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Synthesis a novel Nano Co-polymer and using as carrier drug system

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1442 **٢٠٢٠**

بِســـم الله الرحمـــنِ الرّحِيـــمِ

((وَأَنزَلَ اللَّهُ عَلَيْكَ الْكِتَابَ وَالْحِكْمَةَ وَعَلَّمَكَ مَا لَمْ تَكُن تَعْلَمُ ۚ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا))

صدق الله العلي العظيم

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Amel

Dedication

Specially dedicated

To the owner of the fly glue

Al-Imam Al – Hajjah bin Al Hassan (A)

To those who have fulfilled by their promises…….

my lovely parents

To my husband and my child

To my brothers

To my sisters

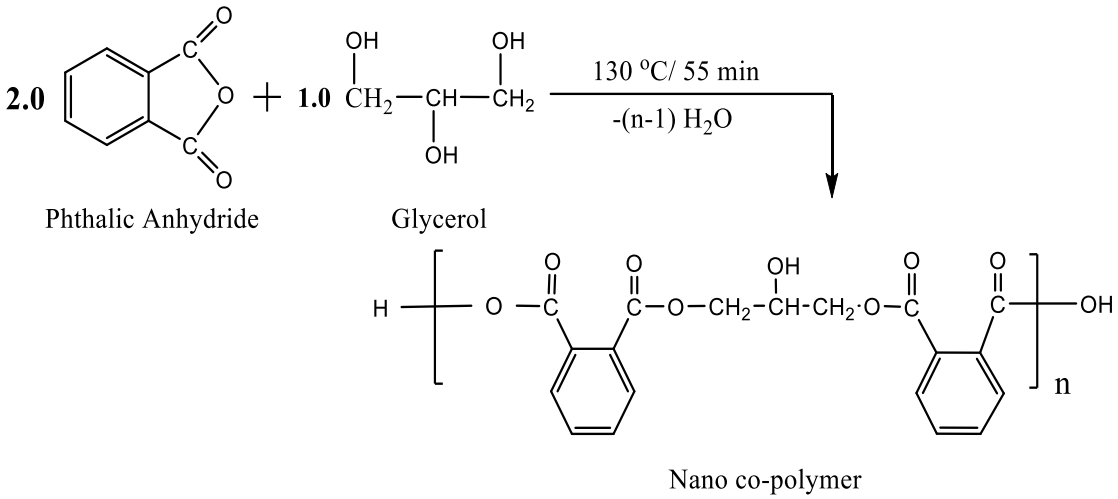
To my friends

***To* Kerbala university**

***To* Babylon university**

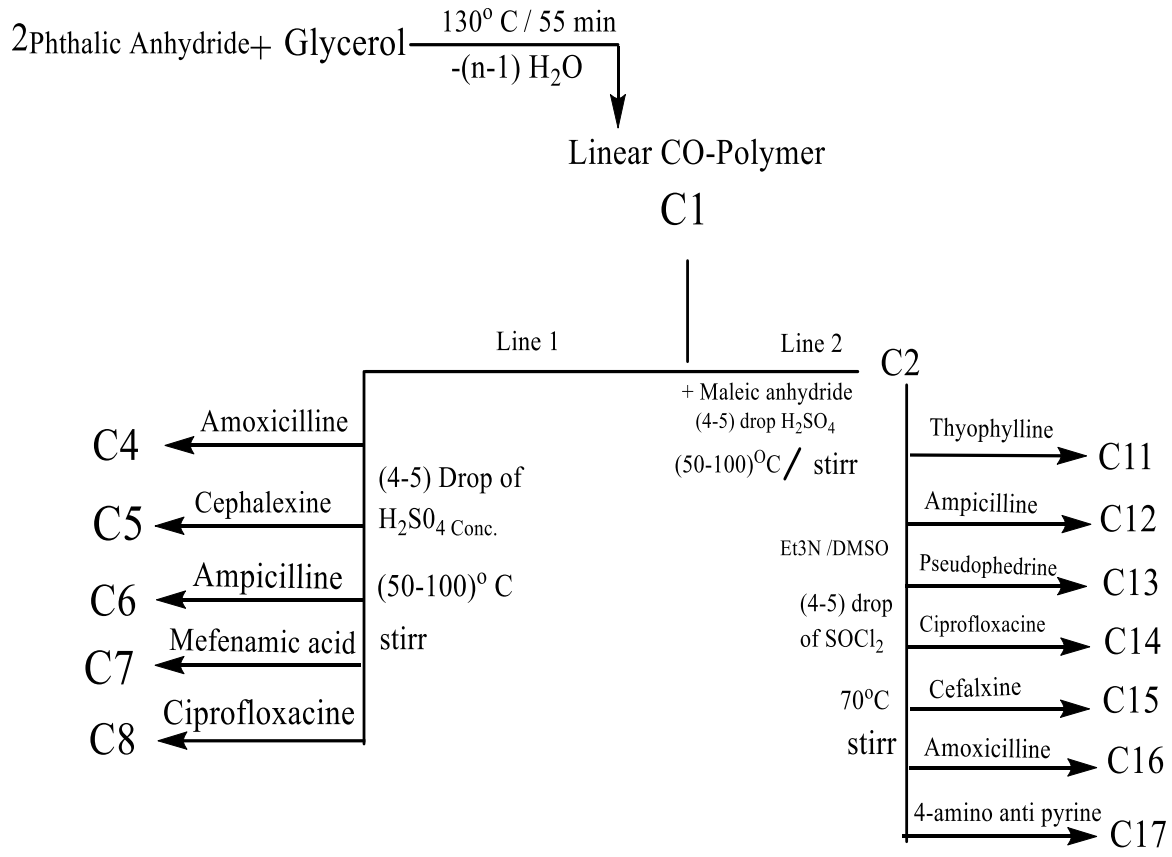
Abstract

In this work, a novel nano co-polymer was synthesized from the reaction of Phthalic Anhydride with Glycerol to form the linear co-polymer at 130°C, as in the following scheme. The product nano co-polymer was identified by (FT-IR, DSC, AFM, XRD and TEM).



(The linear co-polymer)

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



The solubility behavior and swelling ratio was studied for all the synthesis of nano 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 biological activity of some synthesis of nano co-polymer-drug (C5, C6, C7, C8, C11, C13 and C17), was studied by studying their effect on inhibiting the spread of breast cancer. IC50 value was significantly decreased in C8 (IC50=16.83) in comparison with pure drugs and induced apoptotic cell death pathway.

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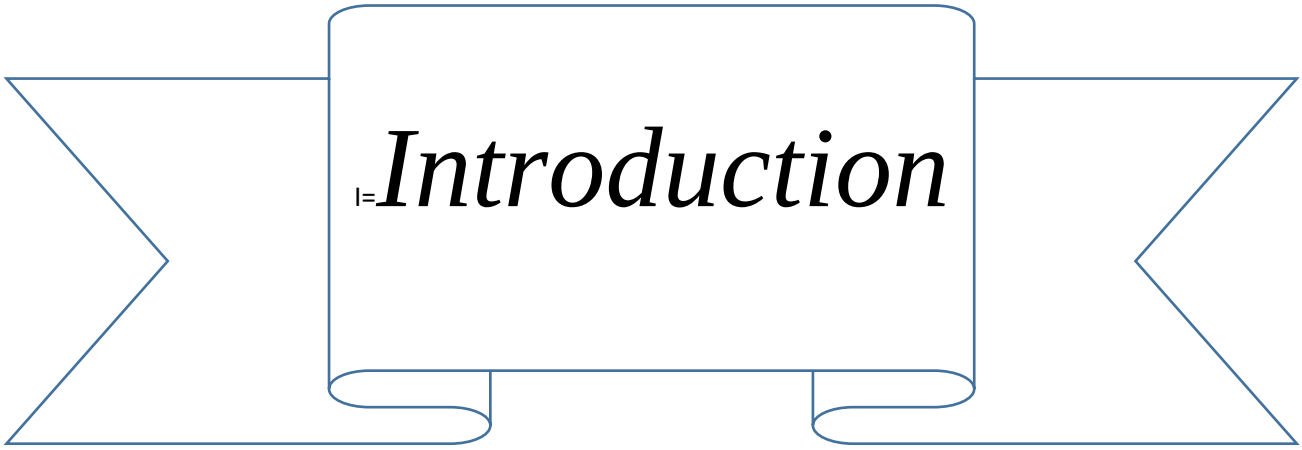
List of Abbreviations

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
$SoCl_2$	Thionyl chloride
PDS	Pro Drug Delivery System
DDS	Drug Delivery System
BD	Biological Distribution
BK	Pharmaco Kinetics
ADME	Absorbtion,Distribution,Metabolism,Excretion
MDR	Multiple Drug Resistance
PDE	Psedophedrine
PBPS	Penicillin Binding Protiens
RPMI 1640	Roswell Park Memorial Institue
MCF-7	Michigan Cancer Foundation

Chapter one



1. Introduction

1.1 polymers

Polymers: are large molecules that are made up of a large number of small units called monomers. [1]The conductive polymers have received a lot of attention (which are connected to each other because they possess many vital applications where they were used to conduct weak electrical signals)[2]. There was a great interest in substances with (inside the human body, i.e. used as industrial nerve agents for biodegradation due to their application in medicine and industry, as the use of biodegradable polymers from renewable sources reduces the use of industrial polymers and reduces problems Many of drugs have different problems such as poor solubility, low stability, shorted time of circulation, and non-specific toxicity limiting their therapeutic efficacy[3]. There is a need for biopolymers with a variety of properties and specific to biological applications. At the present time, industrial biopolymers have become distinct alternatives to biomedical applications [4] Some polymers leave an immune response in the body that may be avoided by using a suitable synthetic polymer [5]

1.2 Drug polymers

Polymers useful as therapeutic agents, that exhibit pharmacological properties, before that can be utilized as carriers for selective and sustained delivery vehicles for small molecule or macromolecular (e.g. proteins, genetic materials, etc) pharmaceutical agents [6] 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 [7] 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[8] 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, inhibiting the crystallization of active pharmaceutical products[9] ,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 to benefit from delayed and continuous drug release for a long time while reducing side effects. And polymers, this condition includes the slow release of water-soluble drugs, the rapid release of low-water-soluble drugs[10].

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 [11] 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 [12].

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. M, soluble in water and should be safe throughout the entire delivery stages of the drug (before and after release of the drug) [13].

1.3 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 [14]. 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. 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 coextrusion of the therapeutic drug with the polymeric material. The therapeutic drug is dispersed and incorporated into the polymer as small particles, preferably having a maximum cross-sectional dimension of 10 microns [15,16,17].

1.4 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[18].

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:

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.

1.5 Modified release

There are many patterns of modified pharmaceutical forms Long-term release A prolonged therapeutic effect has been 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 the drug is taken at least twice than in direct-release forms in which the drug release is initially and sufficient to give an offensive therapeutic effect Gradual release, then for a period of time, in which the medication will be released at a steady level and give appropriate and consistent concentrations with time [19].

In the thirties of the twentieth century, polymers were used to control pharmacokinetic release. Lac gum was used in aspirin pressures and in the period between 1970 and 1990, the use of polymers evolved in the effect prolongation technique where there was a need to adjust the appropriate concentrations of the drug and reduce side effects[20]. Intestinal doses by mouth are used clinically to prevent drug release in the stomach and allow release in the lower areas of the digestive system. Intestinal polymers include sensitive industrial or semi-industrial materials that contain

carboxylic acid groups that remain coherent at pH, it is low in the stomach and becomes ionized in an environment with pH High in the small intestine, thereby enabling the drug to be released [21] The factors that control the speed of pharmacological release differ according to the drug type, from simple diffusion to the chemical reactions that control this spread[22].

In general, the rate of drug release depends on the solubility, biological degradation of materials and propagation, and also depends on the size of nanoparticles and drug loading efficiency [23]. There is a role for many systems of drug release control in the profile, which leads to the regulation of a high level of the drug in the blood and for a long period of time, the level of the drug follows the profile in the blood as in Figures (1-1) and (1-2), where the level of the drug rises after each dose and then decreases Until the next release of the subsequent dose, as the drug level remains variable between the highest value and represents the toxicity level and the lowest value, which is considered effective[24]

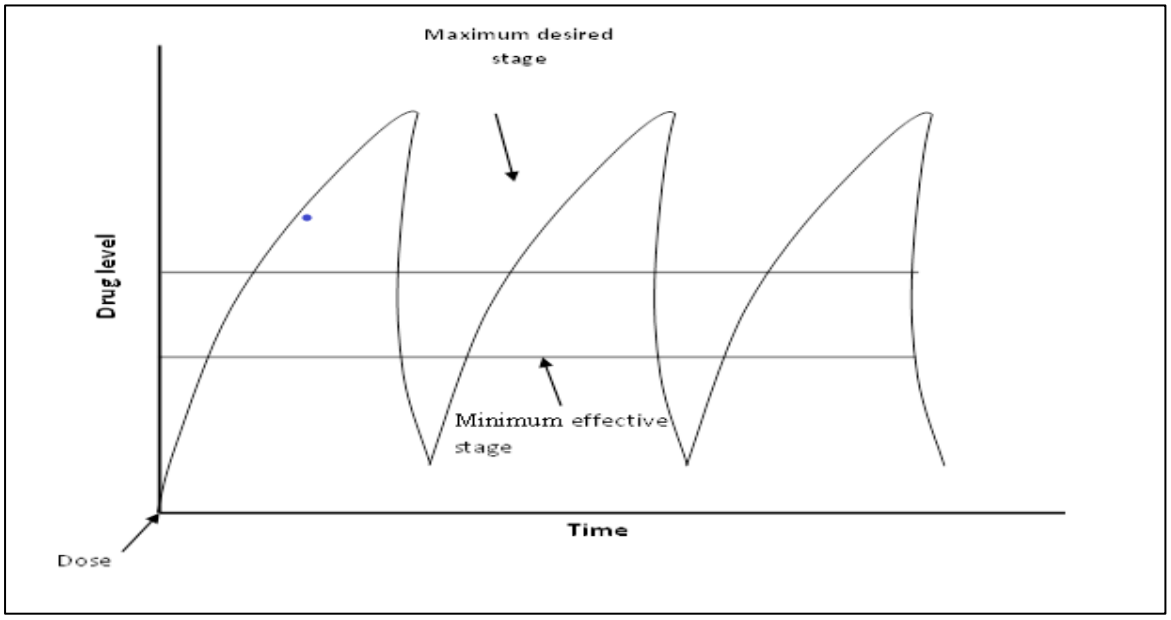


Figure (1-1): Drug level in blood with traditional drug doses

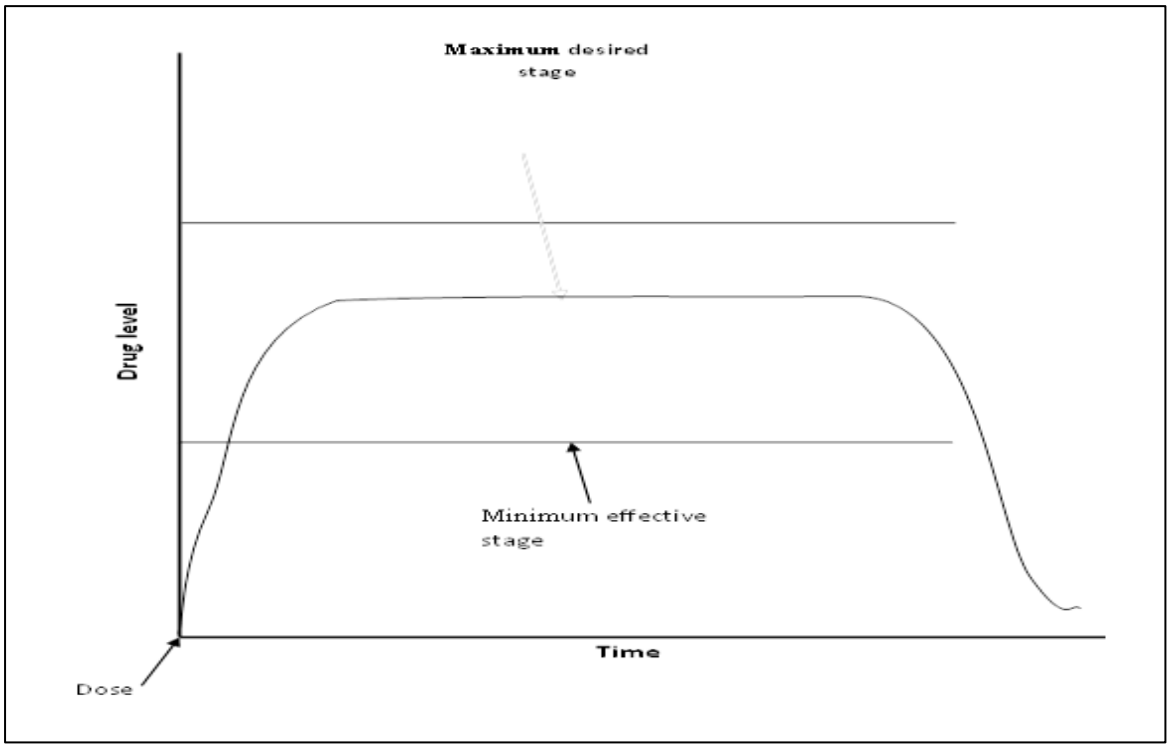


Figure (1-2): Drug level in blood with controlled delivery doses

1.6 Pro-drug

It is a chemical entity of an active main drug and has a changing chemical-physical characteristic and it is an ineffective drug during delivery to the place of the procedure and is activated by specific conditions in the target location, that the use of the auxiliary drug maintains the activity of drugs and their liberation in the target cell, the transformation of primary drugs in the human body (transformation Into an active form) within a tissue, cell, or organ. Sometimes normal metabolic processes such as the breaking of the sphericity between the drug and the polymer by means of certain cell enzymes to achieve re-conversion of polymeric drugs, the polymer conjugation with the drug constitutes what is called the polymeric adjuvant, the polymeric federations of conventional drugs (polymeric adjuvant medication) have advantages that include:

1) Increasing the water solubility of drugs that are low or insoluble and therefore insoluble and thus enhancing the biological availability of drugs.

2) Maintaining drug activity and protecting it from disruption during the transition of the bloodstream to the targeted tissues or organs.

3) An improvement in the performance movement.

4) Reducing the effectiveness of the antagonists from Medicines and lead to a lower immune response to the body.

5) its ability to provide effective or ineffective drug targeting to the job site specifically

6) the possibility of configuring a complex drug delivery system and a developer that may include in addition to the holder of the drug and the polymer many active ingredients that enhance the specific activity of the drug, and because of these advantages of the drug, the polymeric adjuvant takes us to a new era of the PDR delivery system.

The chemical conjugation of the drug or any biological molecule with the polymer has bonds Stable such as (amides, disulfide, ester) and the bonds formed must be stable to prevent the release of the drug during its transfer before reaching the cell site, the covalent bonds such as (ester or amides) are stable bonds and have the ability to deliver the drug to the target site [25].

Auxiliary drugs are designed and developed to overcome medicinal and pharmaceutical barriers in medical drug applications and a number of properties such as chemical instability, patient acceptance of the drug, intoxication, site specificity, low oral absorption, and there are a number of important biopolymers in the past decade, aliphatic polyesters are One of auxiliary biodegradable industrial drugs [26].

The basic traditional medicines are nonspecific and chemically related to masking unwanted drug properties such as: chemical instability, limited bioavailability, and site specificity. On the other hand, the targeted pharmaceutical products represent a new strategy for delivering the drug in a targeted and effective way, especially targeting primary medicines to A specific membrane transporter possessing the potential as a means of delivering the drug orally or as a selective delivery system for the chemotherapy for cancer [27, 28].

1.7 Oral absorption

Many medicinal drugs have the ability to dissolve in water as well as their synthetic analogues of permidine nucleoside, natural purine, antibiotics such as carbicillin, ampicillin, that the cause of poor absorption is the natural and polar factors that are poor metabolism and affinity in the absorption process [29]. The biological effect through the mouth causes a limited water solubility, and this has a negative effect and this problem can be controlled by using an auxiliary drug that increases the solubility and absorption in water [30].

1.8 Solubility of drug

The adjuvant is used to reduce or increase the solubility of the drug, depending on the drug's use The chemical stability of the drug is important for the therapeutic agent to provoke drug activity for a longer period and this instability can be resolved by appropriate combinations requiring a new auxiliary drug, and this adjustment to the auxiliary drug is based on modification of the effective group responsible for this instability or a change in the physical properties of the drug and this leads to the development of bonds between The means of transport and medication as in the Ampsilin NH_2 of the series with the attachment of the beta-lactam ring

with a second molecule of Ampsilin and this generates new types of Ampsilin [31,32,33].

