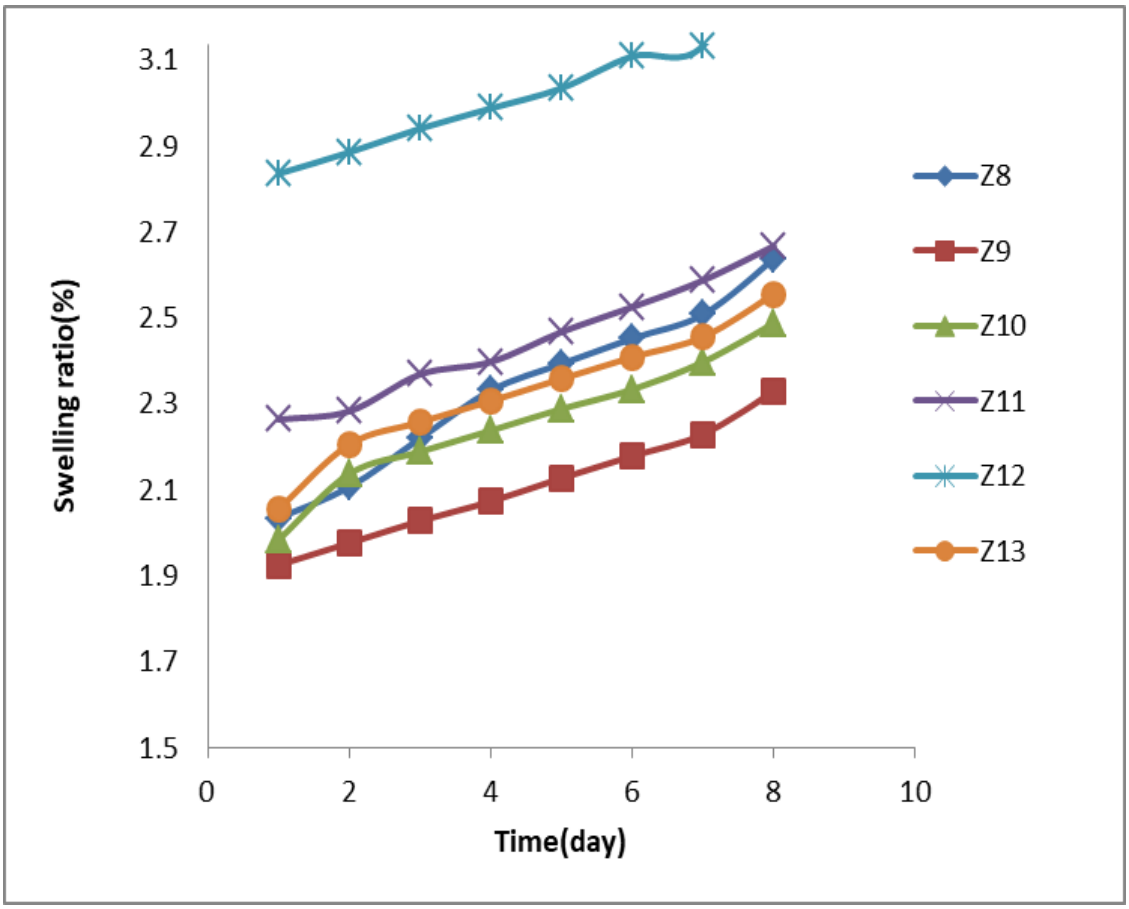


Figure (3-42): Swelling ratio per time (day) of nano co-polymer-drugs in pH=8.0 at 310 K **(Line 2)**

2.6 Release of drug

Using UV.-Vis. spectrophotometer, release the drug from the synthesis nano co-polymer-drugs were determined in three different buffer solutions (2.2, 7.0 and 8.0) at constant temperature 310 K. Tables (3-11) to (3-13), and Figures (3-43) to (3-48) represent the drug release from the synthesis nano co-polymer-drugs **(Line 1).**

Table (3-11): Release of drug per time (hour and day) of nano co-polymer-drugs in pH=2.2 at 310 K **(Line 1)**

Time	**Release of drug (λ)**				
(Hour)	**Types of polymers**				
	Z2	**Z3**	**Z4**	**Z5**	**Z6**
1	0.862	0.184	0.229	0.075	0.129
2	0.961	0.212	0.244	0.079	0.133
3	1.104	0.242	0.279	0.099	0.159
4	1.199	0.279	0.305	0.108	0.169
5	1.211	0.321	0.359	0.124	0.189
6	1.211	0.321	0.359	0.124	0.189
(Day)					
1	1.349	0.403	0.549	0.121	0.243
2	1.396	0.549	0.699	0.134	0.284
3	1.596	0.748	0.856	0.146	0.362
4	1.862	0.868	0.967	0.146	0.499
5	2.226	1.131	1.219	0.146	0.562
6	2.421	1.332	1.442	0.146	0.661
7	2.555	1.442	1.556	0.146	0.791
8	2.555	1.442	1.556	0.146	0.791

Table (3-12): Release of drug per time (hour and day) of nano co-polymer-drugs in pH=7.0 at 310 K **(Line 1)**

Time (Hour)	Release of drug (λ) Types of polymers				
	Z2	**Z3**	**Z4**	**Z5**	**Z6**
1	0.922	0.194	0.419	0.092	0.154
2	1.009	0.223	0.488	0.099	0.196
3	1.131	0.235	0.573	0.101	0.214
4	1.219	0.254	0.667	0.121	0.224
5	1.318	0.269	0.744	0.132	0.244
6	1.318	0.269	0.744	0.132	0.244
(Day)					
1	2.101	0.368	1.331	0.148	0.411
2	2.321	0.429	1.542	0.155	0.599
3	2.569	0.559	1.733	0.162	0.762
4	2.789	0.668	1.914	0.179	0.882
5	3.196	0.791	2.119	0.209	0.961
6	3.556	0.881	2.266	0.224	1.101
7	3.722	0.991	2.457	0.244	1.291
8	3.722	0.991	2.457	0.244	1.291

Table (3-13): Release of drug per time (hour and day) of nano co-polymer-drugs in pH=8.0 at 310 K **(Line 1)**

Time (Hour)	Release of drug (λ)				
	Types of polymers				
	Z2	Z3	Z4	Z5	Z6
1	1	0.197	0.612	0.099	0.182
2	1.152	0.271	0.759	0.122	0.221
3	1.256	0.354	0.866	0.194	0.266
4	1.314	0.421	1.002	0.228	0.334
5	1.366	0.551	1.146	0.254	0.354
6	1.366	0.551	1.146	0.254	0.354
(Day)					
1	2.106	0.668	1.199	0.341	0.442
2	2.241	0.798	1.491	0.362	0.599
3	3	0.881	1.663	0.391	0.671
4	3.553	1.203	2.005	0.421	0.825
5	3.882	1.509	2.444	0.441	1
6	4.121	1.788	2.777	0.488	1.441
7	4.199	2.131	3.199	0.502	2
8	4.199	2.131	3.199	0.502	2

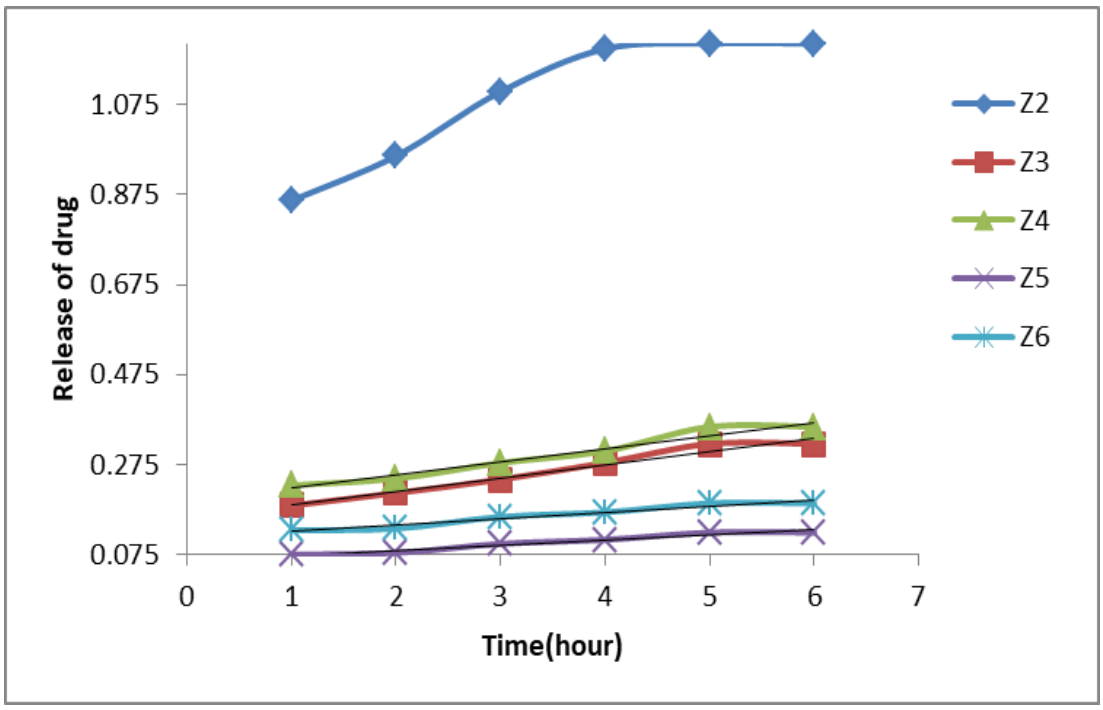


Figure (3-43): Release of drug per time (hour) of nano co-polymer-drugs in pH=2.2 at 310 K **(Line 1)**