1.9 Drug carrier

In 1975, for the first time, the covalent bond between the polymer and the drug was introduced by Ringsdorf , as there are advantages to the polymeric drug carriers: the distribution in the body, the effect of storage, pharmacokinetics, a unique drug. Most drugs with small molecules break down quickly. There is a difficulty in the use of medications, as they are concentrated in the tissues used and diffusion is slow. As for pharmaceutical polymers, they have appropriate behavior and polymeric carriers have desirable advantages: diastolic release, prolonging the effectiveness period, and continuing treatment [34]. Figure (1-3): Ringsdorf's model of polymer drug carrier. Figure (1-3), shows the association of four groups on the main biopolymer chain and has the ability to decompose, namely:

1- The presence of the bridging bond

2- The soluble group of the entire polymer system

3- The drug

4- The transport system. In medicinal release, the drug carrier must have the ability to maintain its original form and its smooth surface during the release process[35].

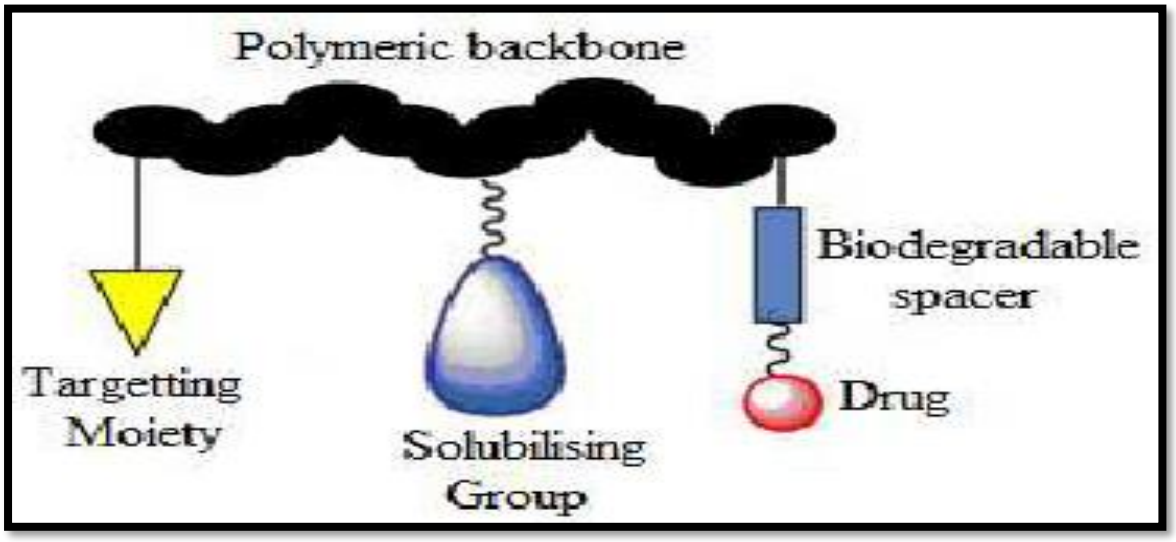


Figure (1-3): Ringsdorf's model of polymer drug carrier

For the efficacy of the drug's action, improving drug loading efficiency is important for drug carriers [36]. The biological availability of drugs can be improved and continuous release achieved by prolonging the duration of drug carriers remaining at the absorption site [37]. The drug carrier has an important advantage in that it increases the accumulation of the drug and its absorption [38] by increasing the molecular weight of the drug. Lymph gland, kidney, liver, spleen or other devices that transfer biopolymers through tissues.

Success in manufacturing and design by predicting the performance in the body in delivering the polymer to the drug is based on molecular weight, There are polymeric vectors for drugs that have more performance than the drug because many variables occur, such as polymer chain formation, multiple compensation, composition and solubility, all of which have an effect on the behavior of the polymeric drug [39]. The sequential drug polymers are considered to be one of the transporting nanoparticles where they dissolve in water and are biologically insoluble because they possess

many groups that allow the combination of anti-cancer drugs with hydrophobic groups on the polymer chain through the enzymatic degradation of the bonds [40].

1.10 Drug delivery system (DDS)

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 [41].

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 [42]. 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 throug 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 [43].

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 [44]. 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 [45].

There are five 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 [46]. The appropriate drug delivery system can alter the behavior of chemotherapy release factors and thereby improve the effectiveness of anti-cancer activity [47]. 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 [48]. 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 [49]. 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 [50]. 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 [51].

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 [52].

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 [53].

1.11 Swelling

1.11.1 Unlimited swelling

It is that process which leads to spontaneous dissolution as shown in Figure (1-4). It is similar to complete mixing process of different liquids like water and alcohol. When the polymer is in direct contact with a low molecular weight liquid, the molecular of the latter will try to pass quickly through the polymer phase starting to fill the spaces present among the structure elements “polymeric chain” [54, 55]. The liquids that possess a high to a certain polymer and known as good solvents to penetrate through the chain to give this type of swelling that led finally to polymeric dissolution[56].

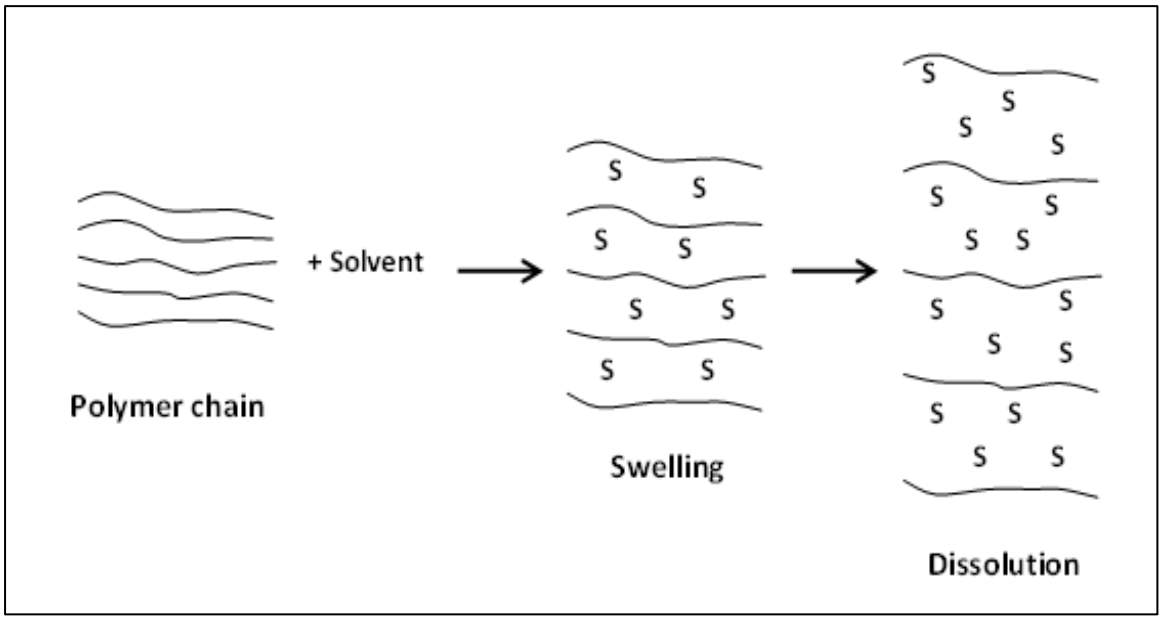


Figure (1-4): Swelling unlimited for some polymers

1.11.2 Limited swelling

It is a process of inter interaction between the polymers and liquids of tiny volume, i.e., the polymeric chains do not separate completely from each other, Figure (1-5). Thus two phases are formed, one separated from the solute in the swelling polymer and the other from the pure solute [57].

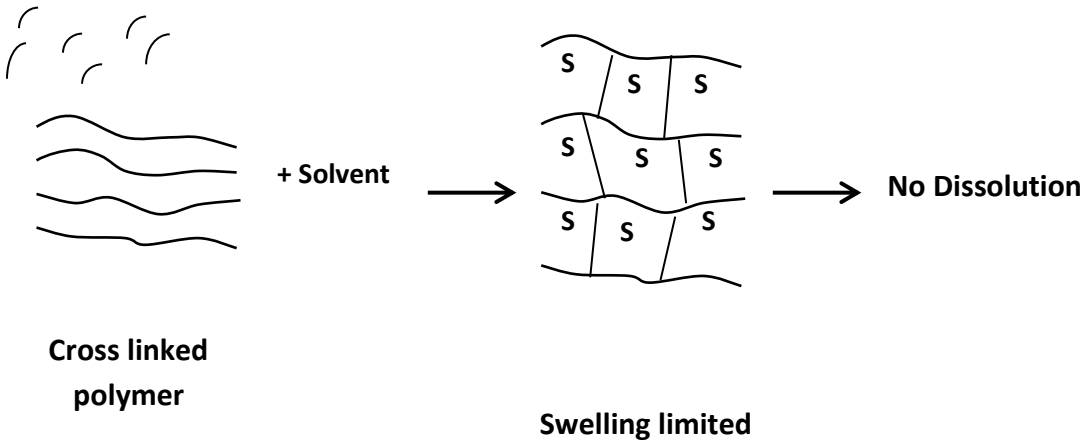


Figure (1-5): Swelling limited for some polymers

1.11.3 Rate and kinetics of swelling [58]

From the scientific point of view, it is necessary to know the ability of the polymer to swell in different liquids. The degree of swelling is determined by a volumetric or gravimetric method. The second is done by weighting the polymer sample before and after swelling, then the swelling degree (Δm) is determined from the following equation [59]:

$$\Delta m = \frac{m_t - m_o}{m_o} \times 100$$

Where m_o = weight of the polymer before swelling

m_t = weight of the polymer after swelling.

We can determine the degree of swelling to the limited swelling polymers only, and cannot be used for the unlimited swelling because of the continuous decreasing of the sample weight due to dissolution[60].

From the figure (1-6) it is obvious that the swelling increase with the time until it reaches the equilibrium state, the point on which on the slope take a horizontal path, a point at which the swelling stops, a point of maximum or equilibrium of swelling.Different polymers take different periods to reach point of equilibrium, this property is very important, thus we observe the maximum swelling for the first sample in Figure (1-6) is greater than the second sample[61].

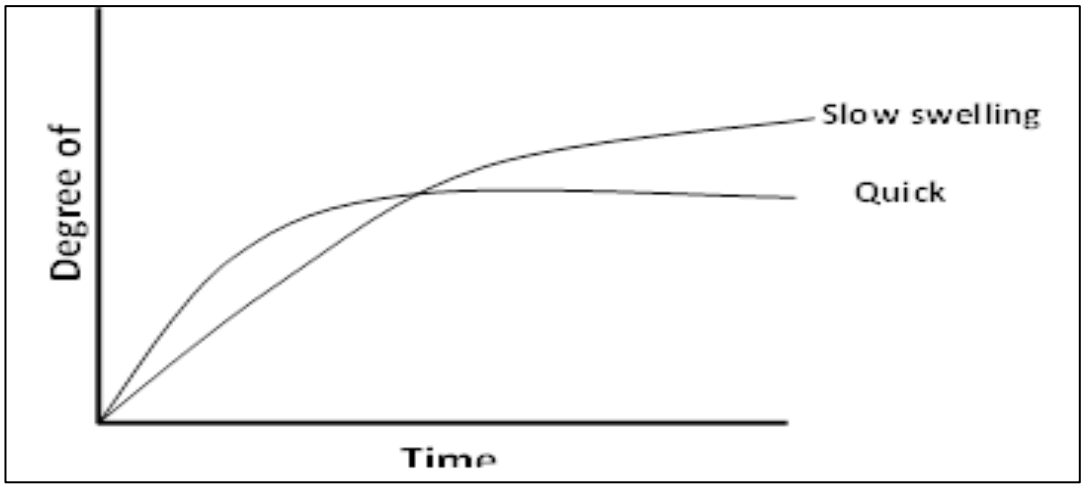


Figure (1-6): Kinetic of swelling

So if we put both samples in a certain solvent for a long period of time, we will notice that the second sample will swell much greater than the first [62], but if the degree of swelling is determined after a short period of time, it is possible to notice the opposite, which means that the quantity of swelling in the first is greater than the second. So we should judge the ability of the polymers to swell from the maximum swelling point [63] show Figure (1-7) kinetic of swelling .

1.12 Biological activity [64,65 and 66]

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. 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. 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.The interactions of living organisms against biotoxicity 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 [67].

1.13 Anticancer

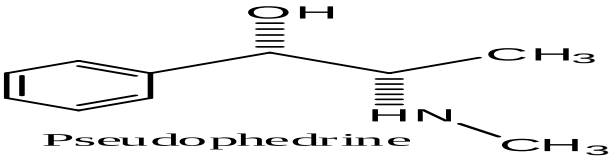
Cancer is a range of diseases characterized by abnormal growth and spread of abnormal cells and is considered one of the most serious diseases in the world, where it represents the second most cause of death in the united States and Europe after cardiovascular diseases according to the facts of cancer numbers 2016[68] . Most type's recurrent cancers are cancers of the colon, prostate, breast, lung and rectum as a sex function. That lung cancer the 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[69] . 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 [70] . 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 [71], 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[72].

1.14 Psedoephdrine

It is one of the oldest molecules known to treat nasal congestion. The action of vasoconstriction on the nasal mucosa makes it effective amines for treating nasal congestion. On the other hand, whether it is alone or associated with other drugs, it is taken orally [73]. Pseudoephedrine has an indirect effect on adrenergic receptors and has indirect activity on alpha-peripheral receptors and beta-polar receptors, since pseudoephedrine eliminates nasal congestion, so there are always side effects on the blood vessels and the heart that pseudoephedrine is well absorbed from the intestine [74].

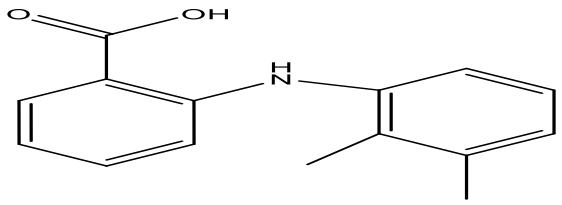
Pseudoephedrine is taken in the form of a syrup or tablets to treat nasal congestion associated with acute upper respiratory infection and allergic reaction [75] Pseudoephedrine is one of the main ingredients required to produce methamphetamine [76].The composition of pseudoephedrine is similar to the synthesis of ephedrine and methamphetamine, but its effect is less in the central nervous system and is used by athletes as an aid to energy generation, and has the ability to increase the muscular nervous system [77] Although pseudoephedrine promotes weight loss, there are negative effects that include headache, insomnia , And tachycardia[78]. when combined with pseudoephedrine with other medications, it plays an important role in anesthetizing headaches [79].



Pseudophedrine

1.15 Mefenamic Acid

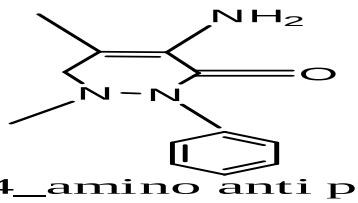
The compound **(**2,3-dimethylphenyl) aminobenzoicacid), which is derived from anthranilic acid, and is a non-steroidal anti-inflammatory drug, and despite its few anti-inflammatory properties, it is used to relieve pain, including dental pain, headache, and postoperative pain, joint disorders such as fragility Bones and musculoskeletal disorders [80].



Mefenamic acid

1.16 (4-aminoantipyrine)

It is an metabolite of aminophenazone and is analgesic with aromatic substance, anti-inflammatory and antipyretic properties, but AAP has side effects such as the risk of agranulocytosis, as AAP is rarely given as an analgesic due to its side effects as raw material [81] . In addition, AAP is used as a reagent for biochemical reactions that produce phenols or peroxides and is also used to detect phenol in the environment. AAP has a toxic effect in experimental animals as well as forms stable complexes with hemoglobin and reduces blood flow [82].



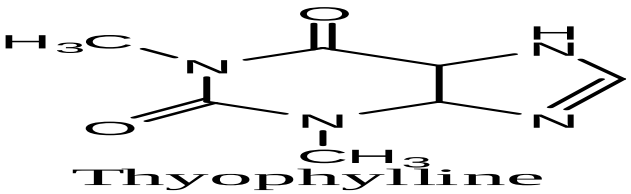
4_amino anti pyrine

There are different methods for estimating AAP and include spectral method, gas and liquid chromatography method, electric capillary, liquid-mass spectrometry, different HPLC methods, solid phase spectrum, volumetric method using pencil graphite electrode [83]. Much of the work reported AAP decomposition by ozone and advanced oxidation processes (AOPS) such as UV / H_2O_2 and photoelectric drilling with Tio_2 / ITO anode [84]. AAP stimulates liver microsomes and is used to measure extracellular water. Compounds derived from AAP have different pharmacological activities such as anti-inflammatory, antipyretic, antioxidant and analgesic, antimicrobial and antifungal properties. In the field of anti-cancer research, AAP offers a promising anti-reproductive activity against human cancer cell lines. And as splitting agents for DNA [85].

APP is an active biological compound that has derivatives and isotopes such as pyrazole and is also anti-inflammatory and antipyretic [86,87]. Compounds that have nuclei of pyrazole derivatives are anthelmintic [88].

1.17 Theophylline drug

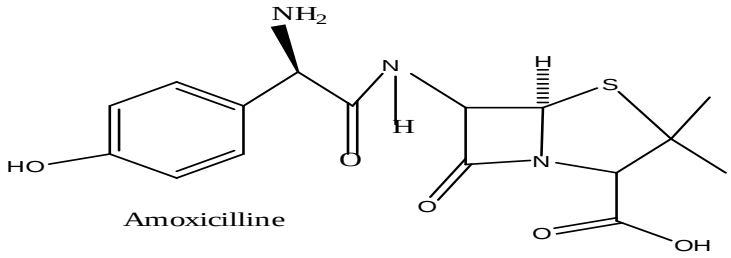
Theophylline , also known as 1,3-dimethylxanthine, is a methylxanthine drug used in therapy for respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma under a variety of brand names. As a member of the xanthine family, it bears structural and pharmacological similarity to theobromine and caffeine , and is readily found in nature, and is present in tea [89].



Thyophylline

1.18 Amoxcillin

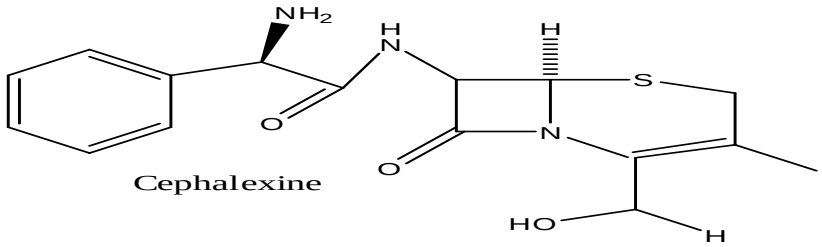
It is a chemically modified form of ampicillin to improve absorption properties and is used to treat bacterial infections caused by sensitive microorganisms, and because it absorbs well after oral administration, it is a preferred drug and therefore amoxicillin produces high concentrations in the blood compared to oral doses similar to penicillin and has Several trade names such as trimox, amoxipen, amoxil, allmox, and bactox. Amoxicillin is an antibiotic and is widely used in veterinary and human medicine [90,91]. Amoxicillin has fast effective degradation in different conditions such as fenton (a solution of hydrogen peroxide and iron) O3, UV / TiO_2, UV / ZNO, H_2O_2 / UV / TiO_2 [92]. In addition to that amoxicillin is an antibacterial it has a high biological activity (90-70)% Orally and the efficacy remains with plasma levels 1-2 hours [93].



Amoxicilline

1.19 Cephalexin

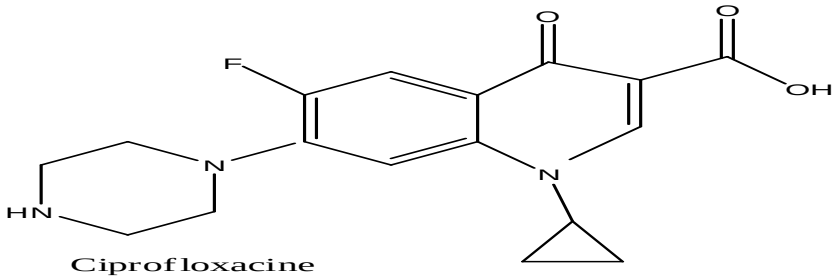
It has a wide range of anti-bacterial activities. As for its structural advantages, it is the presence of a group of peripheral carboxylic acid and a peptide constituent with the alpha-amino group. The oral absorption of cephalexin is safe and fast [94]. Cephalexin is used in veterinary and human medicine all over the world, treats many bacterial infections such as skin infections, respiratory sinuses and bone, many studies have confirmed the presence of cephalexin in wastewater [95]. One of the advantages of cephalexin is that it is a white crystalline powder, soluble in water , Resistant to acid and well absorbed through the nose [96].