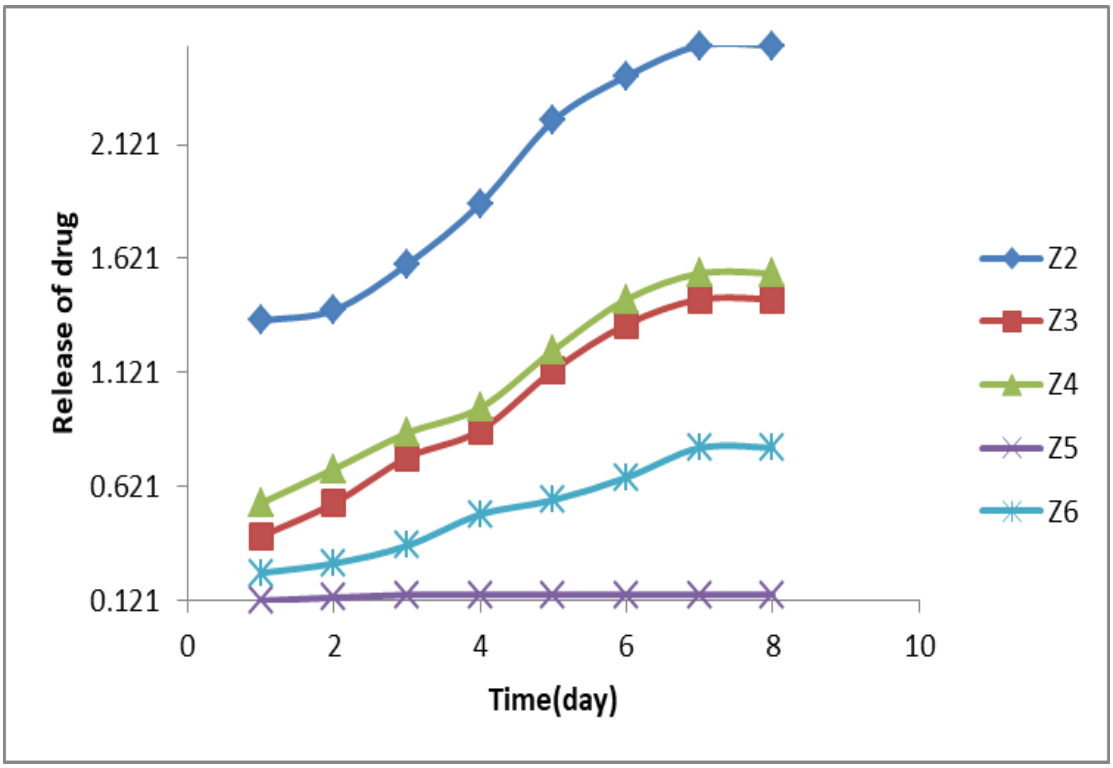


Figure (3-44): Release of drug per time (day) of nano co-polymer-drugs in pH=2.2 at 310 K **(Line 1)**

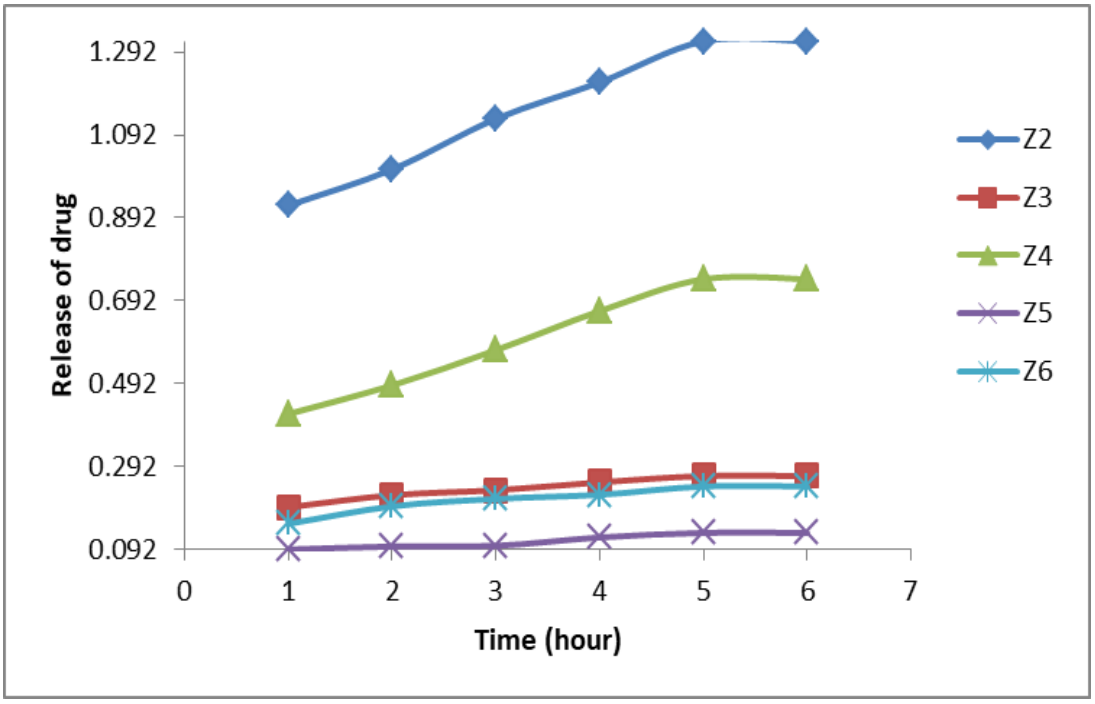


Figure (3-45): Release of drug per time (hour) of nano co-polymer-drugs in pH=7.0 at 310 K **(Line 1)**

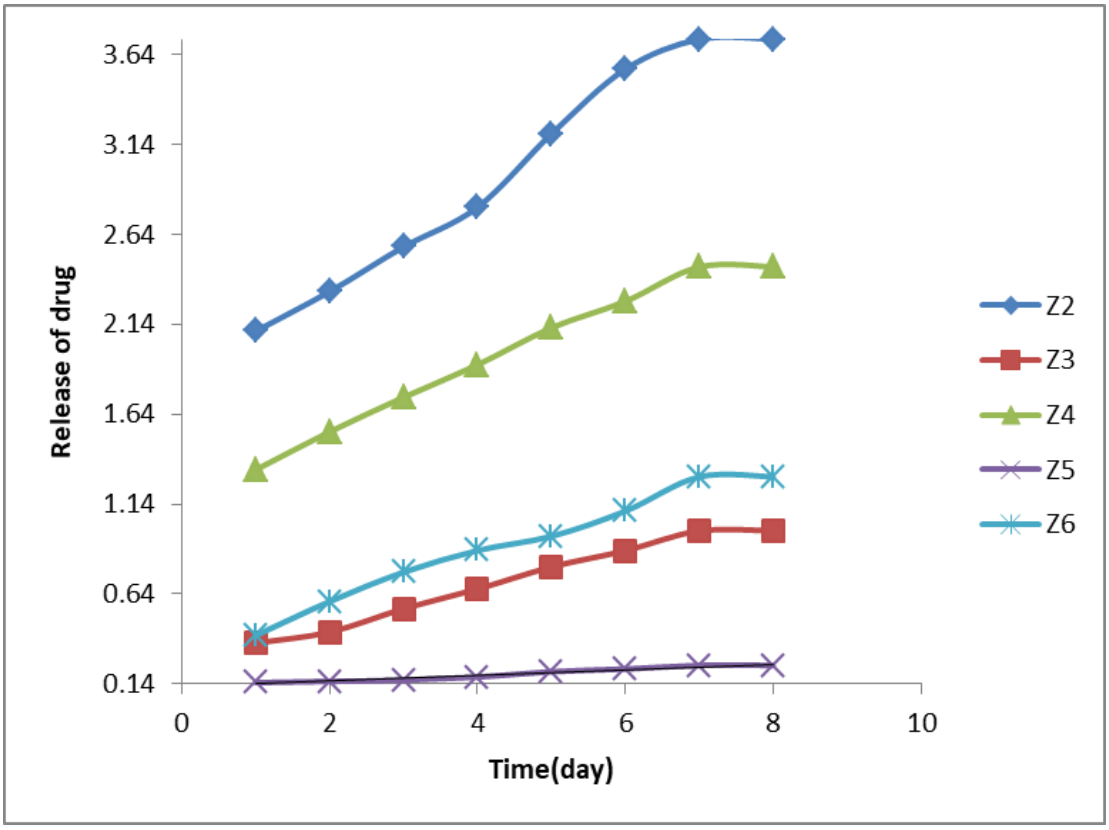


Figure (3-46): Release of drug per time (day) of nano co-polymer-drugs in pH=7.0 at 310 K **(Line 1)**

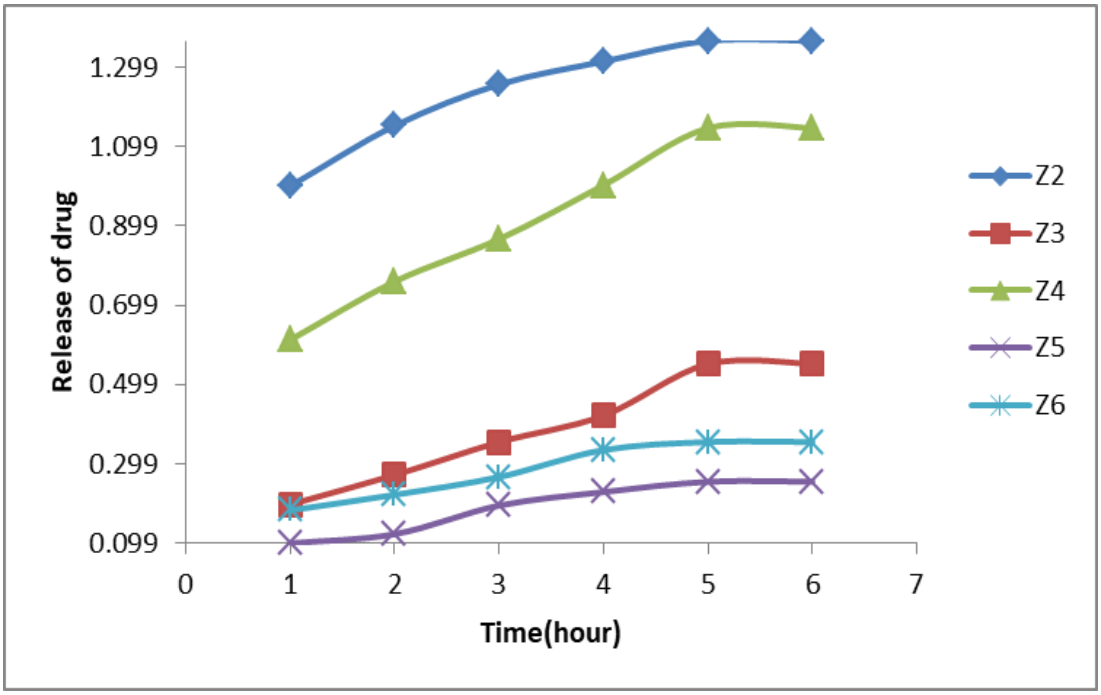


Figure (3-47): Release of drug per time (hour) of nano co-polymer-drugs in pH=8.0 at 310 K **(Line 1)**