Cephalexine

1.20 Ciprofloxacin

It contains groups and guest hosts that are bound to hydrogen and an extended aromatic part, as ciprofloxacin rapidly degrades in a basic solution and is insoluble in water at a neutral acid level [97]. It belongs to the antibiotic family (fluoroquinolone) and is used to treat many types of bacterial infections [98,99]. Its action depends on inhibiting bacterial multiplication by repairing the DNA and disrupting replication processes. The absorption of the compound is fast because the half-life is between 3 and 5 hours [100].

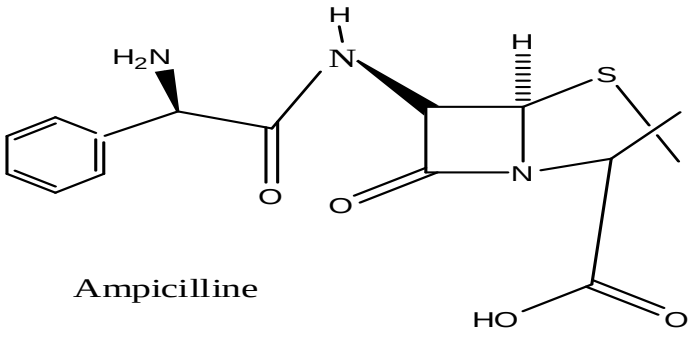


Ciprofloxacine

1.21 Ampicillin

Ampicillin is a penicillin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually gram-positive, organisms. The name "penicillin" can either refer to several variants of penicillin available, or to the group of antibiotics derived from the penicillins. Ampicillin has *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of Ampicillin results from the inhibition of cell wall synthesis and is mediated through Ampicillin binding to penicillin binding proteins (PBPs). Ampicillin is

stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases [101,102].



Ampicilline

1.22 Aim of the work

The aim of this work can be summarized as follows:

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

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

3- Studying some of characterized of a noval nano co-polymer-drug, such as, swelling, solubility, release of drug and biological activity (Brest Cancer)

Chapter two

I=*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
Ortho 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- Melting points were determined using SMP30 melting point; College of Sciences, university of Babylon.

2- FT-IR spectra were recorded on a Bruker**;** College of Sciences, University of Babylon, at (500-4000) cm^{-1}.

3- ^{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.

4- UV-Spectrophotometer, UV-1800, PC–Shimadzu / College of Education for pure Sciences, University of Kerbala

5. 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

6. Atomic Force Microscope (AFM), Oxford, USA / Department of Chemistry/ College of Sciences / Baghdad University.
7. Differential scanning calorimetry (DSC), Shimadzu, Japan / University of Babylon / College of Materials Engineering.
8. X-Ray Diffraction (XRD), Rigaku Ultima iv, Japan, Berta laboratory for laboratory investigations, Iran.
9. Transmission Electron Microscopy (TEM), Philips, CM30, Netherland, Berta laboratory for laboratory investigations, Iran.
10. UV.-Vis. Spectrometer, (Jenway Genova Plus), Department of Chemistry/College of Education for Pure Sciences/ University of Kerbala

2.2 Synthesis of a novel Nano Co-polymer (C1).

In 200 ml two-necked round bottom flask, (2.0 mole, 296gm) of phthalic anhydride and (30 ml) 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 120^{o}C, then about 12 ml of xylene was added carefully to the reaction flask, in the form of batch (three drops in each batch), withdrawal of water formed by the esterification process, and the flask was gently heated. Heating was stopped after 55 min. at 130^{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.

2.2.1 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. [103]

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. [104]

2.2.2 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.[105] 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.[106]

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.[107]

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.[108]

2.2.3 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. [109]

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.[110] Although these waves cancel each other in most directions through destructive interference, they add constructively in some specific directions, determined by Bragg's law:

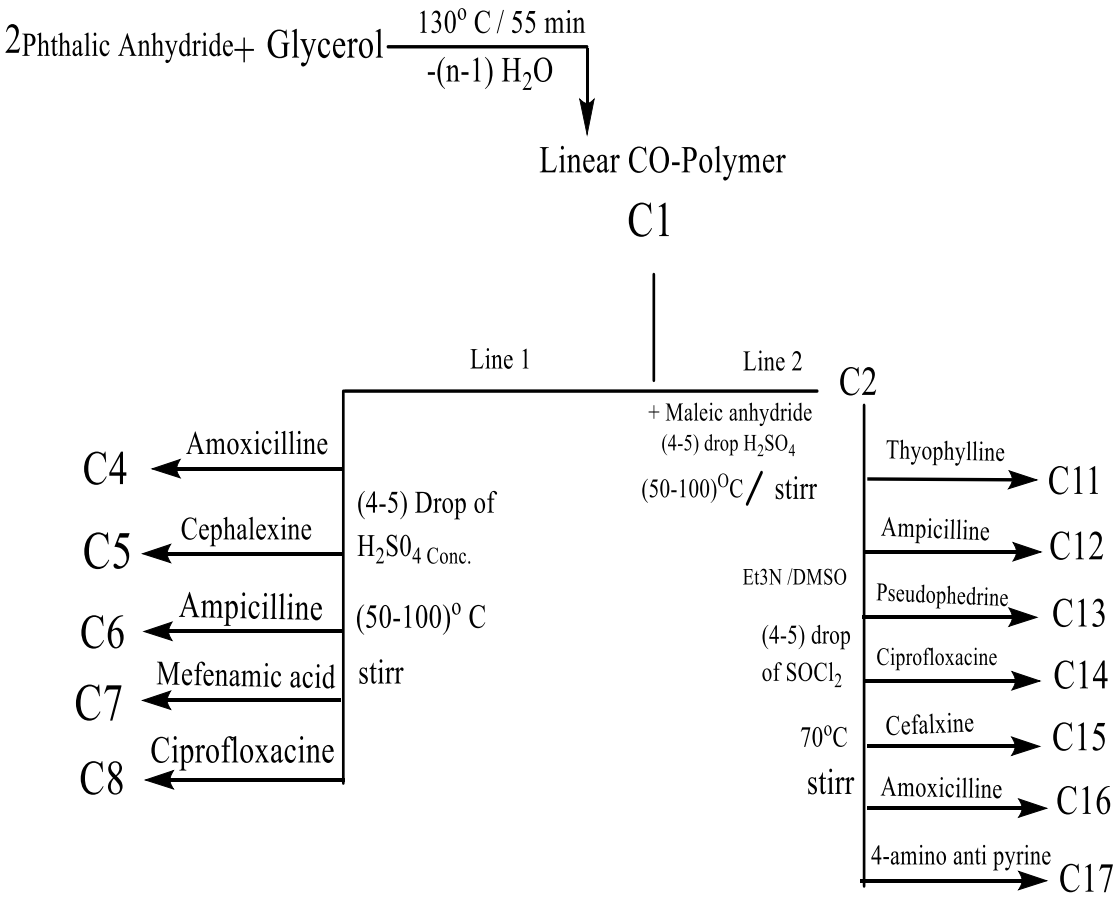
$$n\lambda = 2d\sin\theta$$

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).[111]

2.2.4 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 [112-113]. When preparing samples for studies of nanocomposites, 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 [114, 115]. The following scheme illustrates the steps of the reactions:



2.3 Synthesis of Nano co-polymer with drugs (Line 1) [116,117]

In round bottom flask ,(0.5g) of C1 mixed with (0.5g) of deffrent drugs (Amoxicillin, Cephalexin, Ampicillin, Mefenamic acid and Ciprofloxacin) respectively, placed in the heater and raise temperature gradually starting than 100^{O}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 (C4, C5, C6, C7 and C8).

2.4 Synthesis of Nano co-polymer (Line 2) [116,117]

2.4.1 Synthesis of Nano co-polymer (C2)

In round bottom flask, (5 g) of C1 mixed with (5g) of Malic anhydride placed in the heater and raise temperature gradually starting than 100°C with the addition of 5 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 Synthesis of Nano co-polymer with drugs [118,119]

In round bottom flask, adding (0.5 ml) of Triethylamine to (5.0 ml) of Dimethylsulphoxide, then put it on heater just for starring continuous by using magnetic starre, add (0.5 g) of compound C2, add gradually 5drops of Thionylchloride for 15 Min., after that add (0.5 g) of defferent drugs (Theophylline, Ampicillin, Pseudophedrine, Ciprofloxacin, Cephalxine, Amoxicillin and 4-aminoantipyrine) respectively, for 30 Min. at 70°C and lift the mixture from the heater and starting filteration 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 Dichioromethane as

asolvent. The nano co-polymer products codes are given (C11, C12, C13, C14, C15, C16 and C17).

2.5 Physical properties of the synthesis nano co-polymers

2.5.1 The characteristic of solubility [120,121]

Very small amounts (0.0001g) were taken from the synthesis monomers and polymers (C1-C17) and were placed in small 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 [122]

The swelling ratio was determined by immersing the xerogel (0.05 gm) from polymers, 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:

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

Buffer solutions were prepared by the following methods: [123]

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.

2.5.3 Release of drug [124].

By using UV.-Vis. spectrophotometer, release the drug from the prepared nano co-polymers was determined in three different buffer solutions (2.2, 7.0 and 8.0) at constant temperature 310 K by immersing (0.02 g) of each of the prepared nano co-polymers in (50 ml) beaker. The drug release was monitored for hours and days.

2.6 Biological Activity

2.6.1 Materials

Table (2-2) represent the materials, chemical methods and reagents used and Table (2-3) represent the Instruments used in biological activity.

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

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

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

No.	Item	Company	Country
1	CO_2 incubator	Cypress Diagnostics	Belgium
2	Microtiter reader	Gennex Lab	USA
3	Laminar flow hood	K & K Scientific Supplier	Korea

4	Micropipette	Cypress Diagnostics	Belgium
5	Cell culture plates	Santa Cruz Biotechnology	USA

2.6.2 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.

2.6.3 Cytotoxicity Assays.

To measure the effect of synthesis of nano co-polymer- drug on the spread of breast cancer, 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. 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:-

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

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

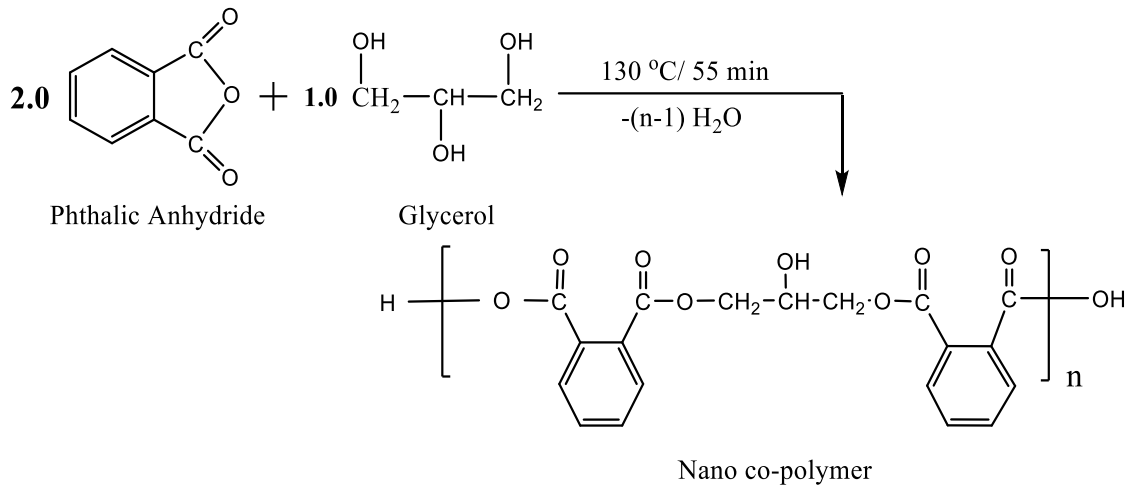
Chapter three

=Result and Discussion

3. RESULT AND DISCUSSION

3.1 Synthesis of Nano co-polymer

The linear Nano co-polymer was synthesized by reacting of 2.0 moles of phthalic anhydride with one mole of glycerol by esterification process, as shown in equation (3-1); This Nano co-polymer was diagnosed with techniques (FT-IR, DSC, AFM, XRD, TEM).



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

Figure (3-1) showed the FT-IR spectrum [131], which appear a weak broad band at (3073 cm^{-1}) attributed to the bond (O-H) alcoholic and H-bond, also showed a stretching band at (3003 cm^{-1}) attributed to the bond (C-H) aromatic, and showed a strong stretching band at (1669 cm^{-1}) back to the bond (C=O) ester, and shows a peak at (1069 cm^{-1}) attributed to the bond (C-O) ester) , and shows bands at (734 and 897 cm^{-1}) attributed to di substitution of aromatic ring. Figure (3-2): Represent the ^{1}H-NMR spectrum

[132], for compound (C1) show appearance single-signal at 13 ppm for $(OH)_{acid}$, and signal doublet at 8ppm for (ph.-H).

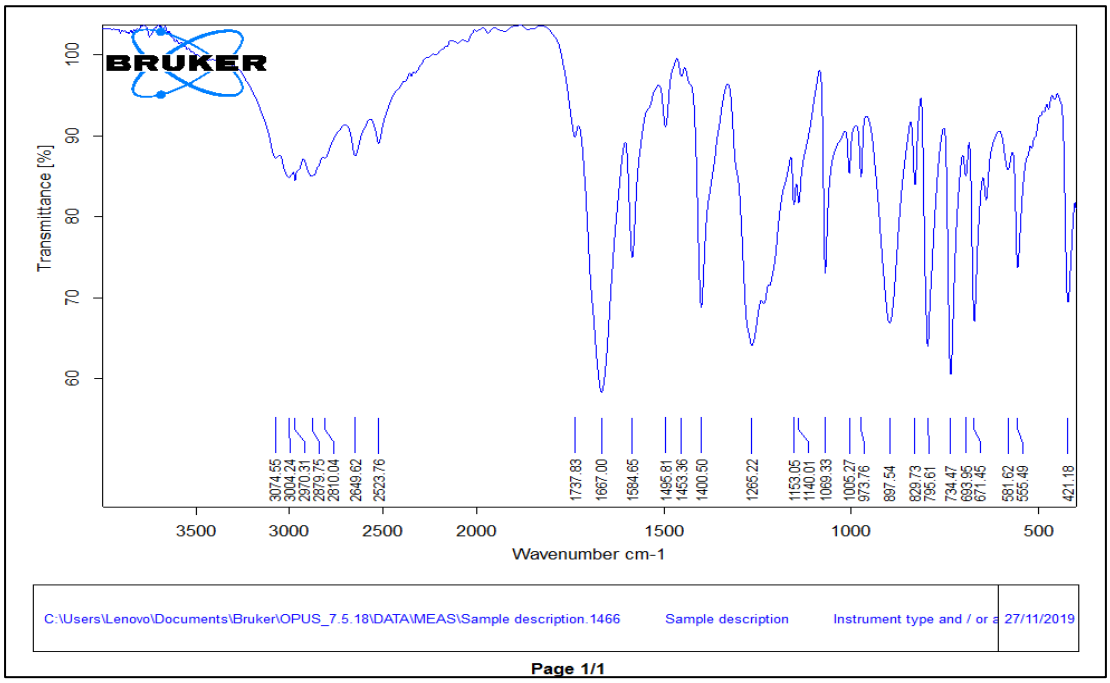


Figure (3-1): The FT- IR spectrum of nano co-polymer compound (C1)

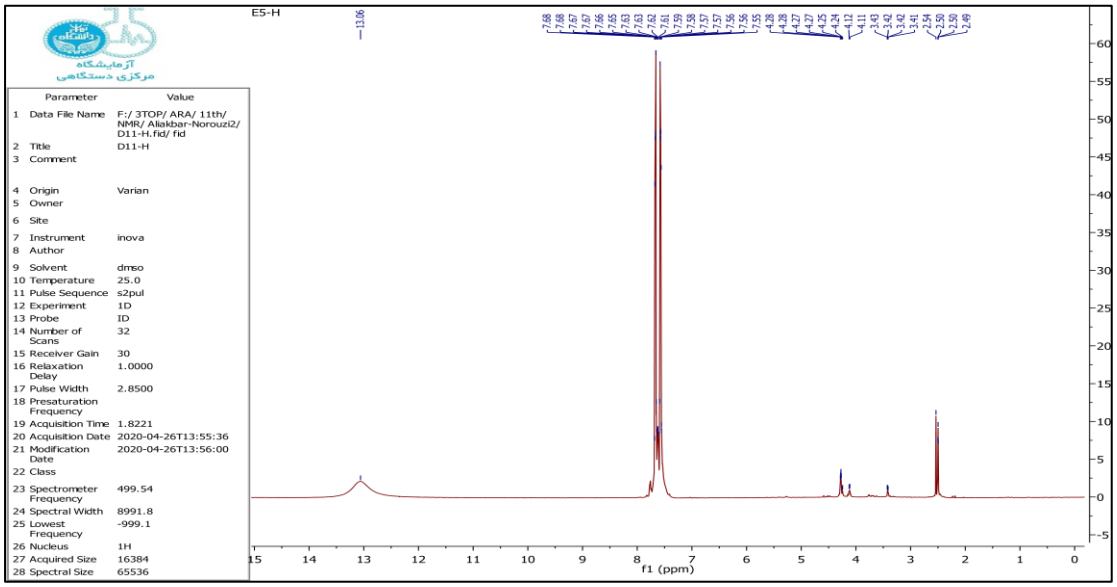


Figure (3-2): The ^{1}HNMR spectrum of nano co-polymer compound (C1)

Figure (3-3 a,b) shows the outer surface of the nanoparticles of co-polymer. The roughness coefficient of a linear co-polymer surface was 1.37 nm and the square root square was equal to 1.58 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 5.26 nm, as observed in figure (3-3 a). Table (3-1) represents the total rate of the particle sizes of the common linear nanoparticle and the different proportions of these volumes; the results indicate that the molecular size of the co-polymer nanoparticle was 97.53 nm and Figure (3-3 b) represents the distribution of the different proportions of particle sizes of the linear co-polymer nanoparticle.

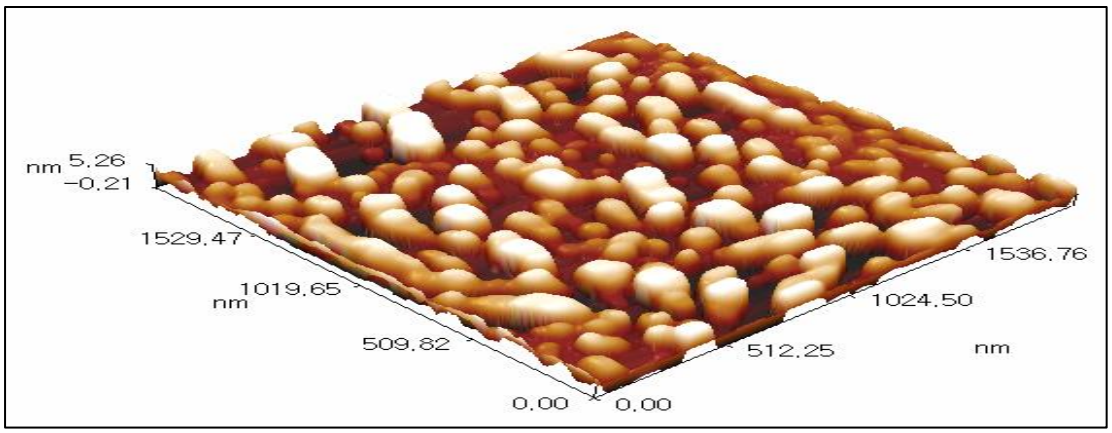


Figure (3-3 a): Image of Atomic Force Microscope for nano co-polymer shows 3D Image.

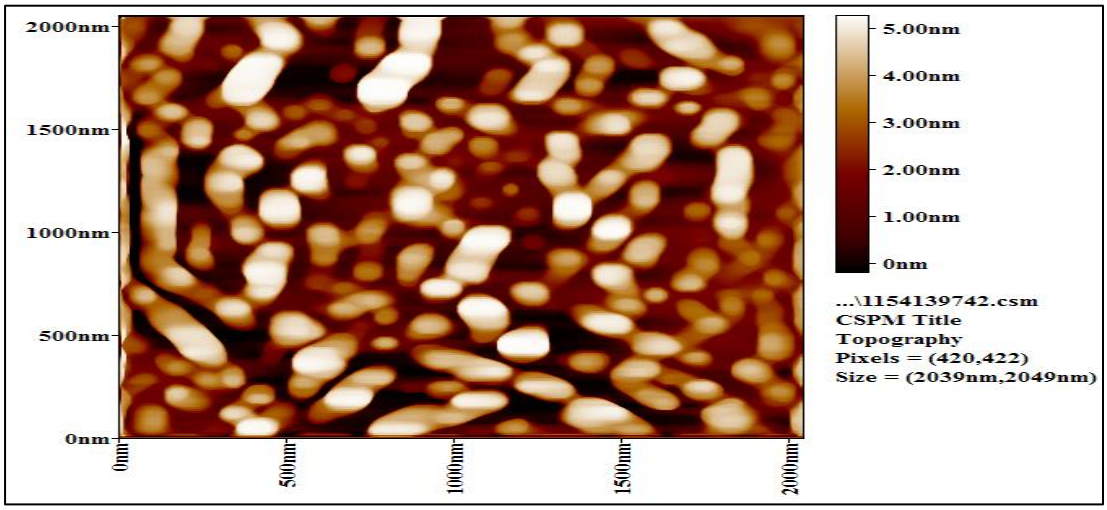


Figure (3-3 b): Image of Atomic Force Microscope for nano co-polymer shows 2D Image.

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

Sample: 3	**Code: Sample Code**
Line No.: lineno	**Grain No.:130**
Instrument: CSPM	**Date: 2019-09-24**
Avg. Diameter: 97.53 nm	**<=10% Diameter: 65.00 nm**
<=50% Diameter: 95.00 nm	**<=90% Diameter: 125.00 nm**

Diameter (nm)<	Volume (%)	Cumulation (%)	Diameter (nm)<	Volume (%)	Cumulation (%)	Diameter (nm)<	Volume (%)	Cumulation (%)
55.00	0.77	0.77	85.00	6.92	30.77	115.00	7.69	79.23
60.00	1.54	2.31	90.00	8.46	39.23	120.00	2.31	81.54
65.00	3.08	5.38	95.00	6.92	46.15	125.00	3.85	85.38
70.00	7.69	13.08	100.00	8.46	54.62	130.00	5.38	90.77
75.00	3.08	16.15	105.00	8.46	63.08	135.00	6.92	97.69
80.00	7.69	23.85	110.00	8.46	71.54	140.00	2.31	100.00

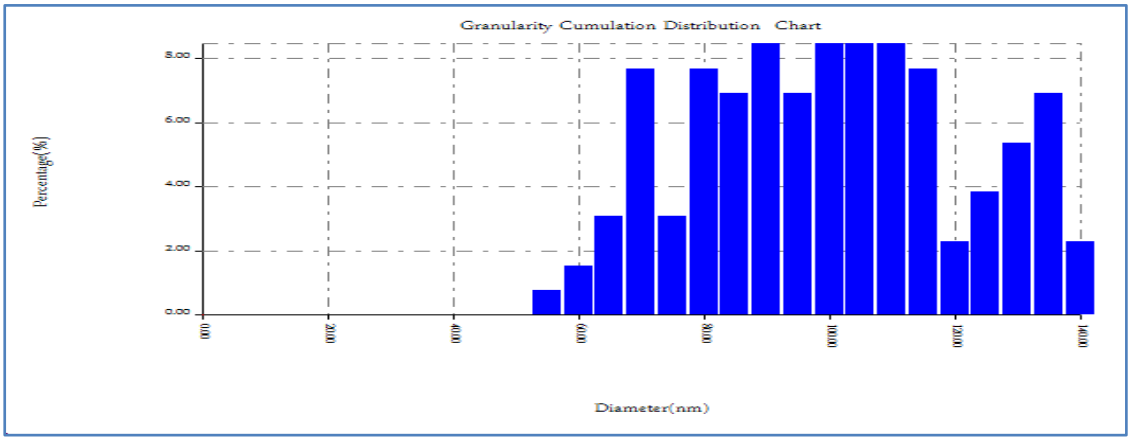


Figure (3-4): Distribution of the different proportions of particle sizes of the nano co-polymer

The x-ray diffraction (XRD) patterns of the nano polymer Figure (3-5) had a diffuse halo at 2q = 20, which is associated to the intra-chain segment distance. More defined peaks can be identified in the diffractogram of all polymer samples. XRD pattern indicated that the presence of rigid aromatic rings, stemmed from the phthalic acid, lead to more rigid structures, which should be more prone to crystallize than fully aliphatic polymers. Molar proportion between phthalic acid and glycerol used for the synthesis of polymer contributed to the formation of ramified polymers having –carbonyl groups, since there is an excess of carbonyl groups in relation to alcohol groups. Furthermore, a higher amount of phthalic acid indicated that the molecular motions, due to the rigidity of the aromatic rings, and should facilitate the packing of the polymer chains in crystalline lattices.

Figure (3-5) shows the x-ray diffraction (XRD) in the nanoparticles co-polymer using origin software. The average inters planer spacing between atoms (d_{hkl}) was 0.416 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 97.27 nm relative to Scherrer's equation:

$$D = \frac{k\lambda}{\beta\cos\theta}q$$

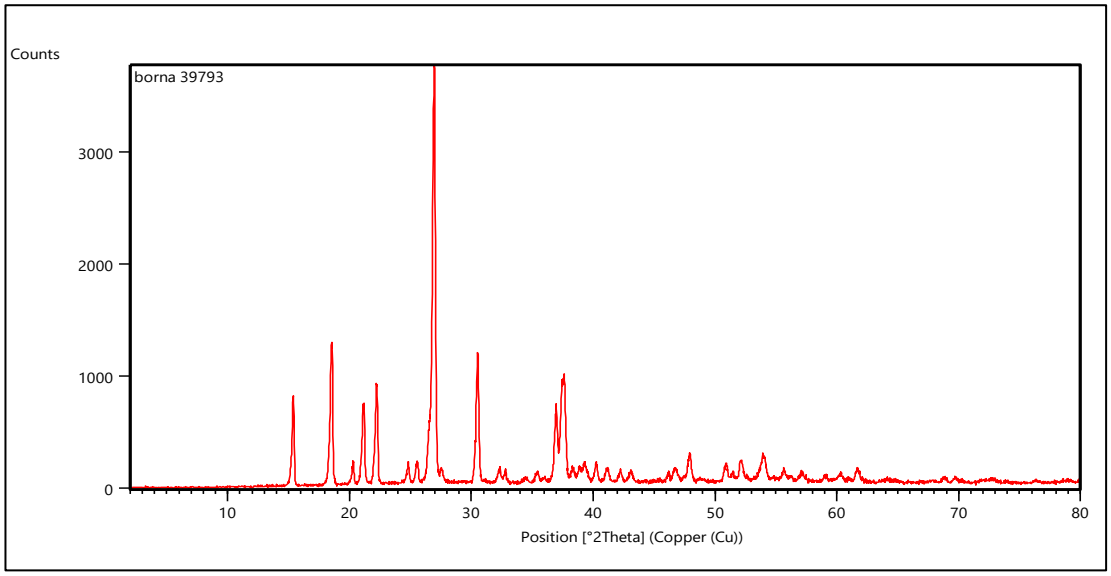


Figure (3-5): The x-ray diffraction in the nanoparticles co-polymer

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
15.37142	7.68571	0.065976	121.5031	0.575973	97.2776	0.4163
18.5194	9.2597	0.082717	97.31015	0.478716		
21.13842	10.56921	0.086017	93.9511	0.419958		
22.21383	11.10692	0.081133	99.78578	0.399864		
26.93075	13.46538	0.102355	79.80898	0.330803		
30.50876	15.25438	0.090184	91.30647	0.292773		

TEM micrograph, Figure (3-6), indicated that synthesized nano co-polymer showed defined form with elongated shapes, like rods, semi-spherical and irregular shapes. The synthesized nano co-polymers are composed of low atomic number elements and therefore scatter electrons weakly, giving poor contrast in the TEM Soft materials having high concentrations of aromatic moieties tend to be somewhat more radiation resistant than fully saturated polymers. This property is usually attributed to the delocalization associated with highly conjugated bonds that provide a source of electron charge and the means to distribute the adsorbed energy over a larger volume of material so micrographs showed the areas with different thickness can have a different interference pattern. It can be destructive on one place but can be constructive o another place and that explain Regions in the specimen which are thicker or of higher density will scatter more strongly and will appear darker in the image because highly scattered electrons are stopped by the objective aperture. The average length estimated from TEM images was ranged between 70 to 95 nm which is comparable with AFM and XRD results which confirm the formation of nanoparticles of co-polymers and support the results of AFM and XRD.

Figure (3-6) sowed the TEM micrographs of the nanoparticles co-polymer with irregular particles like layers with different thicknesses shape, semi-spherical shapes and transparent plates shape. An average particle size of the linear co-polymer nanoparticle was found to be 97.01 nm.; Table (3-3) shows the proportions diameters, angels and standard deviations of the linear 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 linear nano co-polymer.

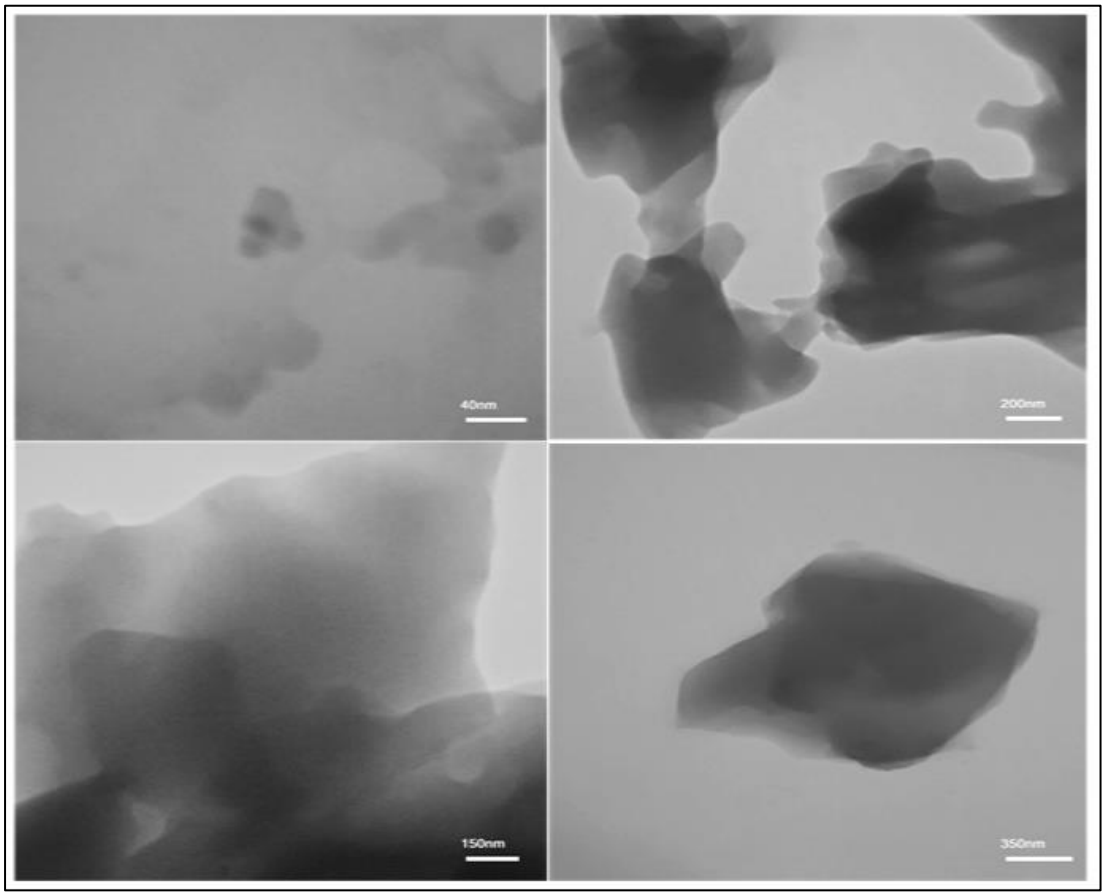


Figure (3-6): TEM micrographs of the nanoparticles co-polymer

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

Area	StdDev	Angle	Diameter Nm	D (av.) nm
64.3	25.718	-169.992	66.18	**97.0188**
65.219	24.007	66.371	66.953	
81.753	8.421	-149.931	84.167	
80.834	11.48	90	84.341	
91.857	8.668	148.241	94.685	
94.613	8.343	-41.82	97.74	
94.613	6.887	131.82	97.74	
96.45	5.718	-105.642	99.528	
97.857	8.764	-104.036	99.84	
100.939	6.234	-101.768	103.984	
102.88	5.632	115.641	106.311	
106.555	8.511	119.249	109.847	
112.066	19.038	-84.289	115.584	
112.066	16.246	82.405	116.029	
119.473	21.615	-40.815	121.441	
121.252	6.858	0	126.512	

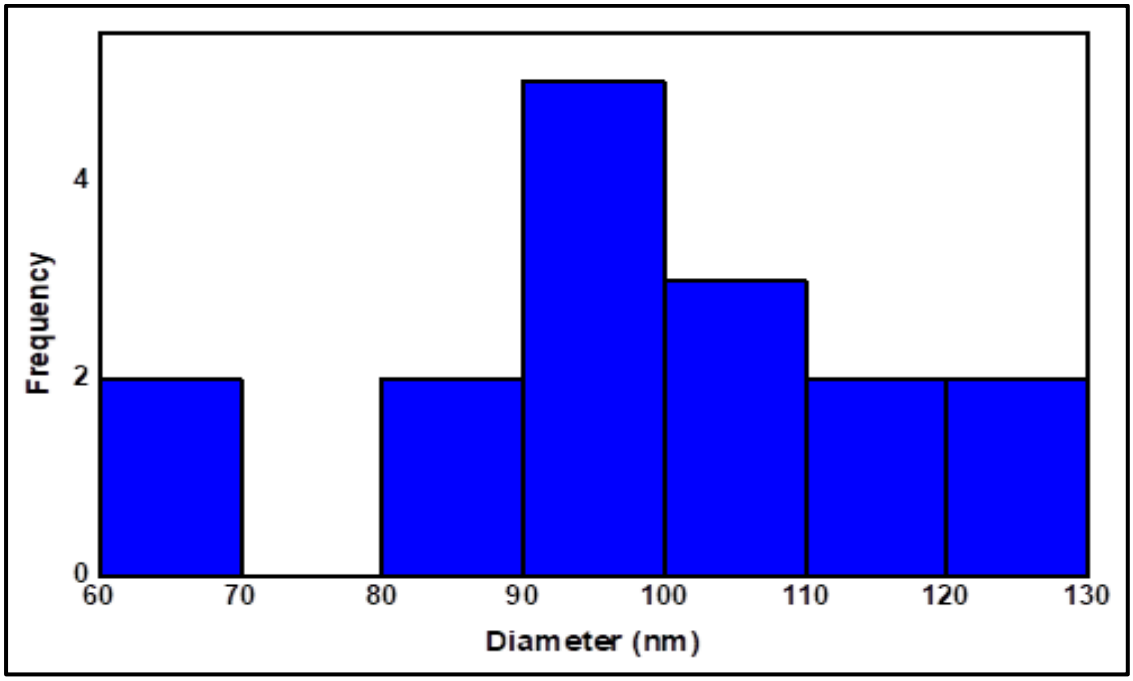


Figure (3-7): Histogram for distribution of the different proportions of particle sizes of the linear nano co-polymer

In DSC thermograms of nano co-polymer, the peak height decreases whereas the peak width considerably decreases as shown in Figure (3-8).

Moreover, the onset temperature also decreases logarithmically as a function of the ratio of phthalic anhydride and glycerol in the prepared nano copolymer. However, thermo grams clearly indicate that the melting process of nano copolymer with increased amount of phthalic anhydride or glycerol a higher amount of energy is required. Interpretation of the results further indicated that benefit of less amount of phthalic anhydride or glycerol is that the peak sharpness is increased and therefore overlapping effects can be easily differentiated.

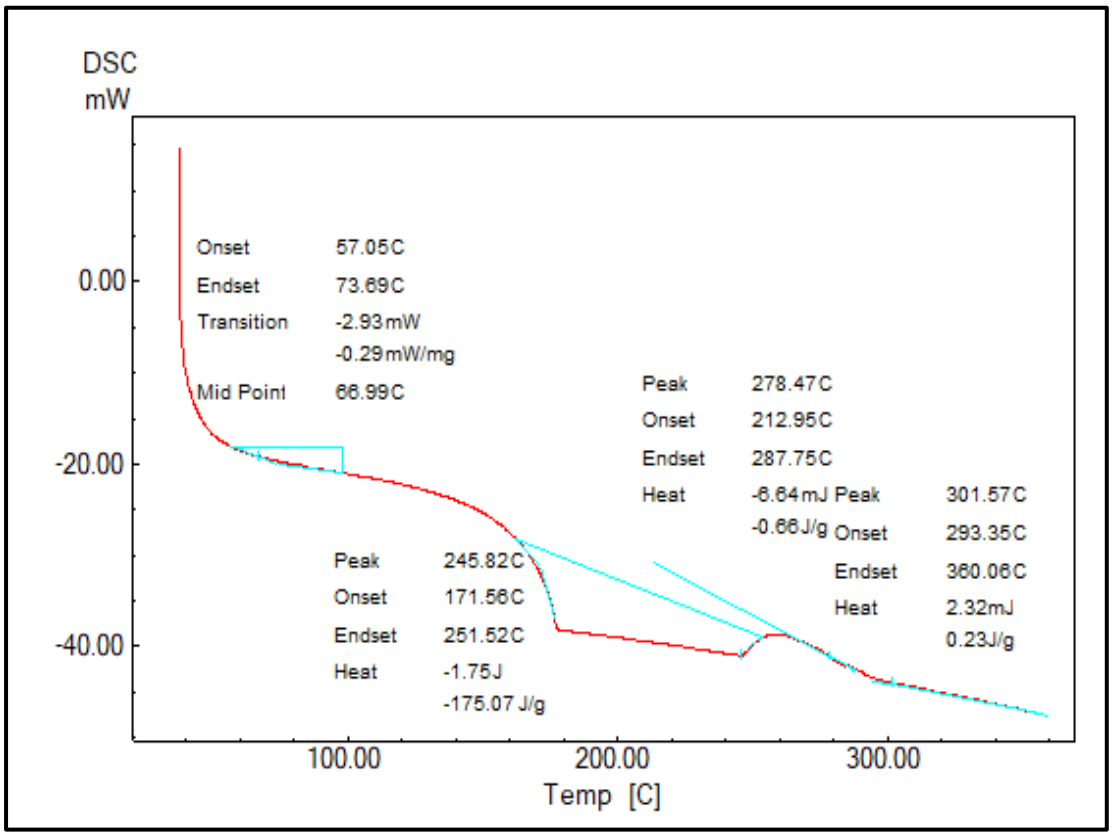


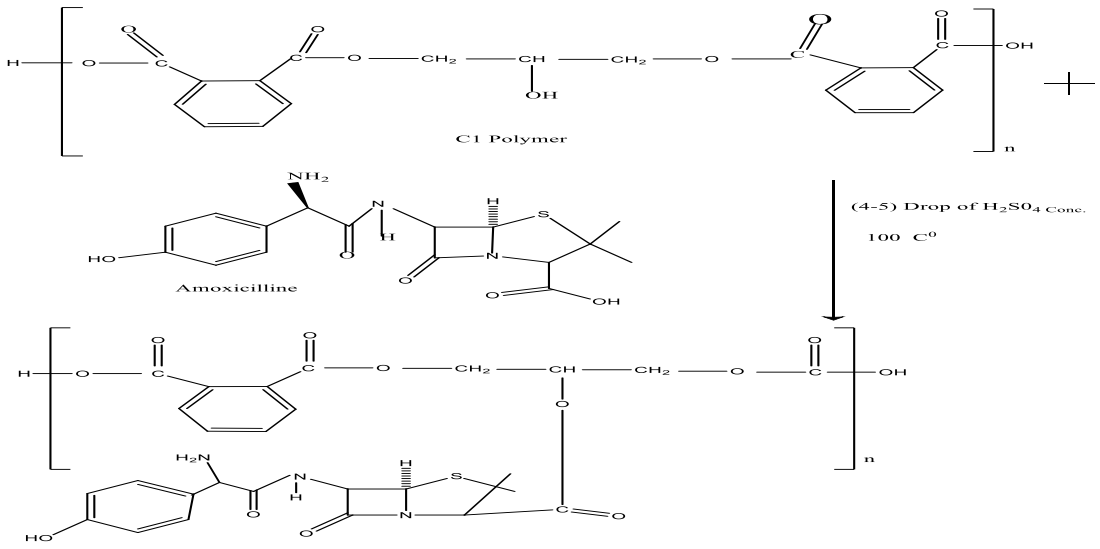
Figure (3-8): DSC thermograms of nano co-polymer

3.2 Synthesis of the nano co-polymer-drug

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

3.2.1.1 Synthesis of compound (C4)

Amount of compound (C1) reacted with Amoxicillin and mixed to gather add to the mixture (3-4) drops of H_2SO_4 Conc. at 100^{o}C. Equation (3-2) represents synthesis the compound (C4).