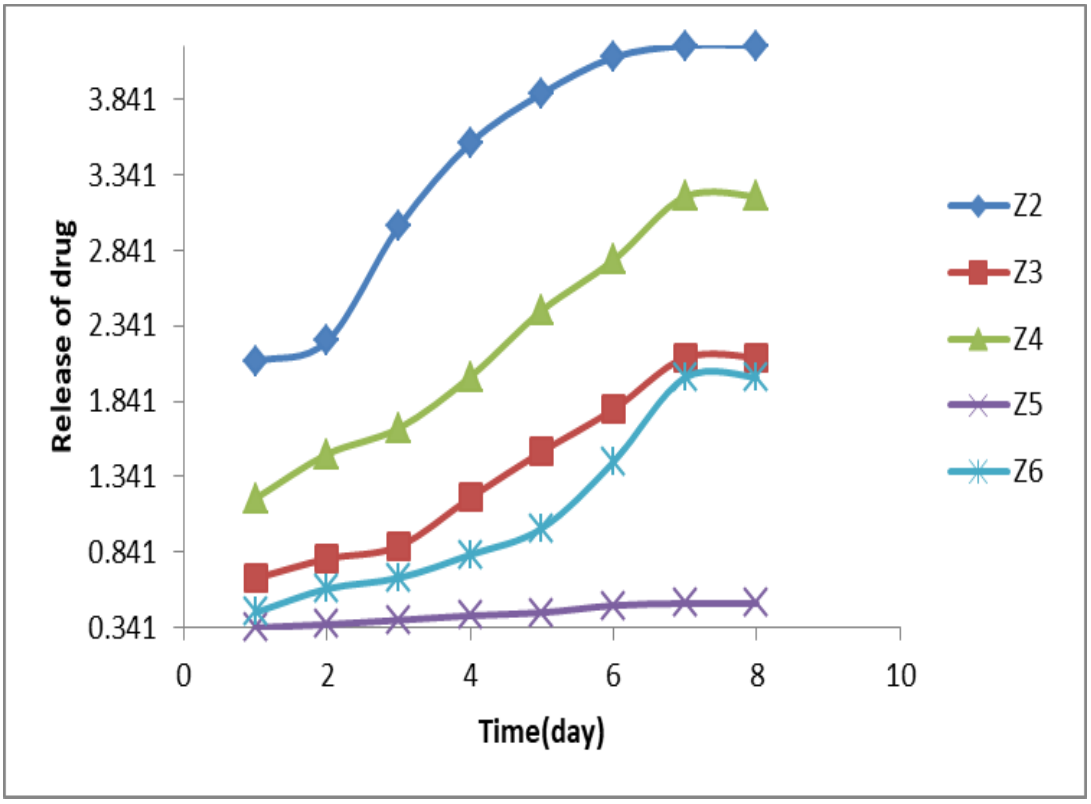


Figure (3-48): Release of drug per time (day) of nano co-polymer-drugs in pH=8.0 at 310 K **(Line 1)**

Tables (3-14) to (3-16) and Figures (3-49) to (3-54) represent the drug release from the synthesis nano co-polymer-drugs **(Line 2).**

Table (3-14): Release of drug per time (hour and day) of nano co-polymer-drugs in pH=2.2 at 310 K **(Line 2)**

Time	**Release of drug (λ)**					
(Hour)	**Types of polymers**					
	Z8	**Z9**	**Z10**	**Z11**	**Z12**	**Z13**
1	1.243	1.271	1.161	1.311	1.352	1.201
2	1.282	1.312	1.201	1.352	1.392	1.242
3	1.322	1.352	1.241	1.392	1.432	1.282
4	1.362	1.392	1.281	1.431	1.471	1.321
5	1.362	1.392	1.281	1.431	1.471	1.321
(Day)						
1	1.411	1.442	1.332	1.482	1.522	1.372
2	1.462	1.491	1.381	1.531	1.571	1.421
3	1.512	1.541	1.431	1.581	1.622	1.471
4	1.562	1.591	1.485	1.631	1.671	1.522
5	1.612	1.642	1.531	1.682	1.721	1.572
6	1.663	1.691	1.582	1.731	1.771	1.622
7	1.713	1.741	1.631	1.781	1.822	1.671
8	1.713	1.741	1.631	1.781	1.822	1.671

Table (3-15): Release of drug per time (hour and day) of nano co-polymer-drugs in pH=7.0 at 310 K **(Line 2)**

Time	**Release of drug (λ)**					
(Hour)	**Types of polymers**					
	Z8	**Z9**	**Z10**	**Z11**	**Z12**	**Z13**
1	1.341	1.381	1.261	1.421	1.461	1.301
2	1.381	1.421	1.301	1.461	1.501	1.341
3	1.421	1.461	1.341	1.501	1.541	1.381
4	1.461	1.511	1.381	1.541	1.587	1.422
5	1.501	1.55	1.421	1.581	1.609	1.461
6	1.501	1.55	1.421	1.581	1.609	1.461
(Day)						
1	1.551	1.601	1.471	1.631	1.671	1.511
2	1.601	1.651	1.521	1.681	1.721	1.561
3	1.651	1.701	1.571	1.731	1.771	1.611
4	1.701	1.751	1.622	1.781	1.821	1.661
5	1.751	1.801	1.671	1.831	1.871	1.711
6	1.801	1.851	1.721	1.881	1.921	1.761
7	1.851	1.901	1.772	1.931	1.971	1.811
8	1.851	1.901	1.772	1.931	1.971	1.811

Table (3-16): Release of drug per time (hour and day) of nano co-polymer-drugs in pH=8.0 at 310 K **(Line 2)**

Time	Release of drug (λ)					
(Hour)	Types of polymers					
	Z8	Z9	Z10	Z11	Z12	Z13
1	1.481	1.55	1.34	1.621	1.691	1.411
2	1.521	1.601	1.381	1.661	1.73	1.451
3	1.561	1.641	1.421	1.701	1.771	1.491
4	1.601	1.681	1.461	1.741	1.811	1.531
5	1.641	1.721	1.501	1.781	1.851	1.571
6	1.641	1.721	1.501	1.781	1.851	1.571
(Day)						
1	1.691	1.771	1.551	1.831	1.934	1.621
2	1.741	1.821	1.601	1.881	1.963	1.671
3	1.791	1.871	1.651	1.93	2.109	1.721
4	1.841	1.921	1.701	2.003	2.191	1.771
5	1.891	1.971	1.751	2.092	2.309	1.821
6	1.941	2.1	1.801	2.147	2.331	1.862
7	1.991	2.109	1.852	2.173	2.341	1.912
8	1.991	2.109	1.852	2.173	2.341	1.912

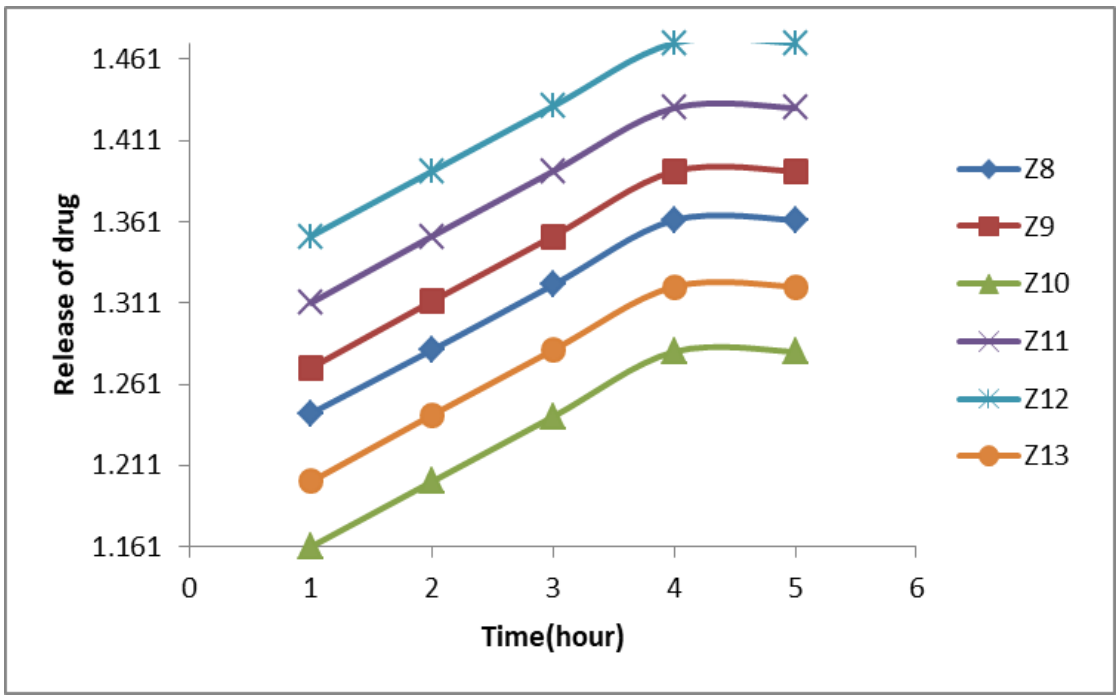


Figure (3-49): Release of drug per time (hour) of nano co-polymer-drugs in pH=2.2 at 310 K **(Line 2)**

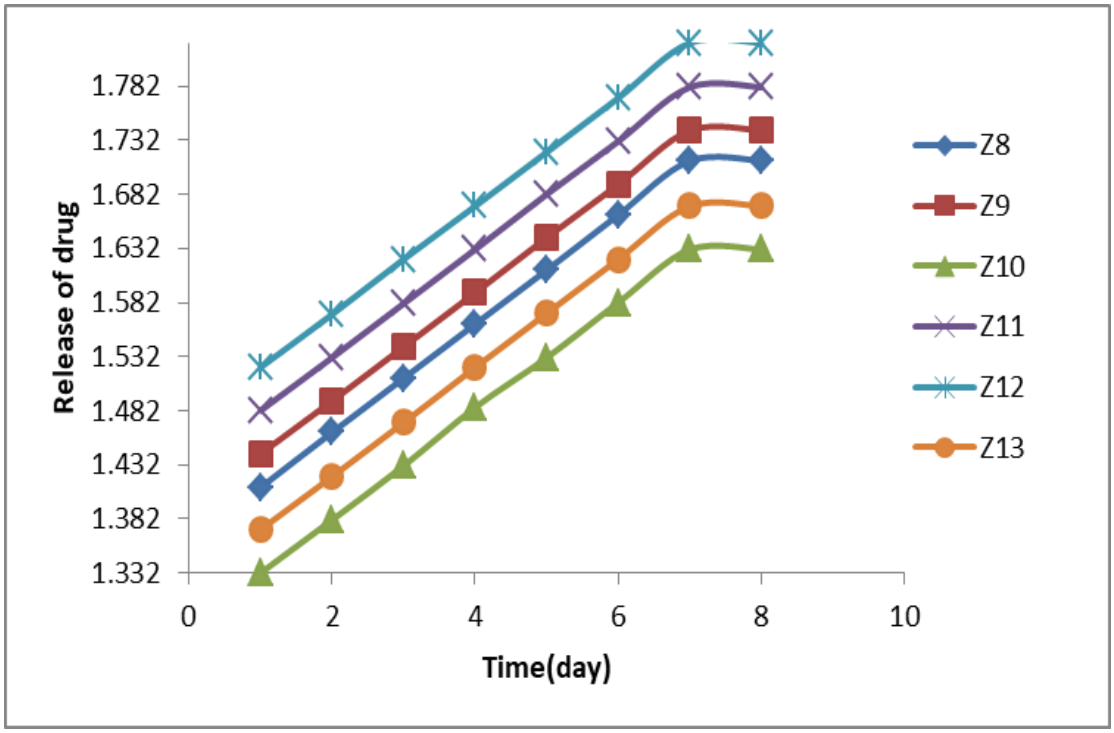


Figure (3-50): Release of drug per time (day) of nano co-polymer-drugs in pH=2.2 at 310 K **(Line 2)**

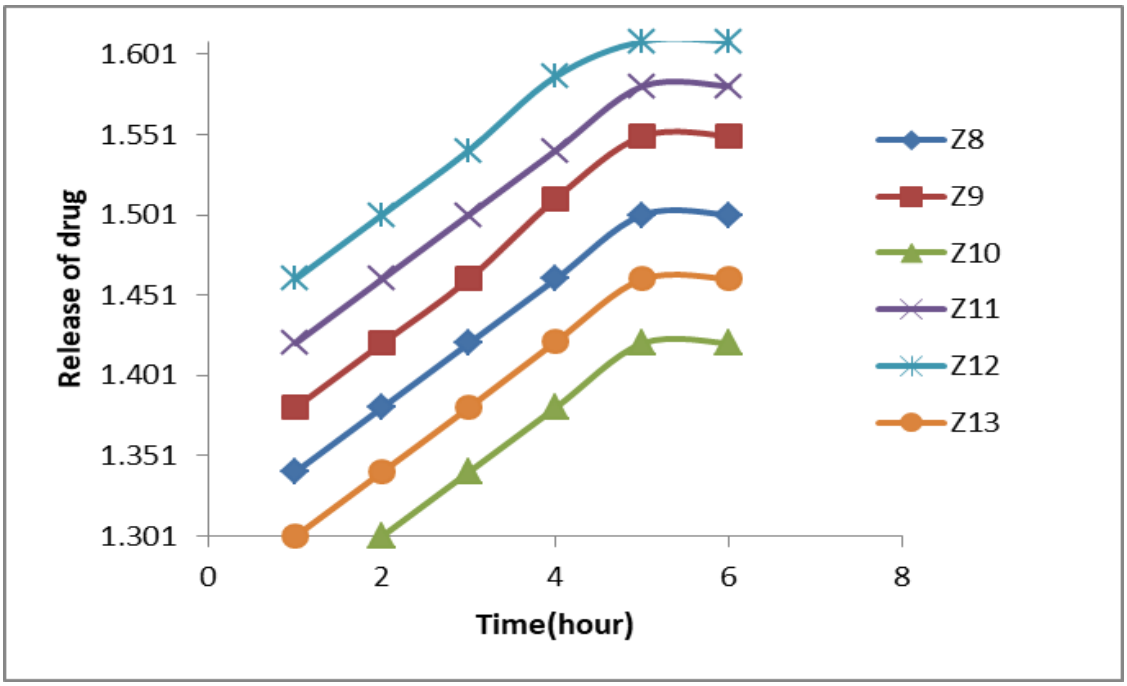


Figure (3-51): Release of drug per time (hour) of nano co-polymer-drugs in pH=7.0 at 310 K **(Line 2)**

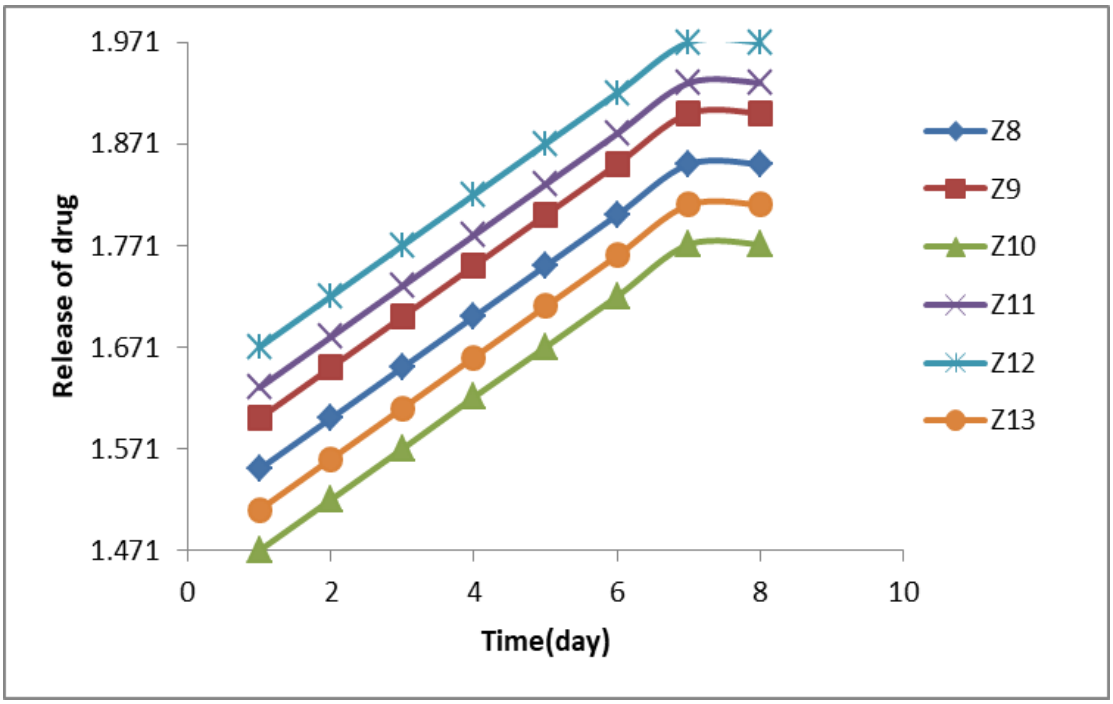


Figure (3-52): Release of drug per time (day) of nano co-polymer-drugs in pH=7.0 at 310 K **(Line 2)**

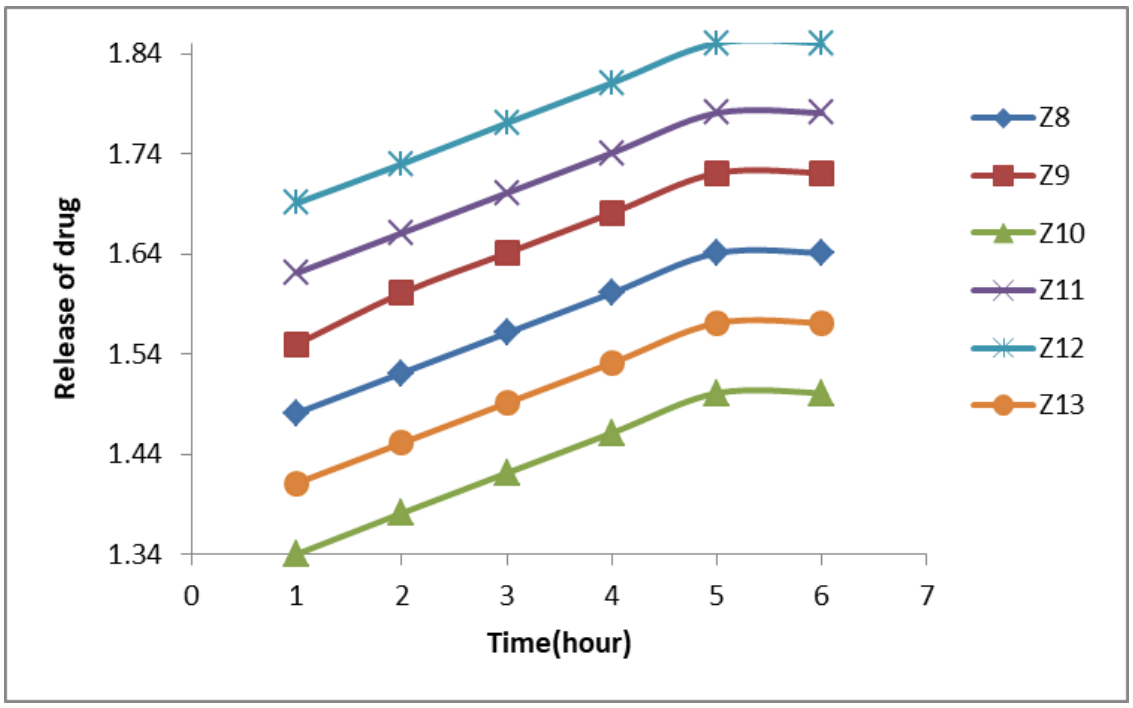


Figure (3-53): Release of drug per time (hour) of nano co-polymer-drugs in pH=8.0 at 310 K **(Line 2)**

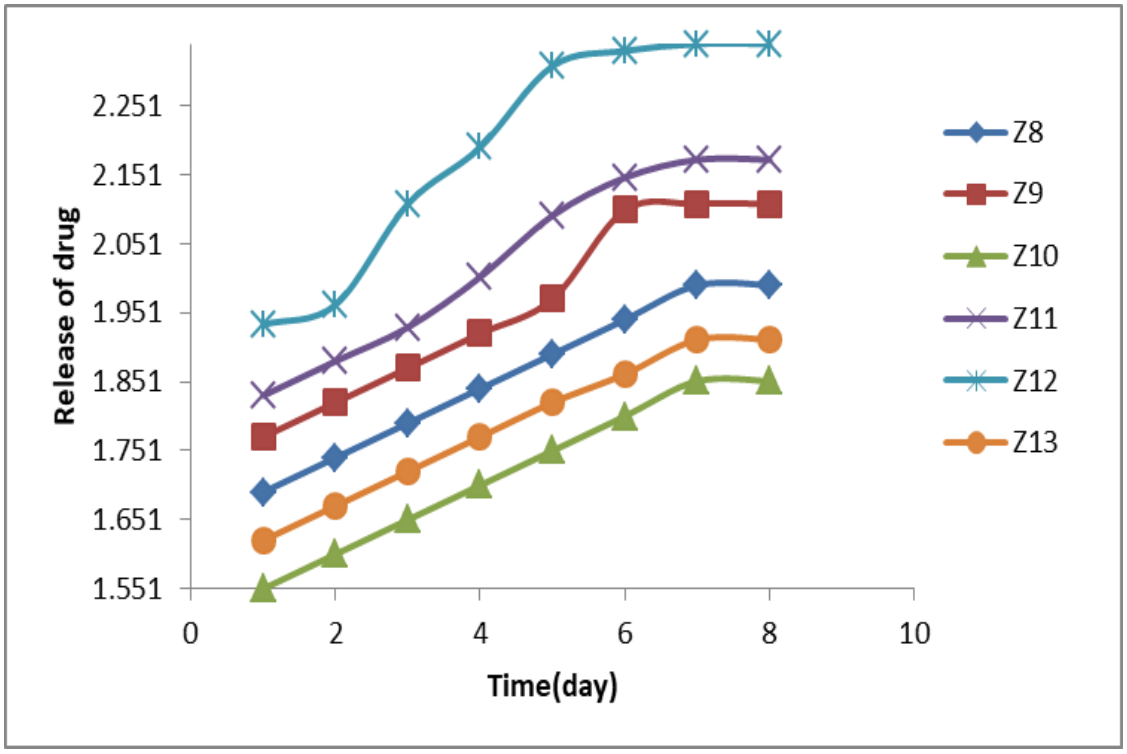


Figure (3-54): Release of drug per time (day) of nano co-polymer-drugs in pH=8.0 at 310 K **(Line 2)**