Equation (3-2): Synthesis the compound (C4)

The FT-IR, shows the spectrum of compound (C4), 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 NH-C=O_{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}.

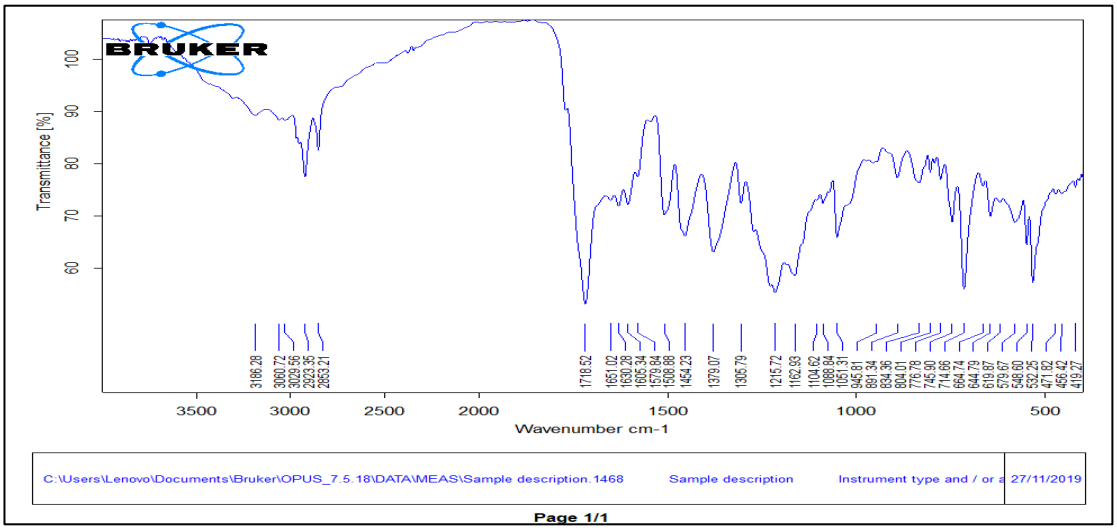
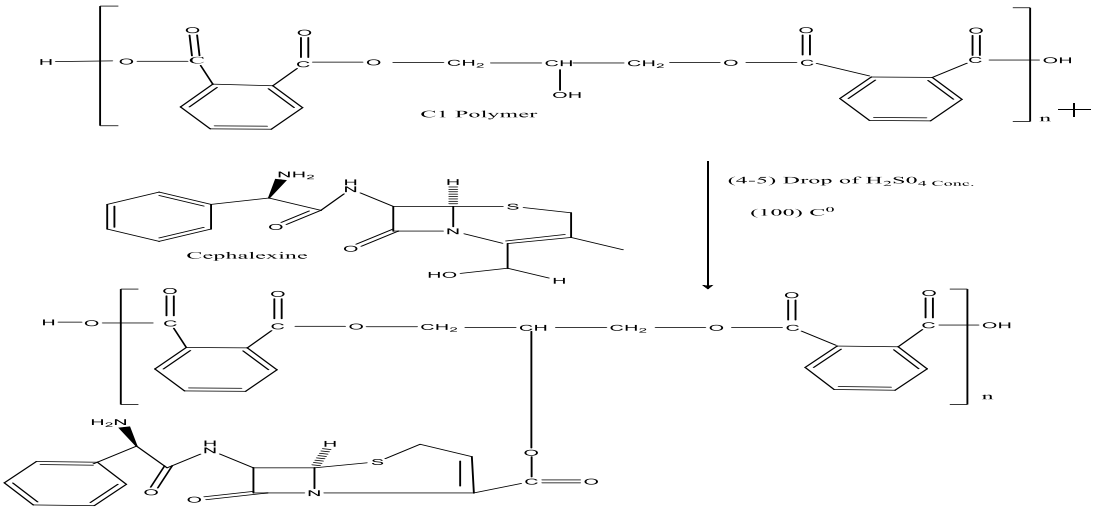


Figure (3-9): The FT-IR spectrum of compound (C4)

3.2.1.2 Synthesis of compound (C5)

Amount of compound (C1) reacted with Cephalexine drug and mixed to gather add to the mixture (3-4) drops of H_2SO_4 Conc. in 100°C, Equation (3-3) represent synthesis the polymer (C5).



Equation (3-3): Synthesis the compound (C5)

The FT-I.R spectrum of compound (C5), Figure (3-10), 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 NH-C=O_{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 (C5), Figure (3-11), 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 $(NH-C=O)_{amid}$,and appear singl at 9.52 for (CHO),and appear signal at 2.5 (C=O) ester and appearance signal at 3 for $(C-H_3)$.

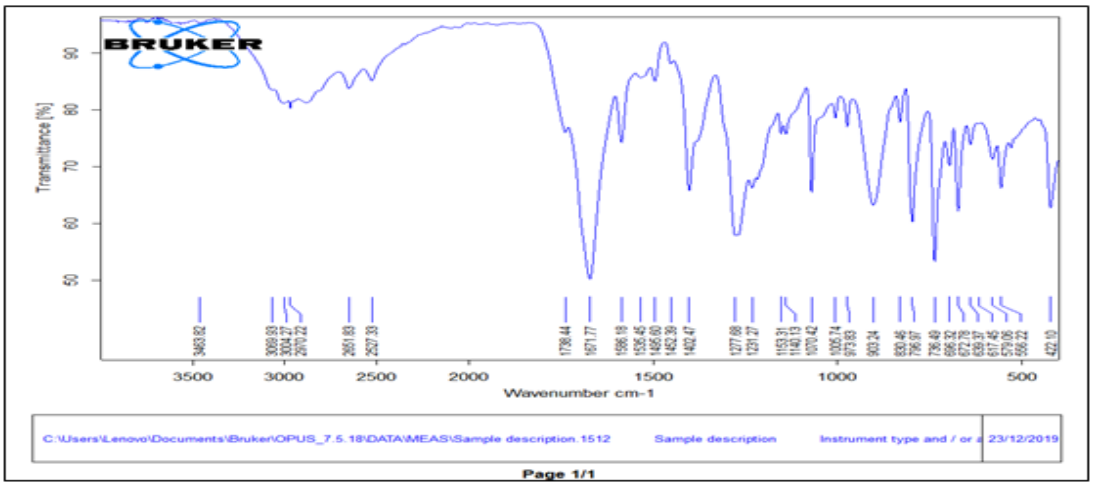


Figure (3-10): The FT-IR spectrum of compound (C5)

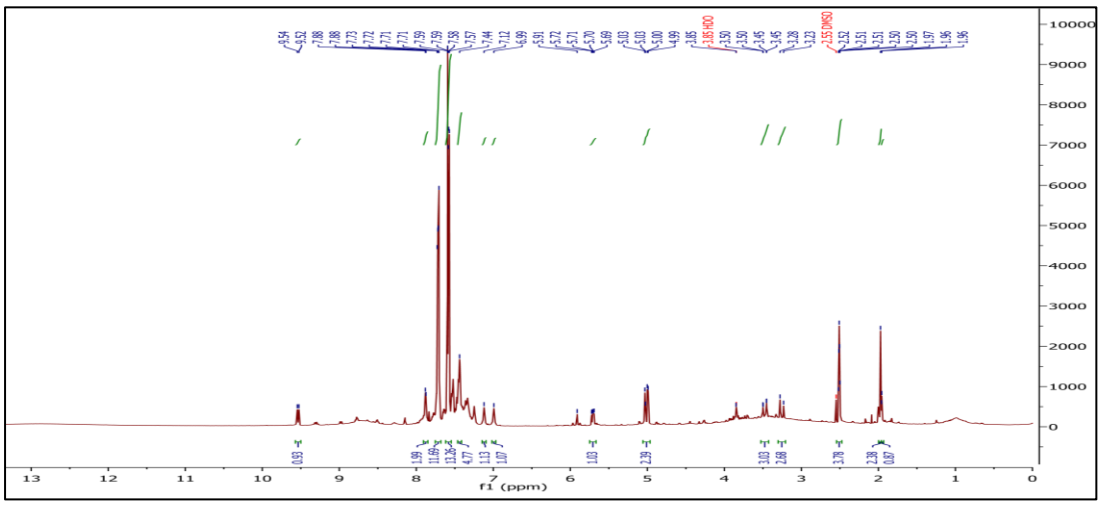
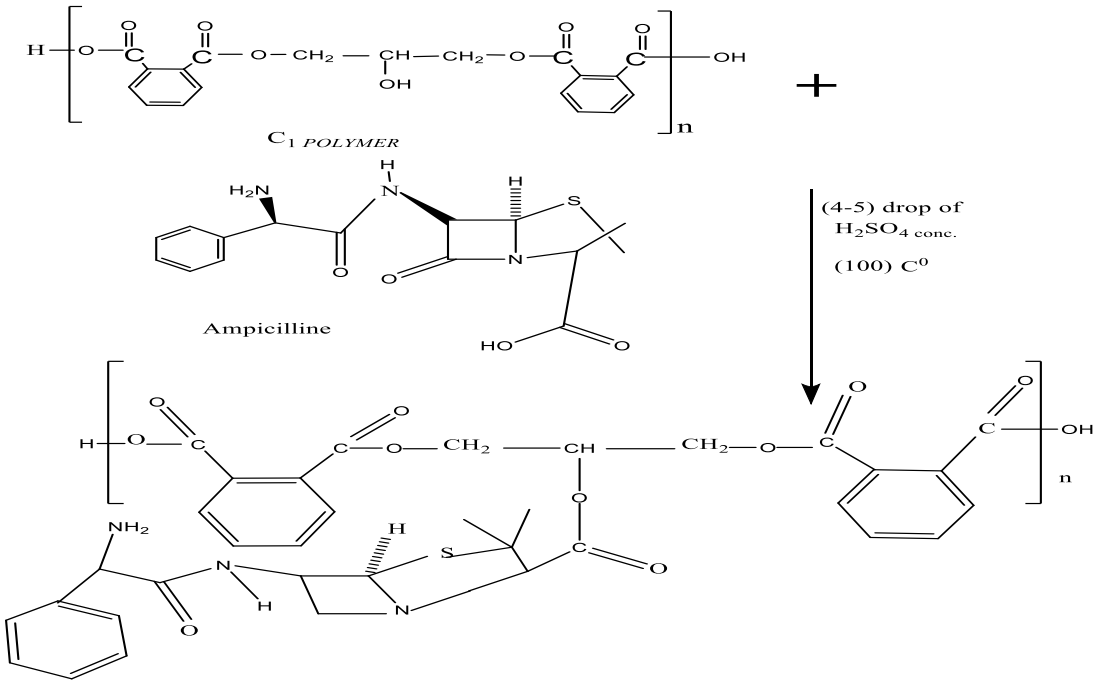


Figure (3-11): The $^{1}HNMR$ spectrum of compound (C5)

3.2.1.3 Synthesis of compound (C6)

Amount of compound (C1) reacted with Ampicillin drug and mixed to gather add to the mixture (3-4) drops of H_2SO_4 Conc. in 100°C, Equation (3-4) represent synthesis the polymer (C6).



Equation (3-4): Synthesis the compound (C6)

The FT-I.R spectrum of compound (C6), Figure (3-12), 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 NH-C=O_{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 (C6), Figure (3-13), 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 $(NH-C=O)_{amid}$.

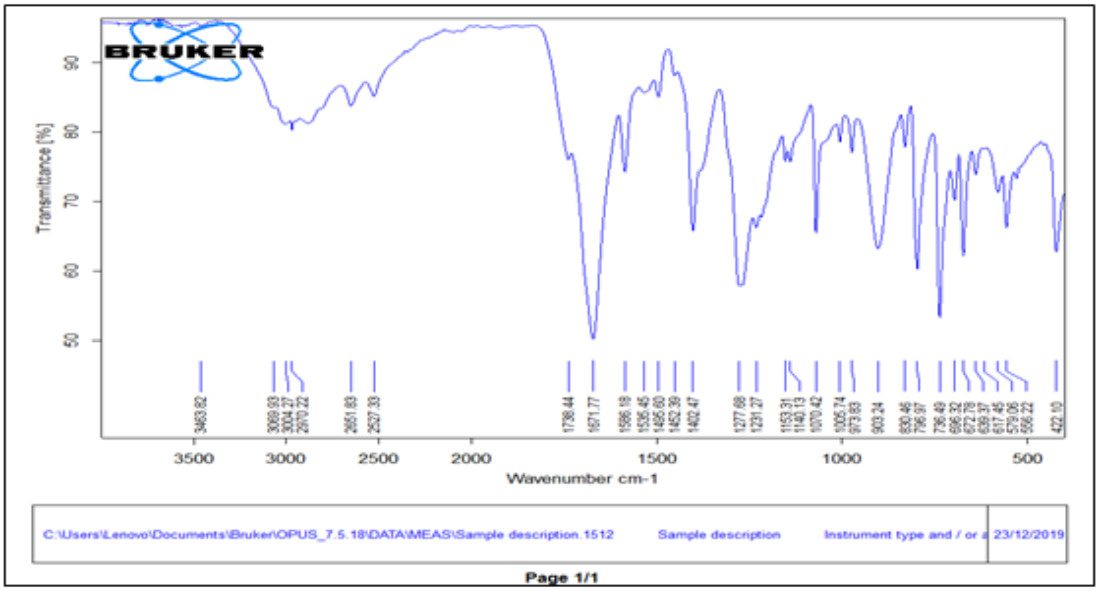


Figure (3-12): The FT-IR spectrum of compound (C6)

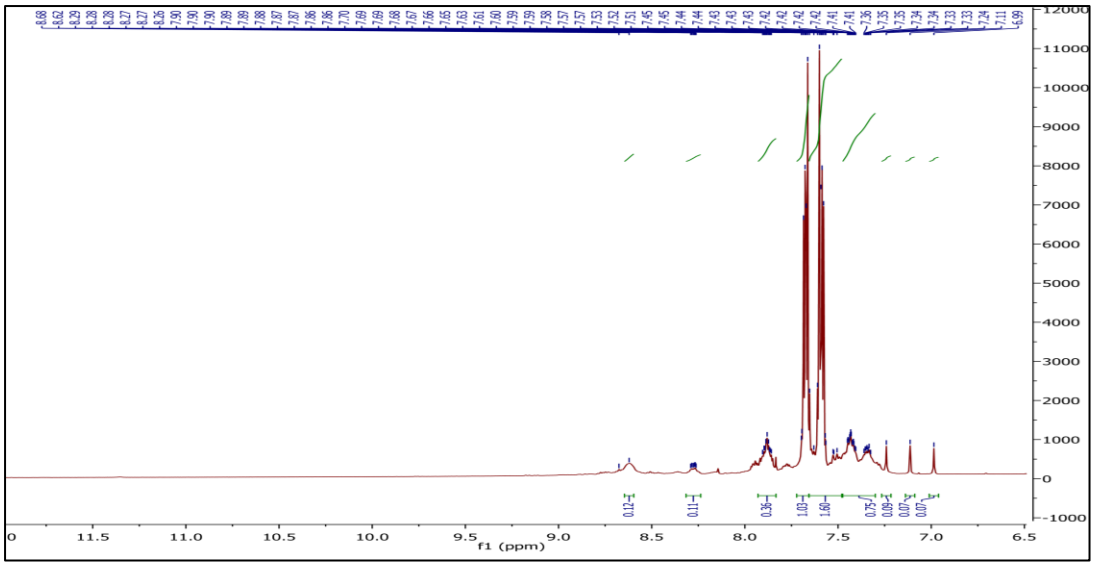
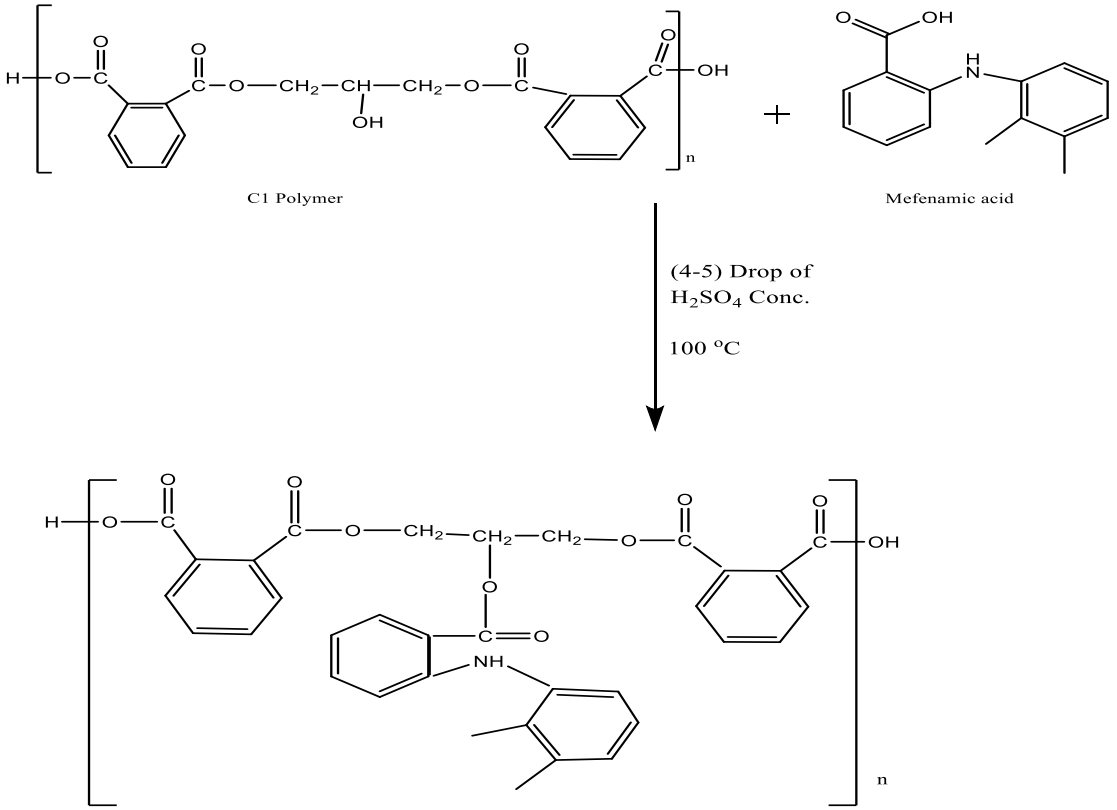


Figure (3-13): The ^{1}HNMR spectrum of compound (C6)

3.2.1.4 Synthesis of compound (C7)

Amount of compound (C1) reacted with Mefenamic acid drug and mixed to gather add to the mixture (3-4) drops of H_2SO_4 Conc. in 100°C, Equation (3-5) represent synthesis the polymer (C7).



Equation (3-5): synthesis the compound (C7)

The FT-I.R spectrum of compound (C7), Figure (3-14), 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 $NH\text{-}C{=}O_{amide}$ at (3009.81) cm^{-1} and absorption band of $C\text{-}C\text{-}H_{aliph}$ 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 (C7), Figure (3-15), 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 $(NH-C=O)_{amid}$ and appear at (2-2.5)ppm (C=O) ester, and appearance signal at 3ppm for $(C-H_3)$.