3.7 Anti- Cancer Measurments

The effect of drugs loaded on the nano co-polymer (Z3, Z4, Z5, Z6, Z8, Z9, Z10, Z11, Z12 and Z13) on inhibition of spread breast cancer was measured, and the results showed that the drugs had a different effect, as they varied between a high effect and a low effect. Table (3-17) and Figures (3-55) to (3-64), shwoed the effectiveness the synthesis nano graft-co-polymer-drugs in inhibiting the spread of breast cancer were as in the following order:

Z8 > Z6 > Z9 > Z12 > Z10 > Z3 > Z13 > Z11 > Z4 > Z5

Increasing efficacy

Table (3-17): Effectiveness the synthesis nano graft-co-polymer-drugs in inhibiting the spread of breast cancer

No.	nano co-polymer-drug	IC50 (µg/ml)
1	Z3	32.10
2	Z4	40.12
3	Z5	62.06
4	Z6	15.71
5	Z8	12.64
6	Z9	20.31
7	Z10	28.70
8	Z11	38.86
9	Z12	25.26
10	Z13	36.24

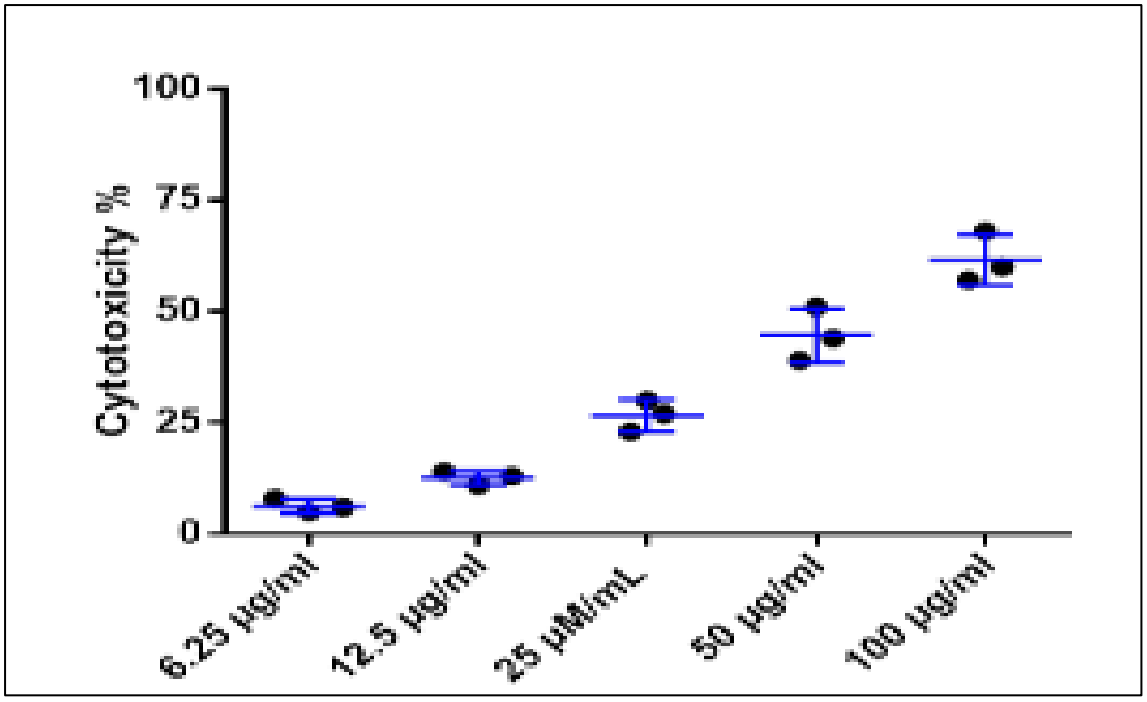


Figure (3-55): Cytotoxicity effects of Z3 in MCF 7cell. IC50=32.10 µg/ml

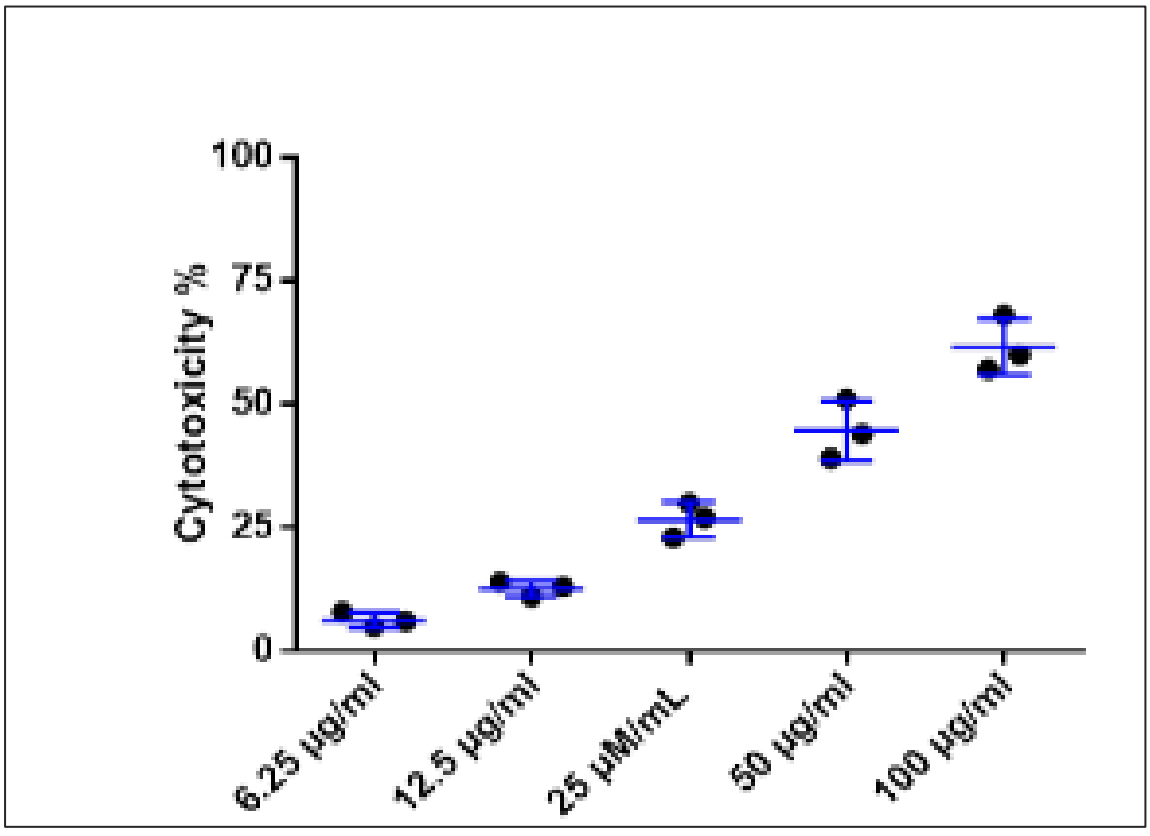


Figure (3-56): Cytotoxicity effects of Z4 in MCF 7 cell. IC50=40.12 µg/ml

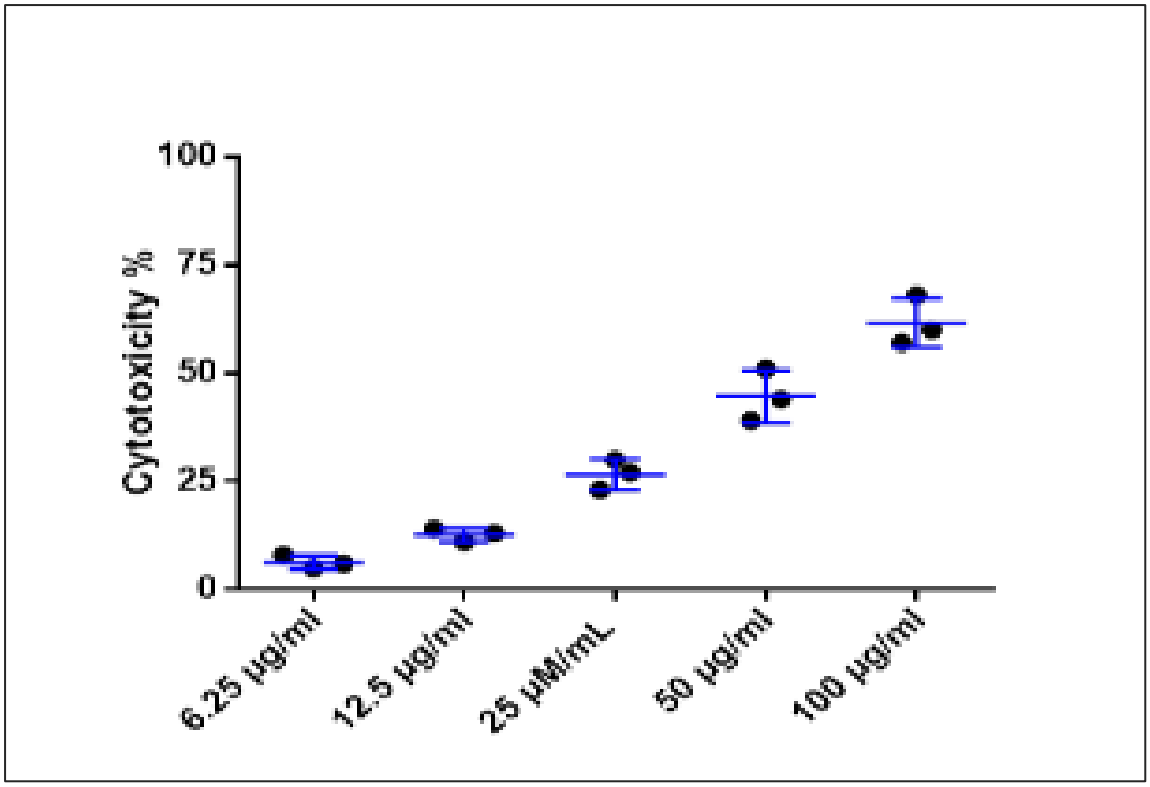


Figure (3-57): Cytotoxicity effects of Z5 in MCF 7 cell. IC50=62.06 µg/ml

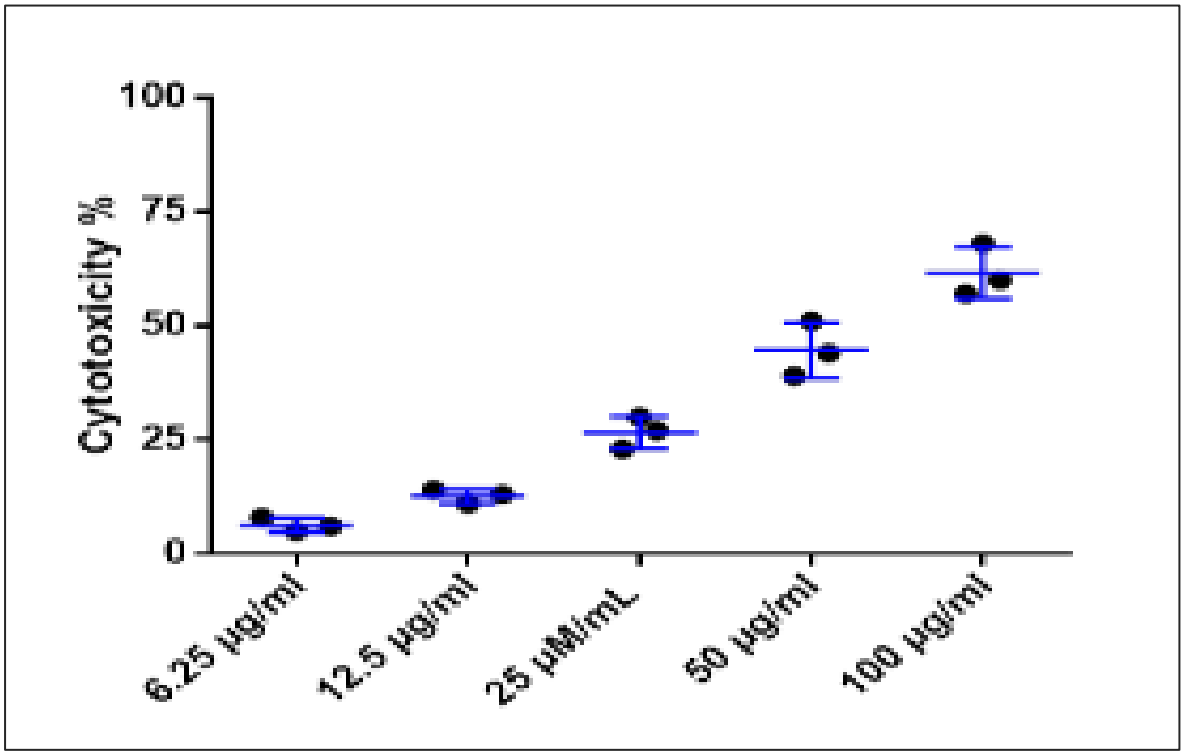


Figure (3-58): Cytotoxicity effects of Z6 in MCF 7 cell. IC50=15.71 µg/ml

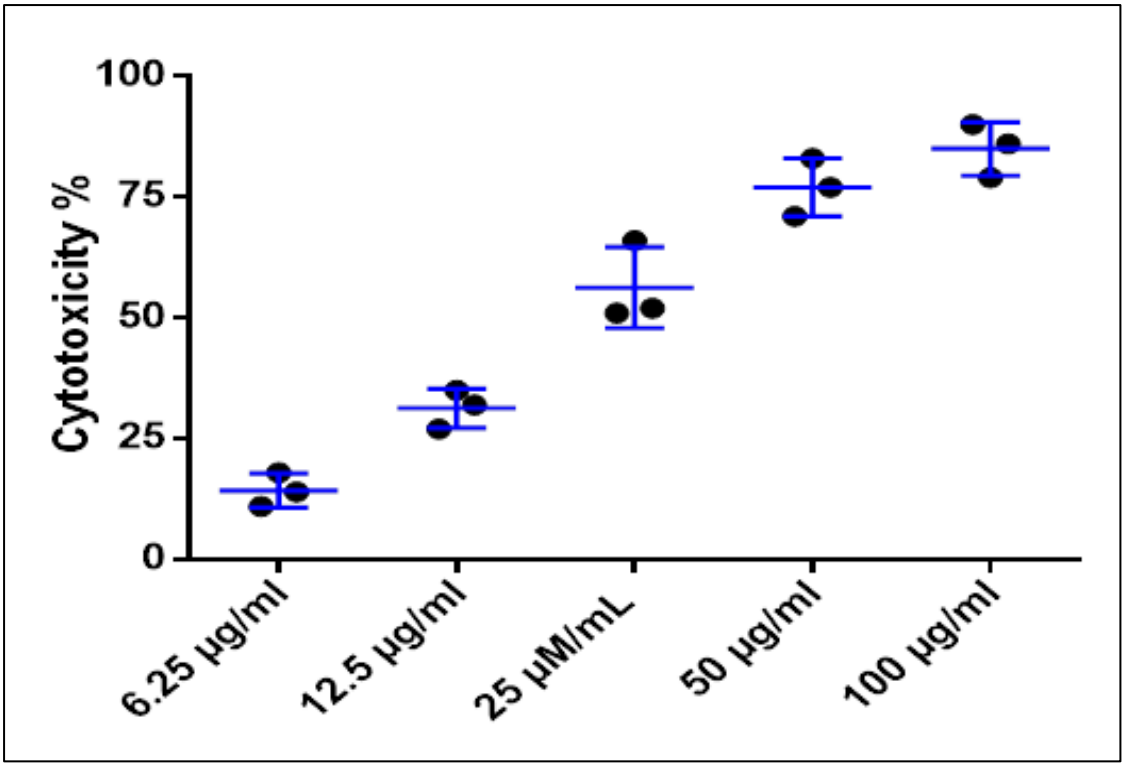


Figure (3-59): Cytotoxic effect of Z8 in MCF-7 cells, IC50=12.64 µg/ml

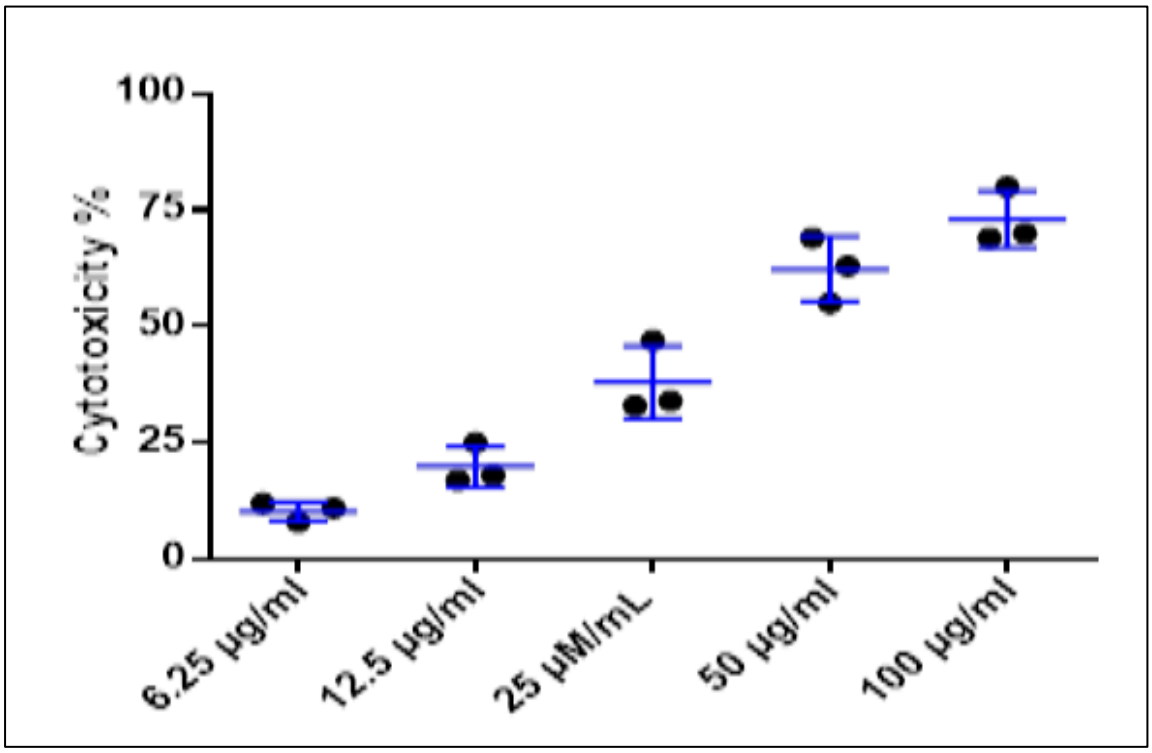


Figure (3-60): Cytotoxic effect of Z9 in MCF-7 cells, IC50=20.31µg/ml

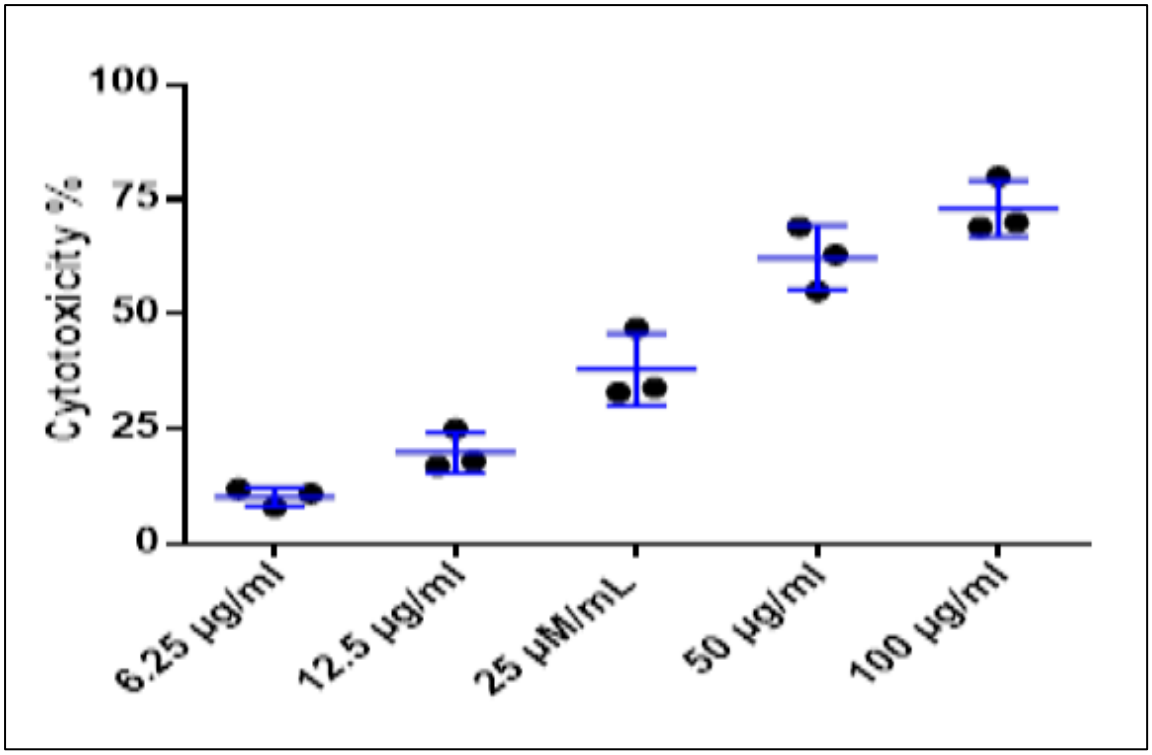


Figure (3-61): Cytotoxic effect of Z10 in MCF-7 cells, IC50=28.70µg/ml

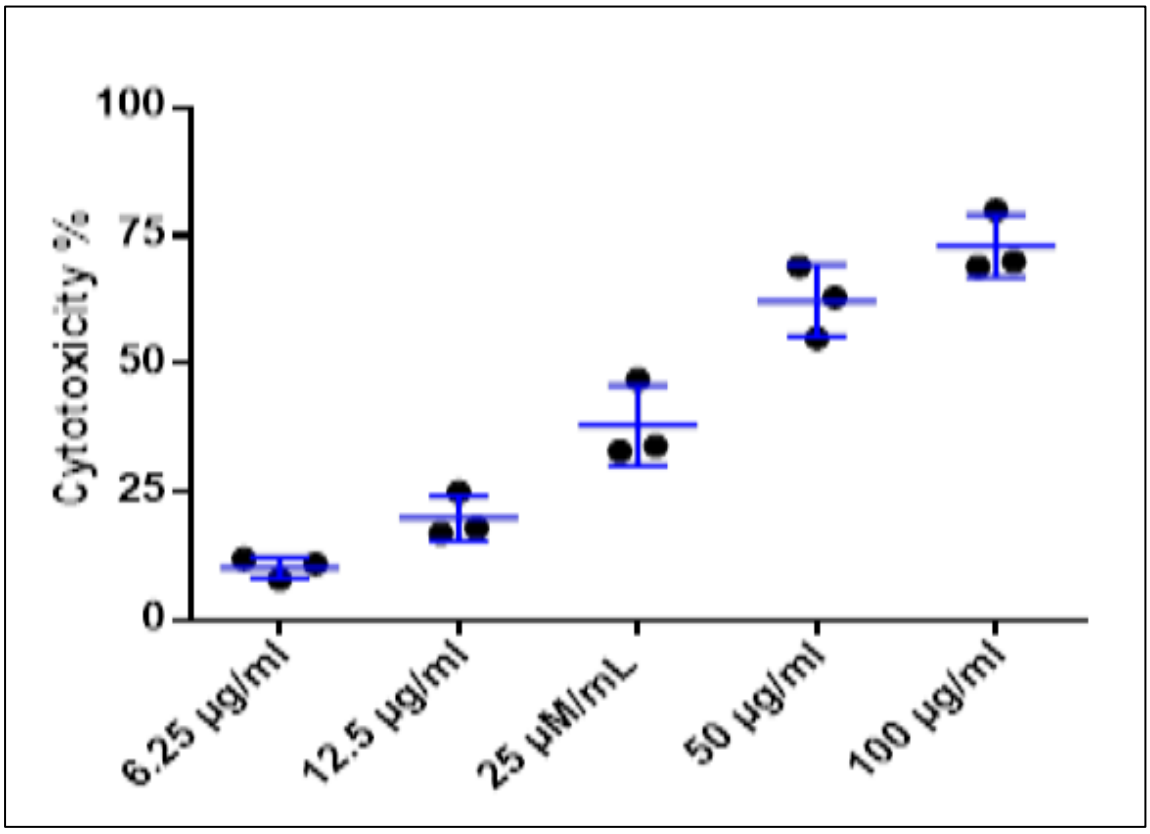


Figure (3-62): Cytotoxic effect of Z11 in MCF-7 cells. IC50=38.86µg/ml

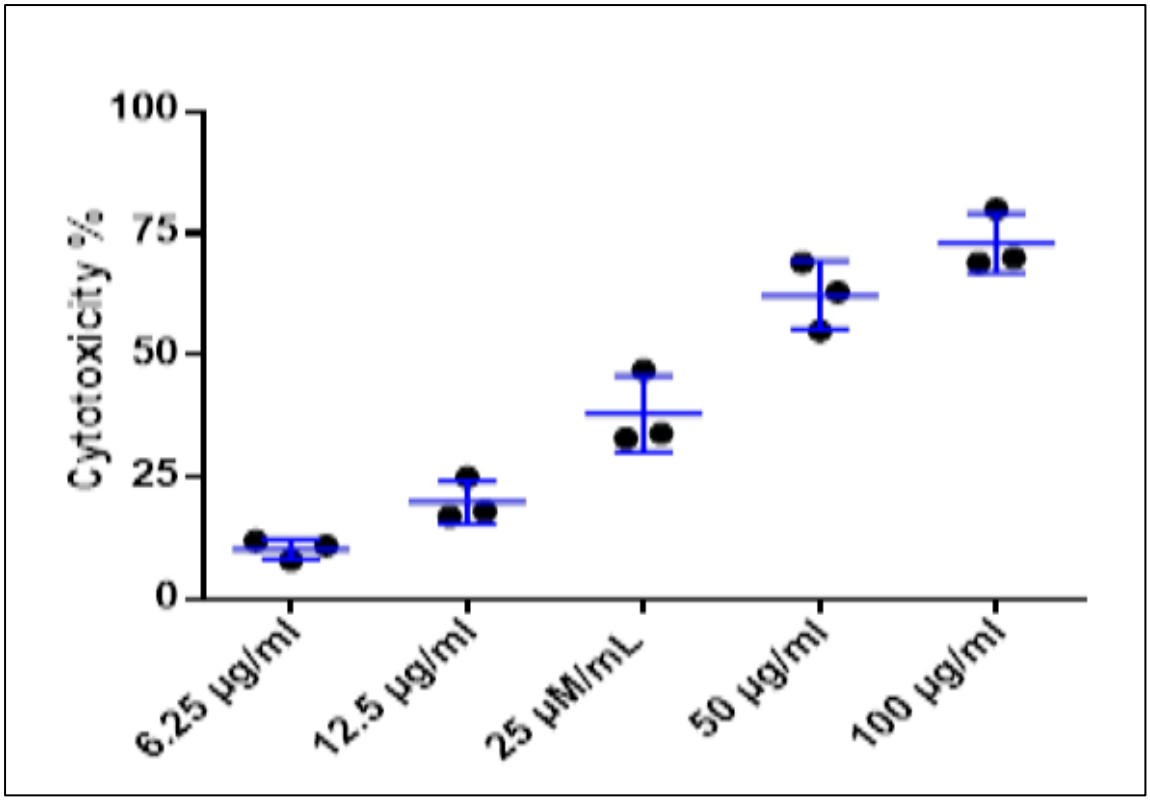


Figure (3-63): Cytotoxic effect of Z12 in MCF-7 cells. IC50=25.26µg/ml

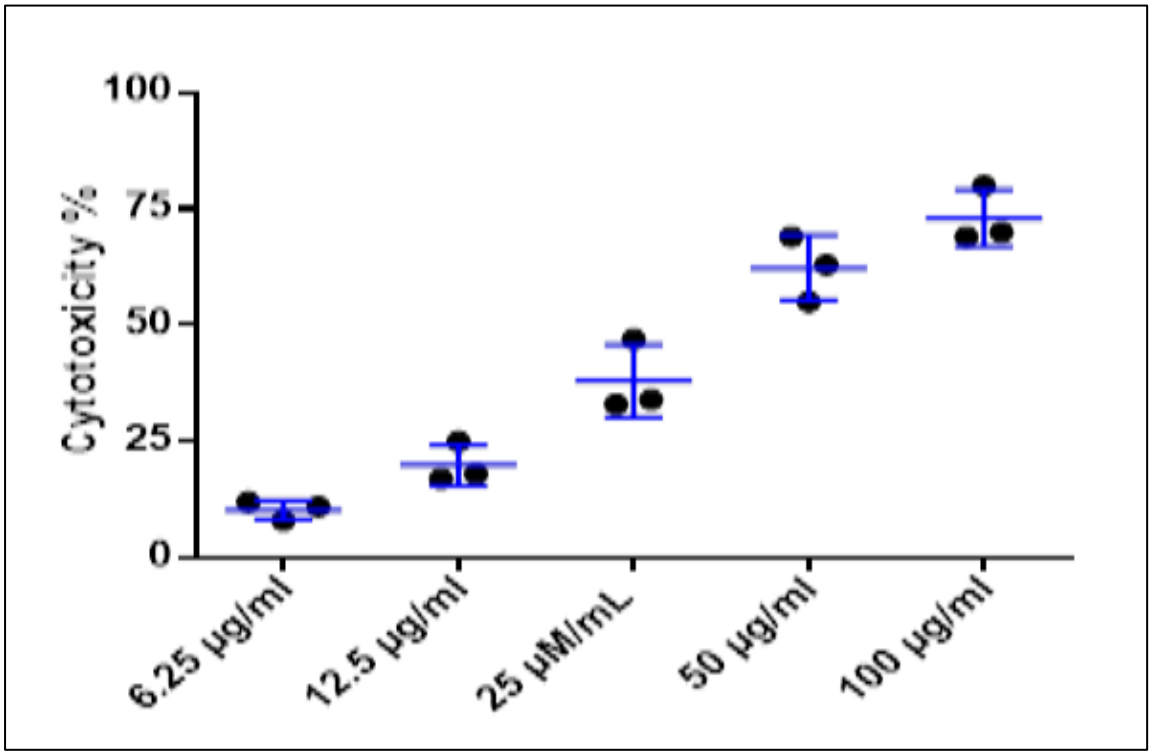


Figure (3-64): Cytotoxic effect of Z13 in MCF-7 cells. IC50=36.24 µg/ml

Conclusions

1- A novel nano graft co-polymer was synthesis and characterized by using FT-IR, ^{1}HNMR, DSC, AFM, XRD and TEM techniques.

2- A novel nano graft co-polymer-drugs were synthesis and characterized by using FT-IR and ^{1}HNMR techniques.

3- Synthesis nano graft co-polymer-drugs and characterized by using FT-IR, ^{1}HNMR techniques.

3- The solubility of the synthesis nano graft co-polymer-drugs was determined in different solvents.

4- Swelling behavior of the prepared nano co-polymer-drugs were determined in different pH value (pH= 2.2, 7.0 and 8.0).

5- The biological effectiveness of the prepared compounds was studied of inhibition of the spread of breast cancer and shows good results.

Future Work

1- Synthesis of other new pharmacological co-polymers by way of bridging connections between the polymer and the drug, as well as the possibility of using other drugs in order to extend the drug life and increase the effectiveness, especially in chronic diseases that need to use a repeated daily dose and also in order to reduce toxicity and determine drug release in site the specific patient.