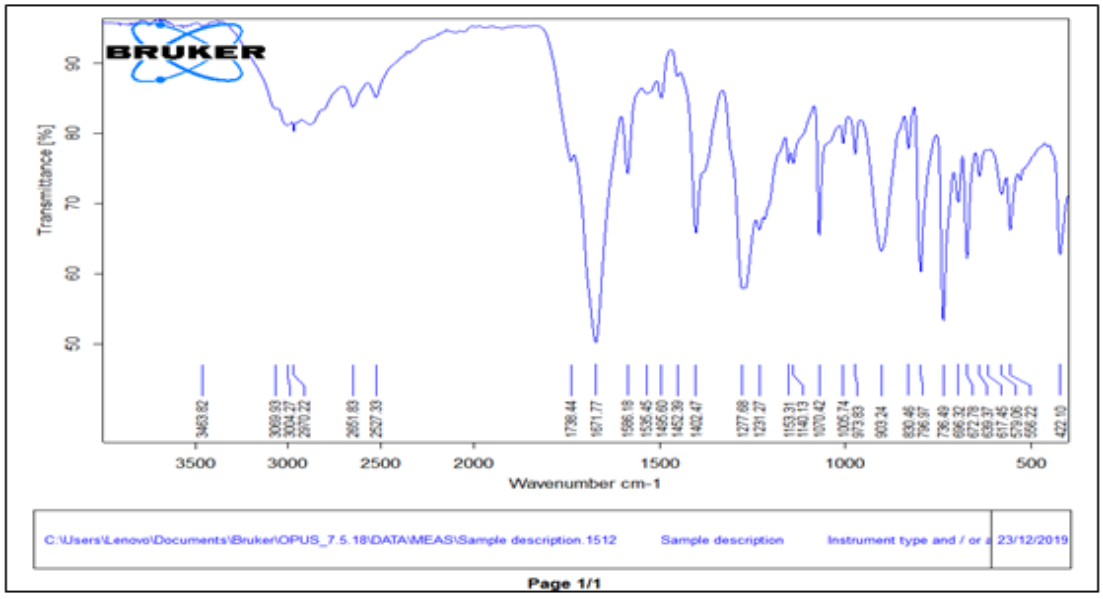


Figure (3-14): The FT-IR spectrum of compound (C7)

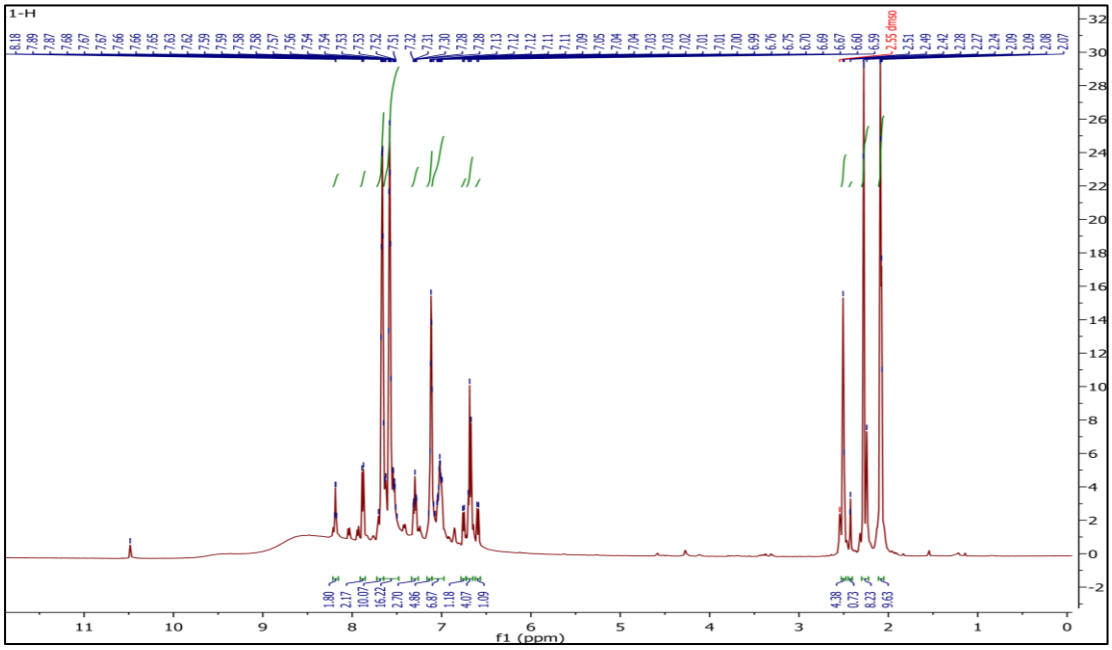
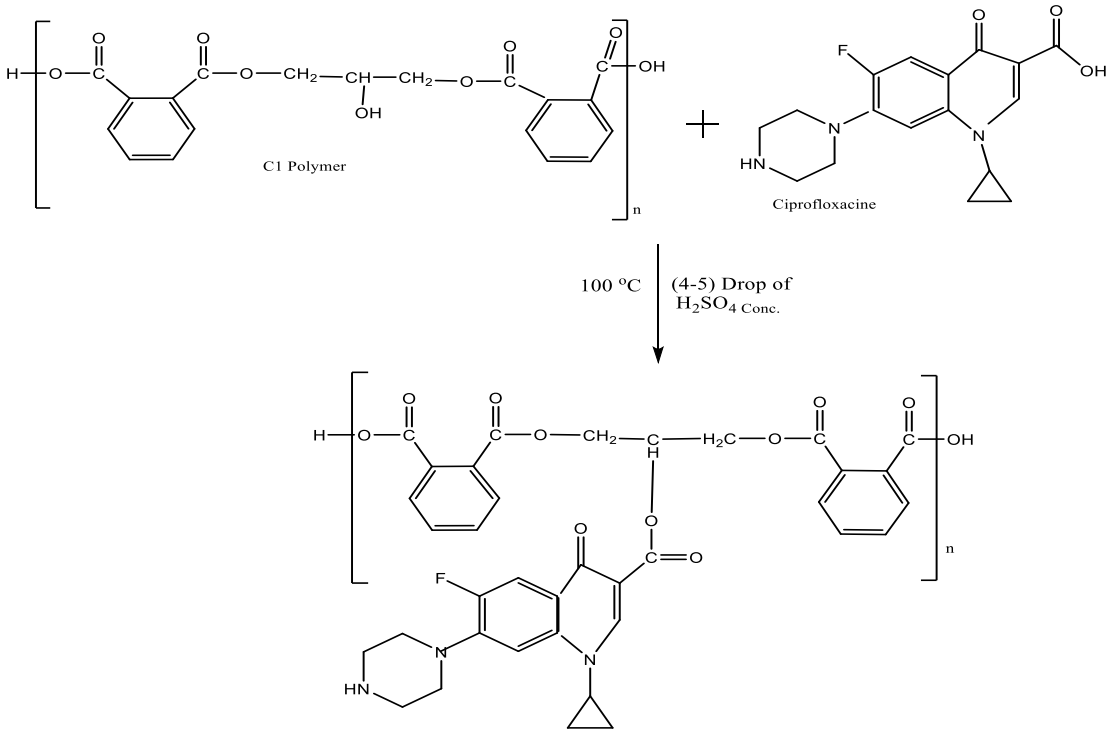


Figure (3-15): The ^{1}HNMR spectrum of compound (C7)

3.2.1.5 Synthesis of compound (C8)

Amount of compound (C1) reacted with Ciprofloxacin drug and mixed to gather add to the mixture (3-4) drops of H_2SO_4 Conc. in 100°C, Equation (3-6) represent synthesis the polymer (C8).



Equation (3-6): Synthesis the compound (C8)

The FT-I.R spectrum of compound (C8), Figure (3-16), 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 $NH\text{-}C{=}O_{amide}$ at (3014.68) cm^{-1} and absorption band of $C\text{-}C\text{-}H_{aliph}$ 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}.

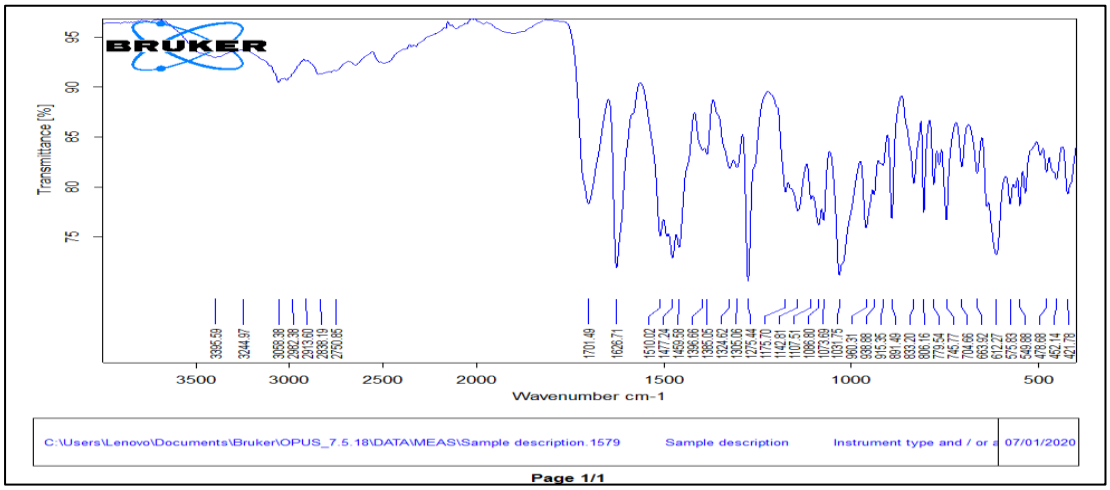
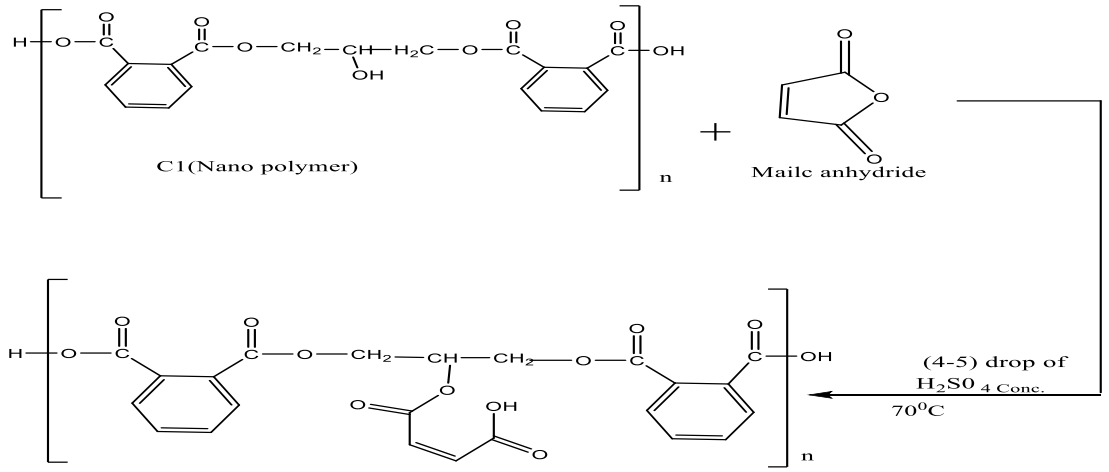


Figure (3-16): The FT-IR spectrum of compound (C8)

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

3.2.2.1 Synthesis of compound (C2)

Amount of compound (C1) reacted with Malic anhydride and mixed to gather add to the mixture (3-4) drops of H_2SO_4 Conc. in 70°C. Equation (3-7) represents synthesis of the polymer (C2).



Equation (3-7): Synthesis the nano co-polymer (C2)

Figure (3-17) showed the FT- I.R spectrum of compound (C2), shows appearance absorption band appear a weak broad band at (3075 cm^{-1})

attributed to the bond (O-H) alcoholic and, appearance absorption band at (2967) cm^{-1} of C=C-H aromatic, and appearance absorption band of $C=O_{ester}$ at (1667.40 cm^{-1}) and appear absorption bond C-O ester at (1069 cm^{-1}) and appear absorption bond di substation aromatic ring at (796 cm^{-1}). The ^{1}H-NMR spectrum of compound (C2), Figure (3-18) shows appearance a single signal at 13ppm for $(OH)_{drug}$, and appearance doublet signal at 8ppm for (C=C-H) aromatic , and appearance a single signal at 6ppm for (C=C-H) , and appearance a single signal at 2ppm for (CH_3).

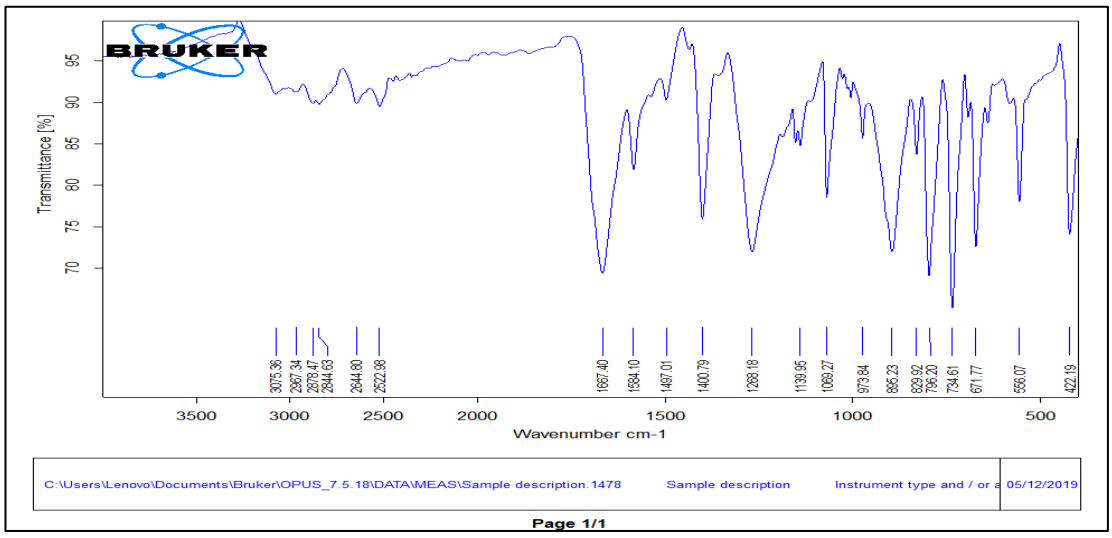


Figure (3-17): The FT-IR spectrum of compound (C2)

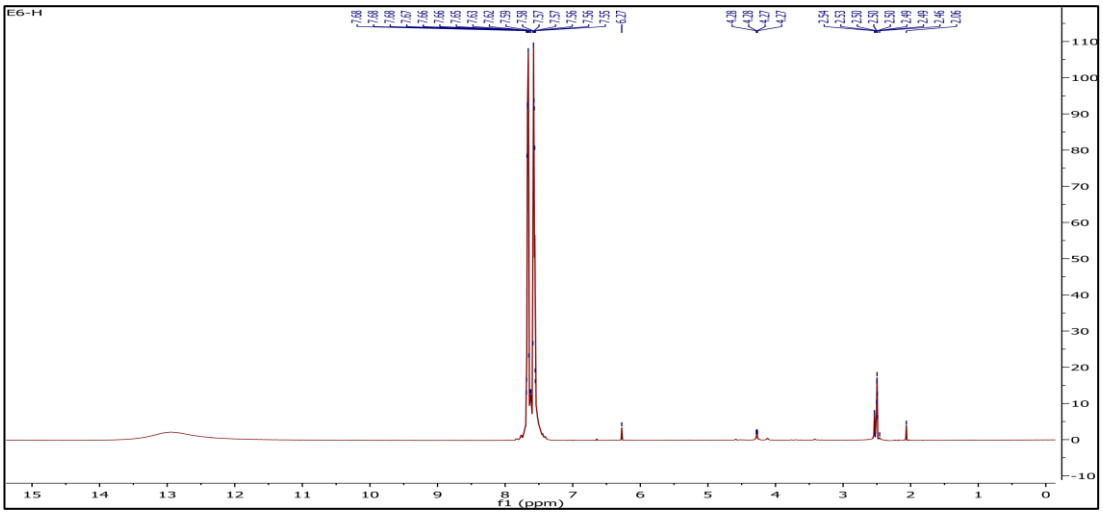
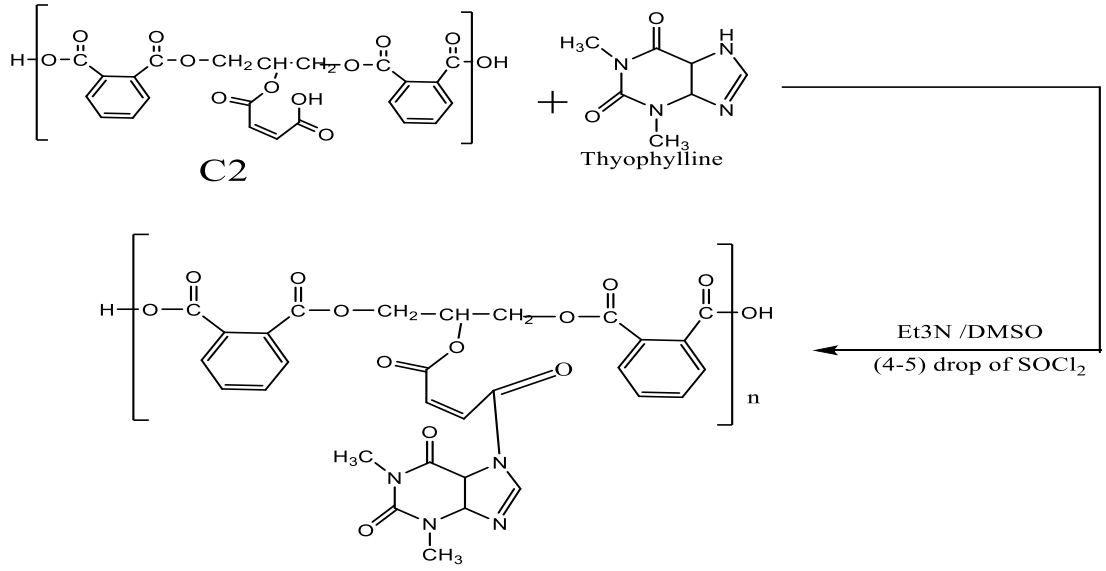


Figure (3-18): The ^{1}HNMR spectrum of compound (C2)

3.2.2.2 Synthesis of compound (C11)

Amount of compound (C2) and added dimethylsulfoxide (DMSO) then add thionylchloride ($SOCl_2$), were mixed together and heating at 20°C, and then added triethylamine, after 15 Min., add the Theophylline drug at 70°C to30 Min. Equation (3-8) represents synthesis the compound (C11).



Equation (3-8): Synthesis the compound (C11)

The FT-I.R spectrum of compound (C11), Figure (3-19), shows appearance absorption band appear a weak broad band at (3119.74 cm^{-1}) attributed to the bond (O-H) alcoholic and appearance of absorption band of NH-C=O_{amide} at (3055.04) cm^{-1} and absorption band of C-C-H_{aliph} at (2980.44) cm^{-1} and absorption band at (1659.82) cm^{-1} of C=O ester , and absorption band of C=C ph. at (1441.46) cm^{-1} , and absorption band of C-O at (1186.89) cm^{-1}, and absorption band of C-N at (1047.91) cm^{-1} , and appear absorption bond disubstation aromatic ring at 763.46 cm^{-1}.

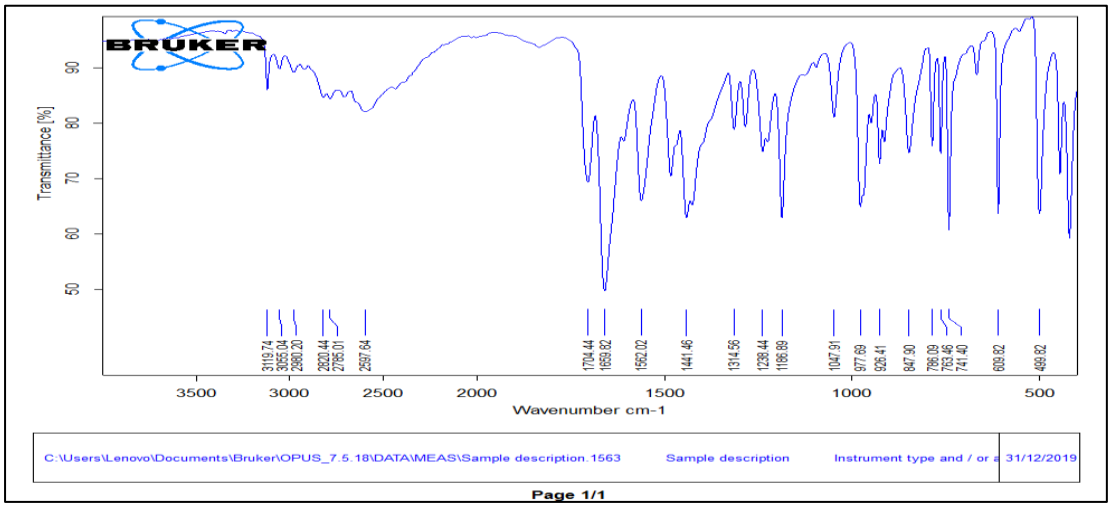
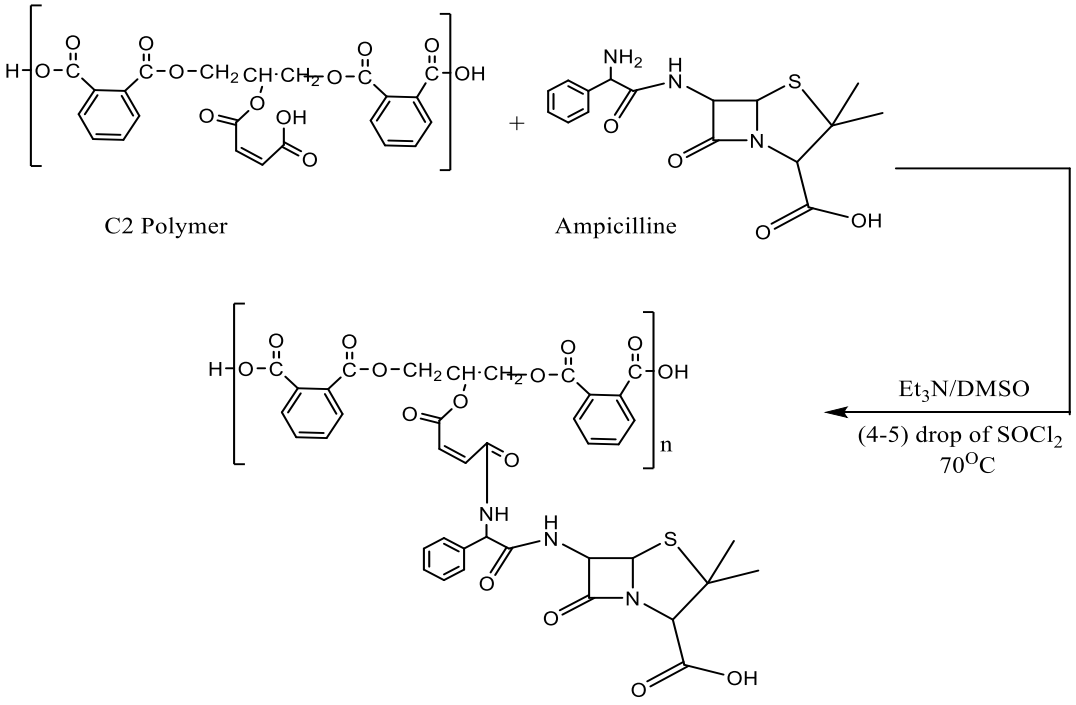


Figure (3-19): The FT-IR spectrum of compound (C11)

3.2.2.3 Synthesis of compound (C12)

Amount of compound (C2) and added dimethylsulfoxide (DMSO) then add thionylchloride ($SOCl_2$), were mixed together and heating at 20° C, and then added triethylamine, after 15 Min., add the drug of Ampicillin at 70°C to30 Min., Equation (3-9) represent synthesis the monomer (C12).