2- It is possible to study the nano scale properties of some synthesis pharmaceutical polymers and their fields of veterinary application.

3- Study the biological activity extensively and on different bacteria and fungi.

4- Treatment of the defects of the medicines that have a bitter taste and which are characterized by irritating odors or less soluble in water.

5- Characterization and evaluation of pharmaceutical polymers in order to obtain properties that facilitate use for various therapeutic purposes.

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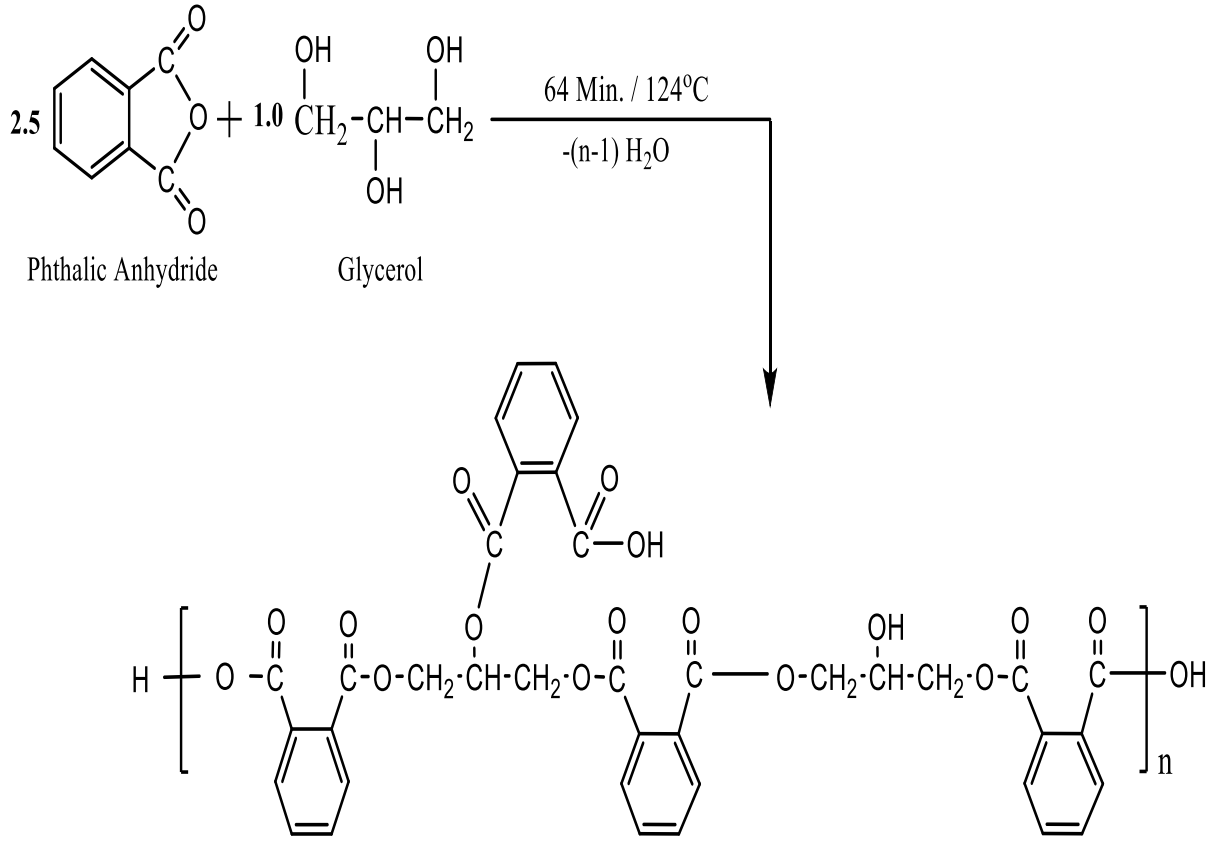
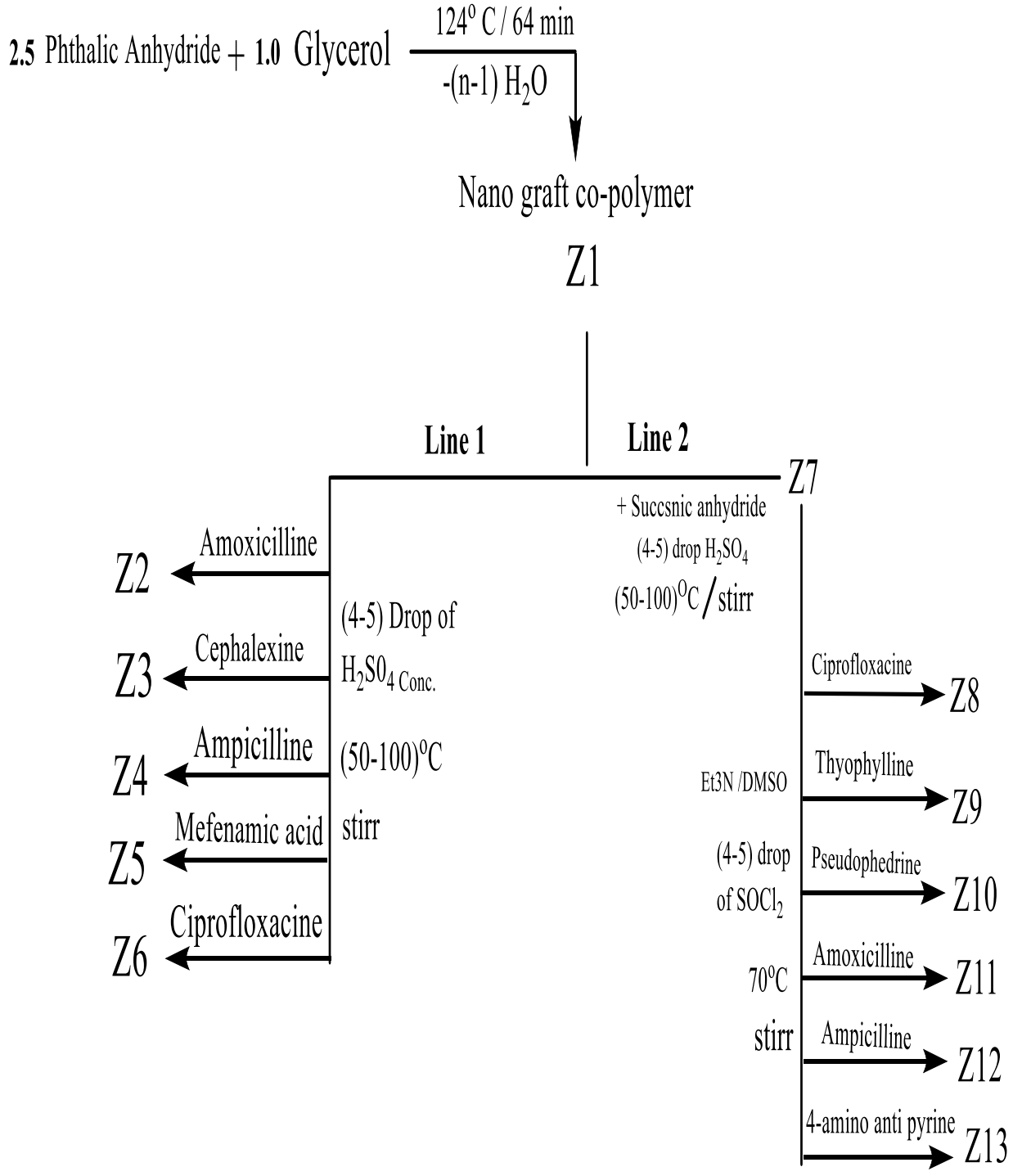
الخلاصة

في هذا العمل ، تم تحضير جسيمات النانو للبوليمر المشترك الجديد المطعم ، باستخدام عملية الذوبان عن طريق بلمرة التكثيف ، من تفاعل مول واحد من الكلسرين مع 2.5 مول من أنهيدريد الفثاليك عند 124 درجة مئوية و 64 دقيقة. مع سحب الماء كناتج ثانوي ، كما هو موضح في المعادلة. تم تشخيص البوليمر النانوي المحضر بواسطة (FT-IR ، ^{1}HNMR ، DSC ، AFM ، XRD و TEM).



(Nano graft co-polymer)

تم تحضير عدة عقاقير نانو بوليمرية باستخدام أدوية مختلفة (أموكسيسيلين ، سيفاليكسين ، أمبيسيلين ، حمض الميفينياميك وسيبروفلوكساسين) على التوالي ، بطريقتين مختلفتين كما هو موضح في المخطط التالي:



تمت دراسة سلوك الذوبانية ونسبة الانتفاخ لجميع عينات العقاقير النانوية المكونة من البوليمر المشترك النانوية مع العقاقير ، في ثلاثة أوساط حامضية مختلفة (2.2 ، 7.0 و 8.0) عند درجة حرارة ثابتة 310 كلفن كدالة للوقت (الساعة واليوم).

تم قياس إطلاق الأدوية (.Abs) باستخدام مقياس الطيف الضوئي UV-Vis في ثلاثة أوساط حامضية مختلفة (2.2 ، 7.0 و 8.0) عند درجة حرارة ثابتة 310 كلفن كدالة للوقت (الساعة واليوم).

تم قياس تأثير الأدوية المحملة على البوليمر النانوي (Z3 ، Z4 ، Z5 ، Z6 ، Z8 ، Z9 ، Z10 ، Z11 ، Z12 و Z13) على تثبيط انتشار سرطان الثدي ، وأظهرت النتائج أن الأدوية تحتوي على تأثير مختلف ، حيث يتفاوتان بين تأثير مرتفع وتأثير منخفض. انخفضت قيمة IC50 بشكل ملحوظ في حيث كانت في المركب Z8 مساوية الى (IC50 = 12.64) ، مقارنة بالعقاقير النقية ومسار موت الخلايا المبرمج المستحث. كانت فعالية الأدوية النانوية المصنعة من البوليمر المركب في منع انتشار سرطان الثدي على النحو التالي:

$$Z8 > Z6 > Z9 > Z12 > Z10 > Z3 > Z13 > Z11 > Z4 > Z5$$

$$\xleftarrow{\text{Increasing efficacy}}$$

جمهورية العراق
وزارة التعليم العالي و البحث العلمي
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كلية التربية للعلوم الصرفة
قسم الكيمياء

تحضير و تشخيص بوليمر مشترك نانوي جديد كناقل للدواء و دراسة قابليته على تثبيط أنتشار سرطان الثدي

هذه الرسالة مقدمة إلى
مجلس كلية التربية للعلوم الصرفة - جامعة كربلاء ، كجزء من متطلبات نيل
درجة الماجستير في علوم الكيمياء

من قبل

زينب موسى شاكر

بكالوريوس كيمياء / جامعة كربلاء (2018)

إشـــــراف

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