Equation (3-9): synthesis the compound (C12)

The FT-I.R spectrum of compound (C12), Figure (3-20), shows appearance of absorption band of NH-C=O$_{amide}$ at (3057.26) cm^{-1} and absorption band of C-C-H$_{aliph}$ at (2970.23) cm^{-1} and absorption band at (1663.64) cm^{-1} of C=O ester and absorption band of C=C ph. at (1400.62) cm^{-1} and absorption band of C-O at (1069.53) cm^{-1}, and absorption band of C-N at (1230.02) cm^{-1} , and appear absorption bond Di substation aromatic ring at (737.6) cm^{-1}. The ^{1}H-NMR spectrum for compound (C12), Figure (3-21), shows appearance a single signal at 13ppm for (OH)$_{acid}$, and appearance signal at 8ppm for (C=C-H) $_{ph}$, and appearance signal at 3.5ppm for (NH-C=O) $_{amid}$, and appear signal single at 2.5ppm for(CH_3).

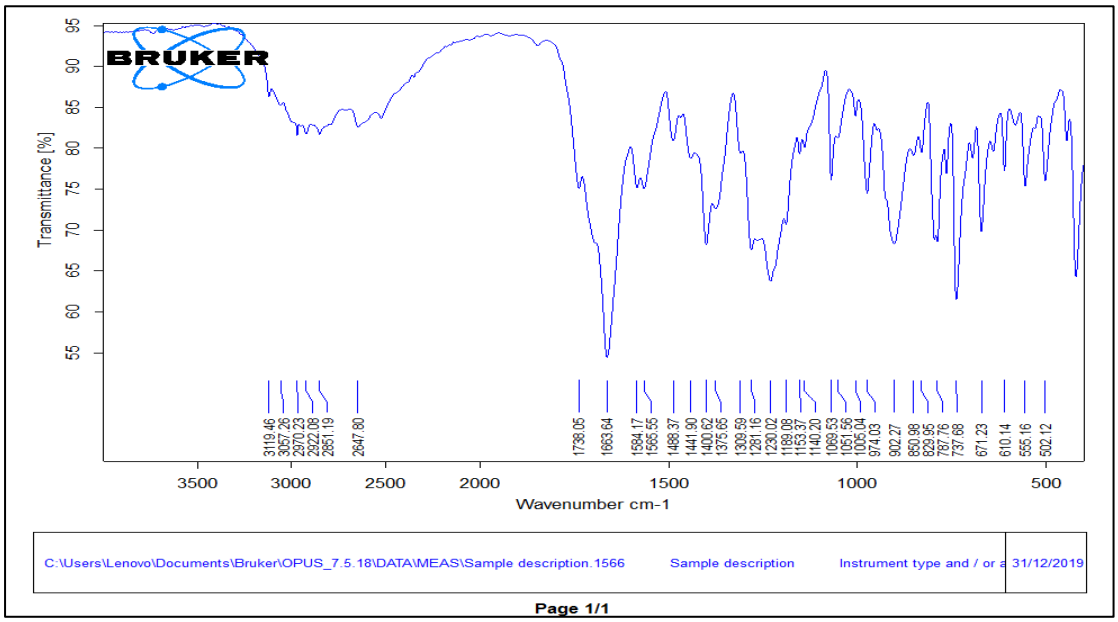


Figure (3-20): The FT-IR spectrum of compound (C12)

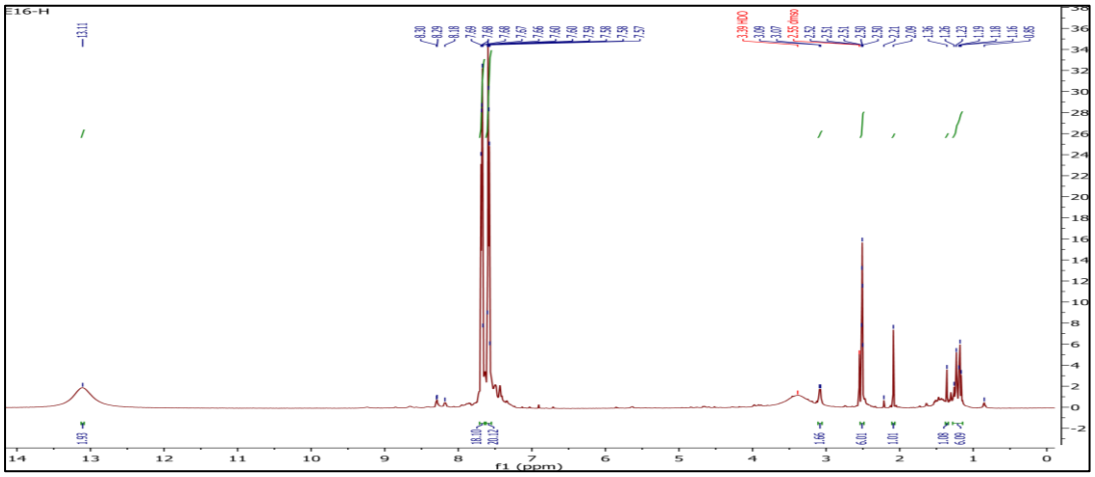
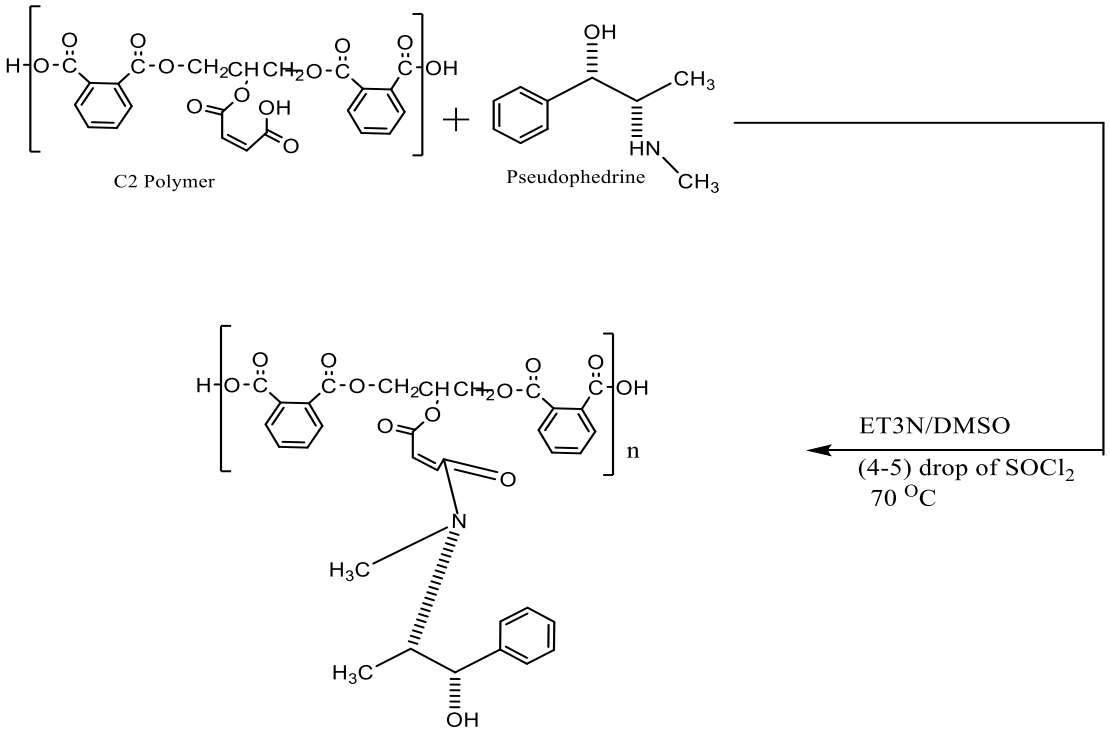


Figure (3-21): The ^{1}HNMR spectrum of compound (C12)

3.2.2.4 Synthesis of compound (C13)

Amount of compound (C2) 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 Pseudophedrine drug at 70°C to 30 Min., Equation (3-10) represent synthesis the polymer (C13).



Equation (3-10): Synthesis the compound (C13)

The FT-I.R spectrum of compound (C13), Figure (3-22), shows appearance of absorption band of N-C=O$_{amide}$ at (3065.50) cm^{-1} and absorption band of C-C-H$_{aliph}$ at (2883.04) cm^{-1} and absorption band at (1694) cm^{-1} of C=O ester , and absorption band of C=C ph. at (1400.55) cm^{-1} , and absorption band of C-O at (1069.54) cm^{-1}, and absorption band of C-N at (1254.75) cm^{-1} , and appear absorption bond Di substation aromatic ring at (735.69) cm^{-1}. The ^{1}H-NMR spectrum for compound (C13), Figure (3-23), shows disappearance a single signal at 13ppm for (OH)$_{acid}$, and appearance signal at 8.5ppm for (C=C-H)$_{ph}$, and appearance signal at 6.7ppm for (N-C=O)$_{amid}$, and appear single signal at 2.5ppm for (CH$_3$)

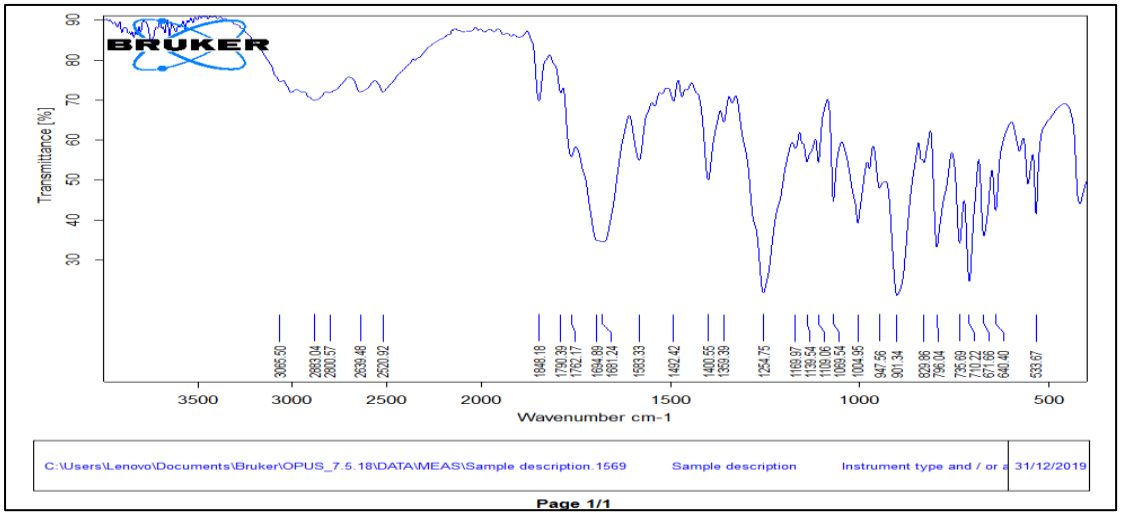


Figure (3-22): The FT-IR spectrum of compound (C13)

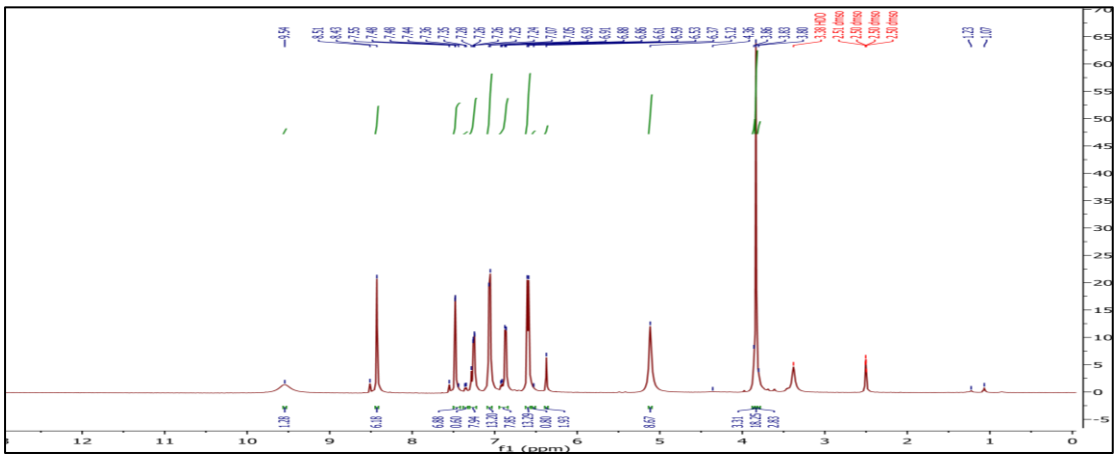
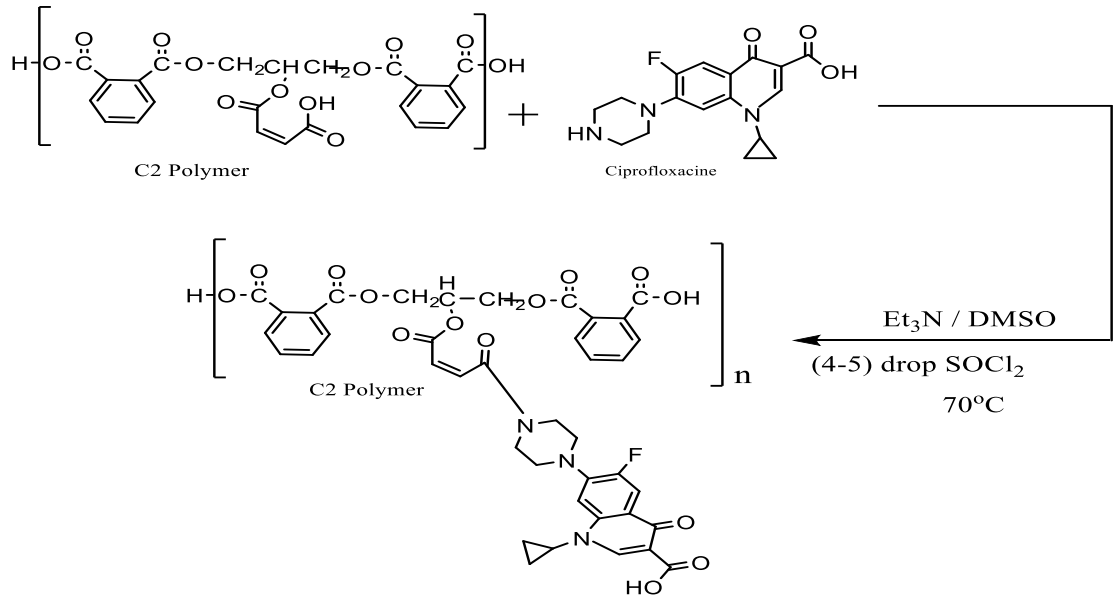


Figure (3-23): The ^{1}HNMR spectrum of compound (C13)

3.2.2.5 Synthesis of compound (C14)

Amount of compound (C2) and added dimethylsulfoxide (DMSO) then add thionylchloride($SOCl_2$), were mixed together and heating at 20° C and then added triethylamine, after 15 Min., add the Ciprofluxacine drug at 70°C to 30 Min., Equation (3-11) represent synthesis the compound (C14).



Equation (3-11): Synthesis the compound (C14)

The FT-I.R spectrum of compound (C14), Figure (3-24), shows appearance of absorption band of N-C=O_{amide} at (3073.60) cm^{-1} and absorption band of C-C-H_{aliph} at (2998.92) cm^{-1} and absorption band at (1669.63) cm^{-1} of C=O ester , and absorption band of C=C ph. at (1401.11) cm^{-1} , and absorption band of C-O at (1069.64) cm^{-1}, and absorption band of C-N at (1266.05) cm^{-1} , and appear absorption bond di substation aromatic ring at (734.97)cm^{-1}. The ^{1}H-NMR spectrum for compound (C14), Figure (3-25), shows appearance a single signal at 15ppm for $(OH)_{acid}$, and appearance signal at 8ppm for $(C=C-H)_{ph}$, and appearance signal at 7.5ppm for $(N-C=O)_{amid}$, and appear signal at (2.5-3)ppm for (CH_3).

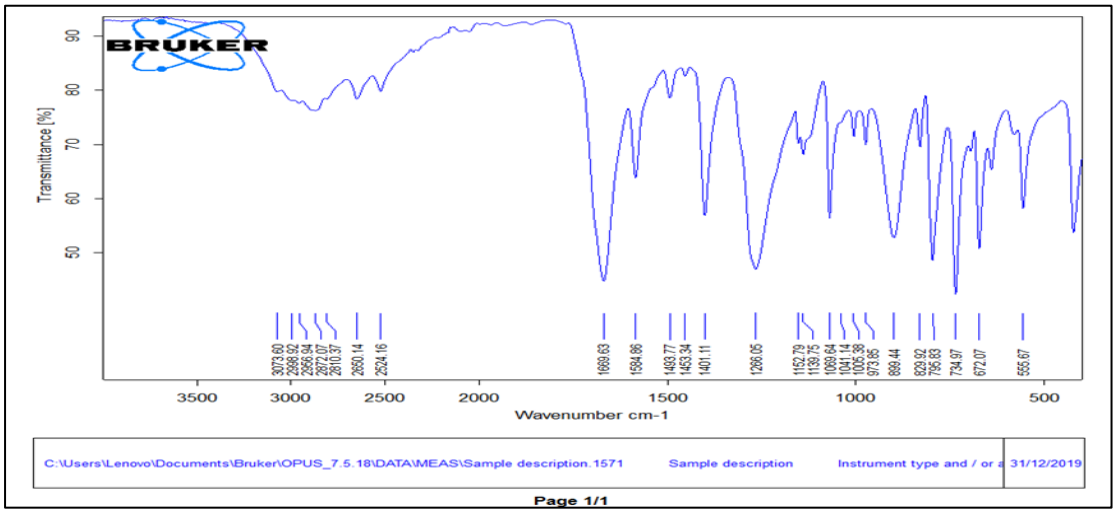


Figure (3-24): The FT-IR spectrum of compound (C14)

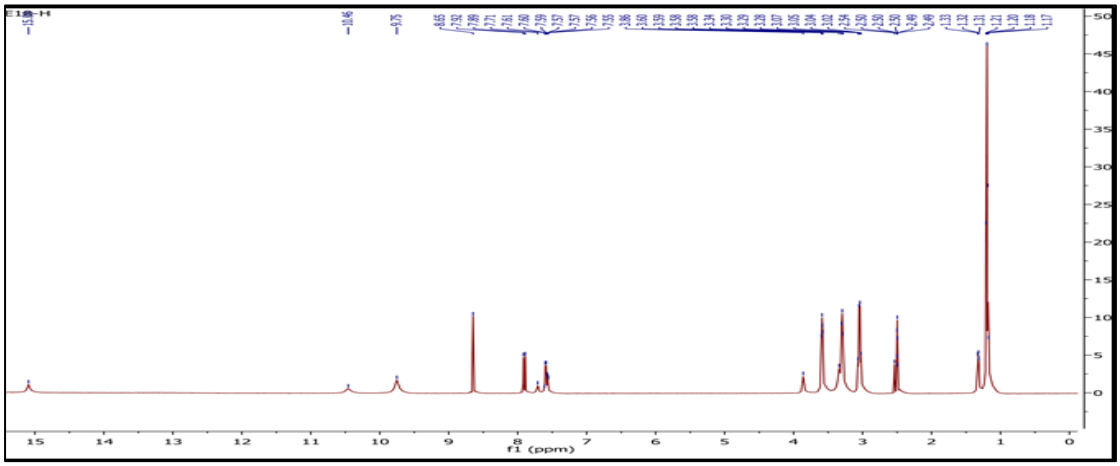
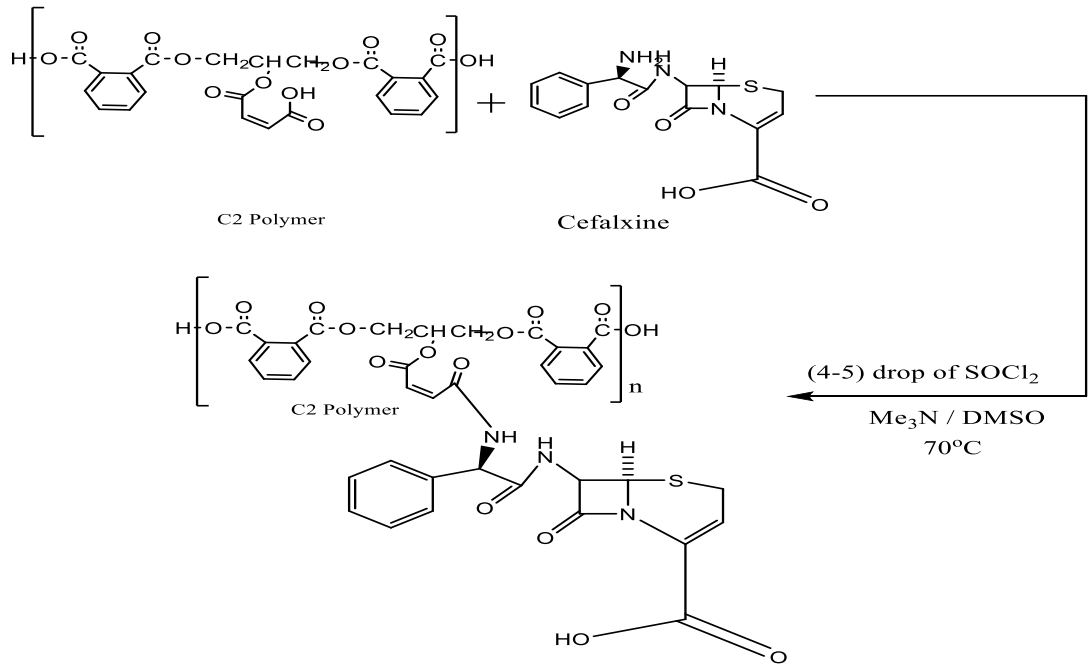


Figure (3-25): The 1HNMR spectrum of compound (C14)

3.2.2.6 Synthesis of compound (C15)

Amount of compound (C2) 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 Cephalexin drug at 70°C to 30 Min., equation (3-12) represent synthesis the polymer (C15).



Equation (3-12): Synthesis the compound (C15)

The FT-I.R spectrum of compound (C15), Figure (3-26), shows appearance of absorption band of NH-C=O_{amide} at (3070.56) cm^{-1} and absorption band of C-C-H_{aliph} at (2922.34) cm^{-1} and absorption band at (1669.22) cm^{-1} of C=O ester and absorption band of C=C ph. at (1400.46) cm^{-1}, and absorption band of C-O at (1069.76) cm^{-1}, and absorption band of C-N at (1258.61) cm^{-1} , and appear absorption bond Di substation aromatic ring at (735.14)cm^{-1}. The ^{1}H-NMR spectrum for compound (C15), Figure (3-27), shows appearance a single signal at 13ppm for $(OH)_{acid}$, and appearance signal at 7.5ppm for $(C=C-H)_{ph}$, and appearance signal at 6.8ppm for $(NH-C=O)_{amid}$, and appear signal at 2.5ppm for (CH_3).

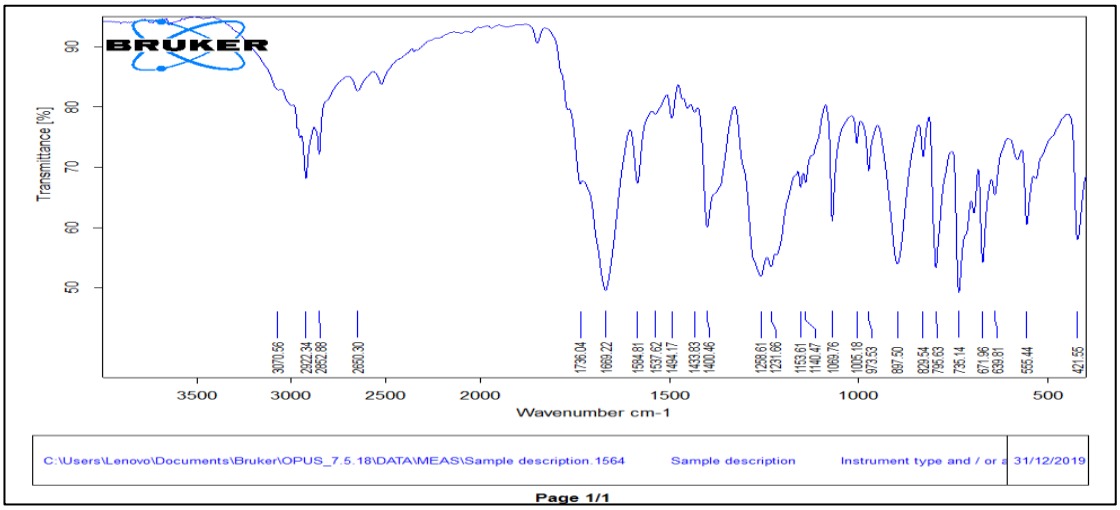


Figure (3-26): The FT-IR spectrum of compound (C15)

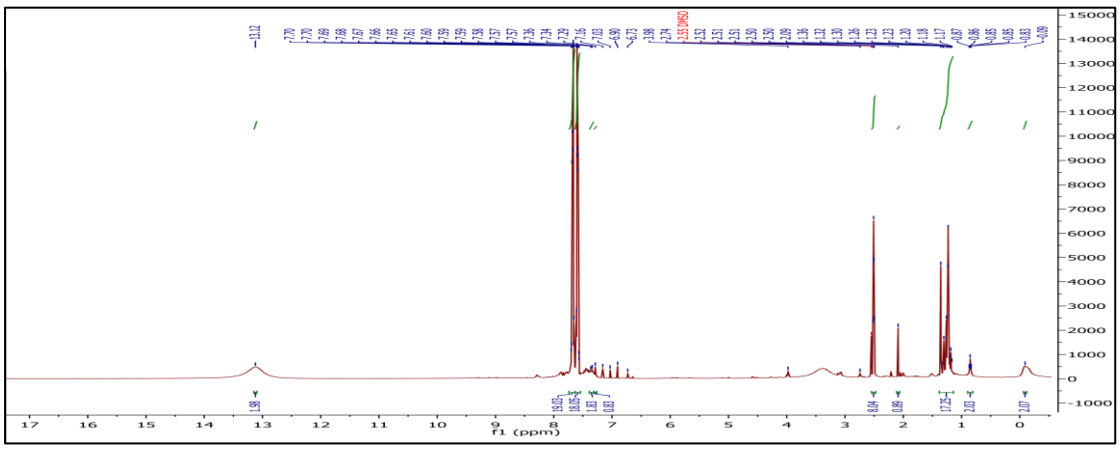
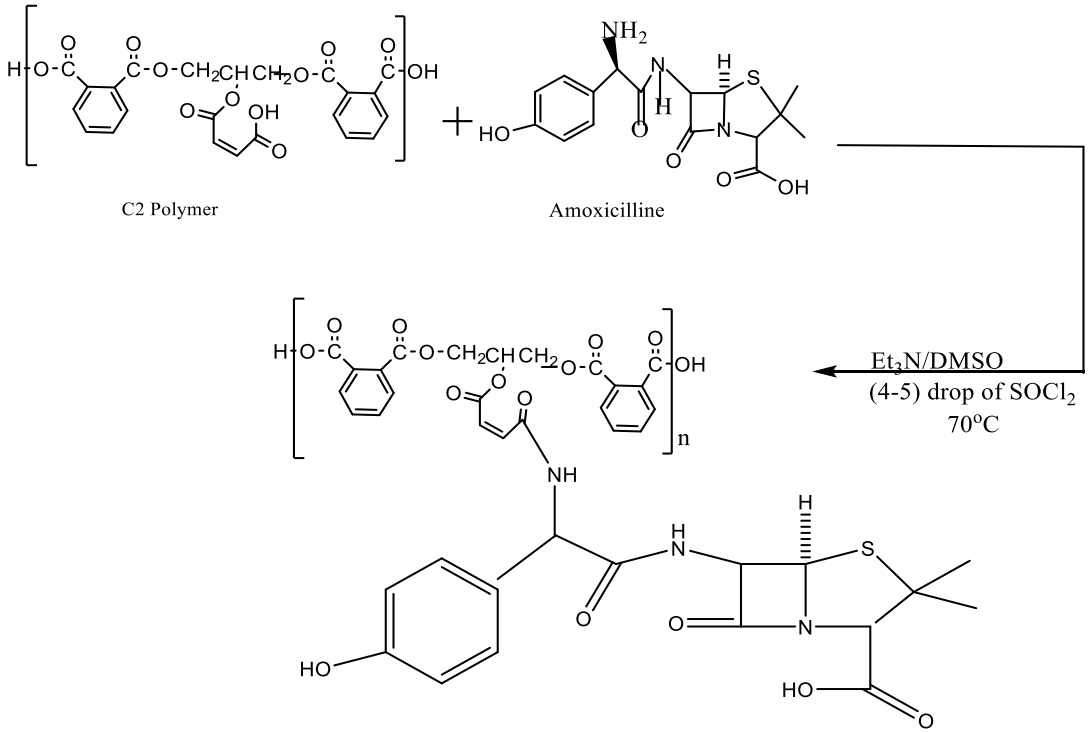


Figure (3-27): The ^{1}HNMR spectrum of compound (C15)

3.2.2.7 Synthesis of compound (C16)

Amount of compound (C2) and added dimethyl sulfoxide (DMSO) then add thionylchloride ($SOCl_2$), were mixed together and heating at 20^{o}C, and then added triethylamine, after 15 Min., add the Amoxicillin drug at 70^{o}C to30 Min., Equation (3-13) represent synthesis the compound(C16) .



Equation (3-13): synthesis the compound (C16)

The FT-I.R spectrum of compound (C16), Figure (3-28), shows appearance of absorption band of NH-C=O$_{amide}$ at (3010) cm^{-1} and absorption band of C-C-H$_{aliph}$ at (2919.69) cm^{-1} and absorption band at (1697) cm^{-1} of NH-C=O amide , and absorption band of C=C ph. at (1397.91) cm^{-1}, and absorption band of C-O at (1069.86) cm^{-1}, and absorption band of C-N at (1397.91) cm^{-1} , and appear absorption bond Di substation aromatic ring at (736.35) cm^{-1}. The ^{1}H-NMR spectrum for compound (C16), Figure (3-29), shows disappearance a single signal at 13 for (OH)$_{acid}$, and appearance signal at 7.5 ppm for (C=C-H)$_{ph}$, and appearance signal at 6.5ppm for (NH-C=O)$_{amid}$, and appear signal at 2.5 ppm for (CH_3)

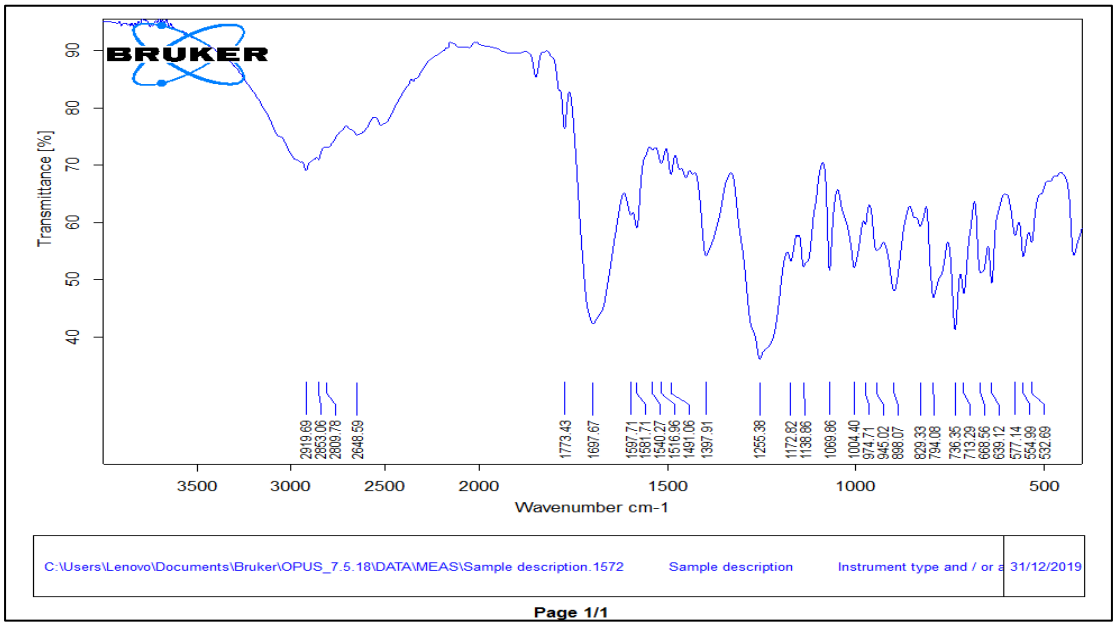


Figure (3-28): The FT-IR spectrum of compound (C16)

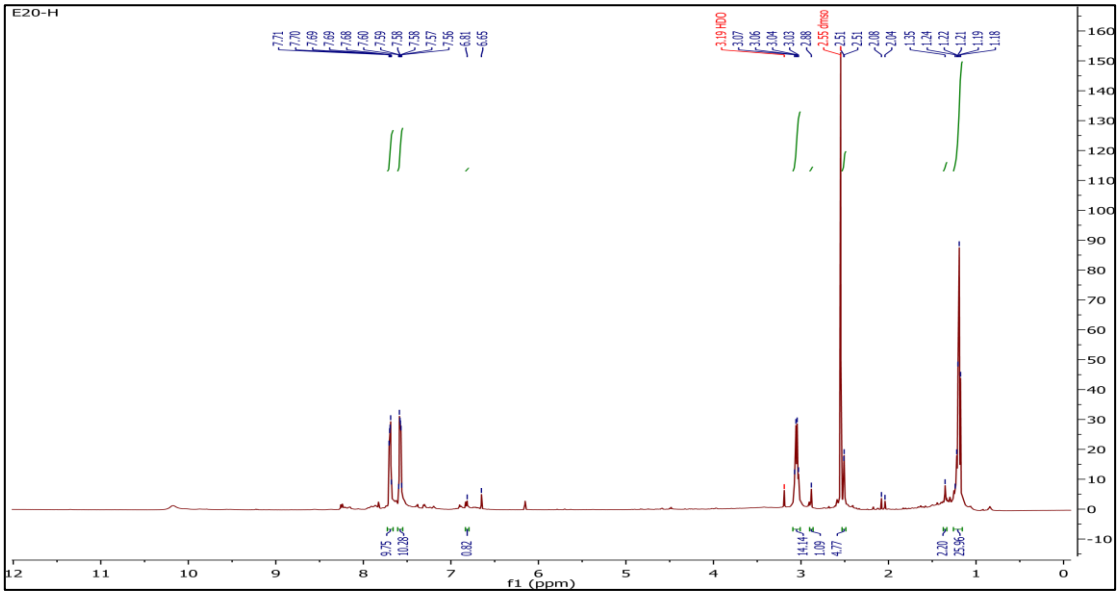
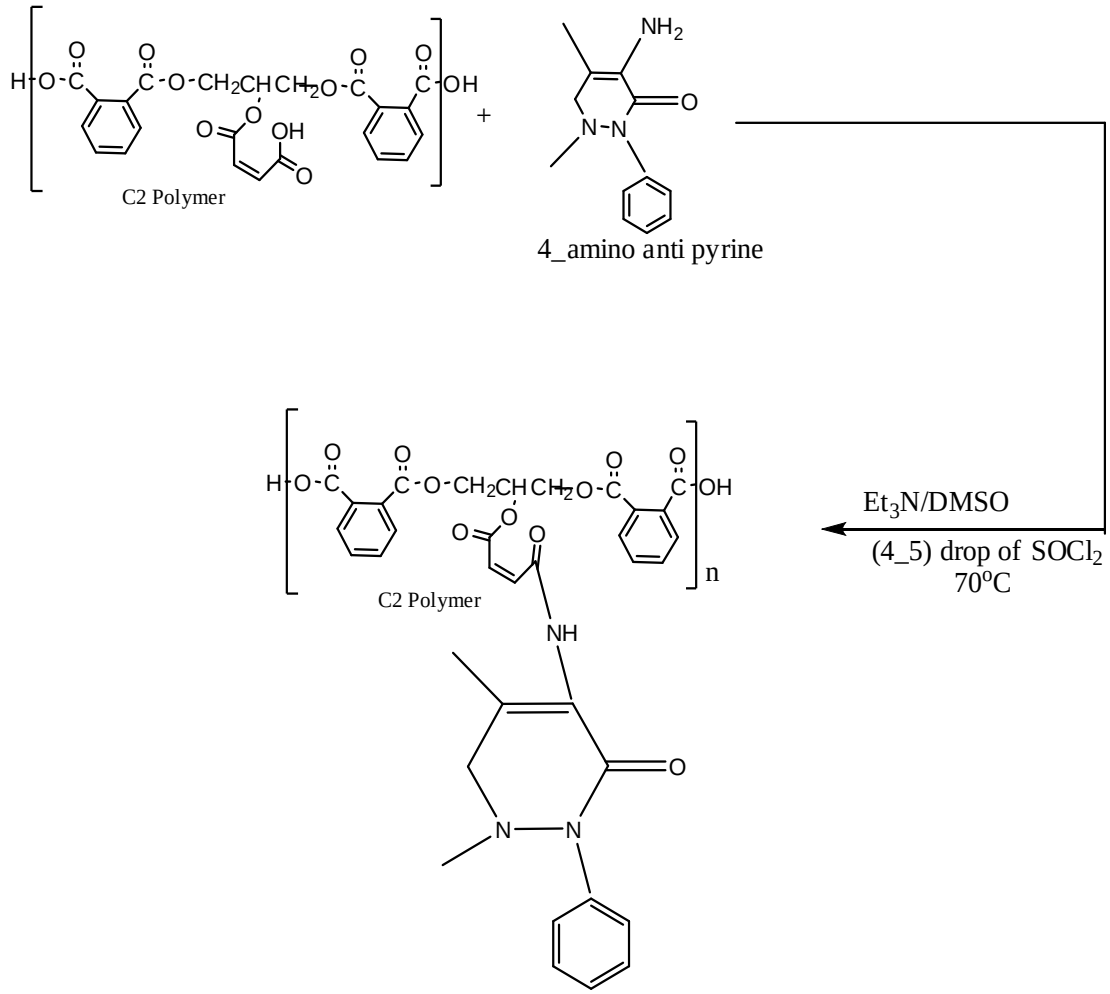


Figure (3-29): The ^{1}HNMR spectrum of compound (C16)

3.2.13 Synthesis of compound (C17)

Amount of compound (C2) and added dimethyl sulfoxide (DMSO) then add thionylchloride($SOCl_2$), were mixed together and heating at 20^{o}C, and then added triethylamine, after 15 Min., add the 4-aminoantipyrine drug at 70^{o}C to30 Min., Equation (3-14) represent synthesis the compound (C17).



Equation (3-14): Synthesis the compound (C17)

The FT-I.R spectrum of compound (C17), Figure (3-30), shows appearance of absorption band of NH-C=O_{amide} at (3006.03) cm^{-1} and absorption band of C-C-H_{aliph} at (2917.54) cm^{-1} and absorption band at (1715.56) cm^{-1} of (NH-C=O) amide and absorption band of C=C ph. at (1381.24) cm^{-1}, and absorption band of C-O at (1003.04) cm^{-1}, and absorption band of C-N at (1248.24) cm^{-1} , and appear absorption bond di substation aromatic ring at (740.96)cm^{-1}.

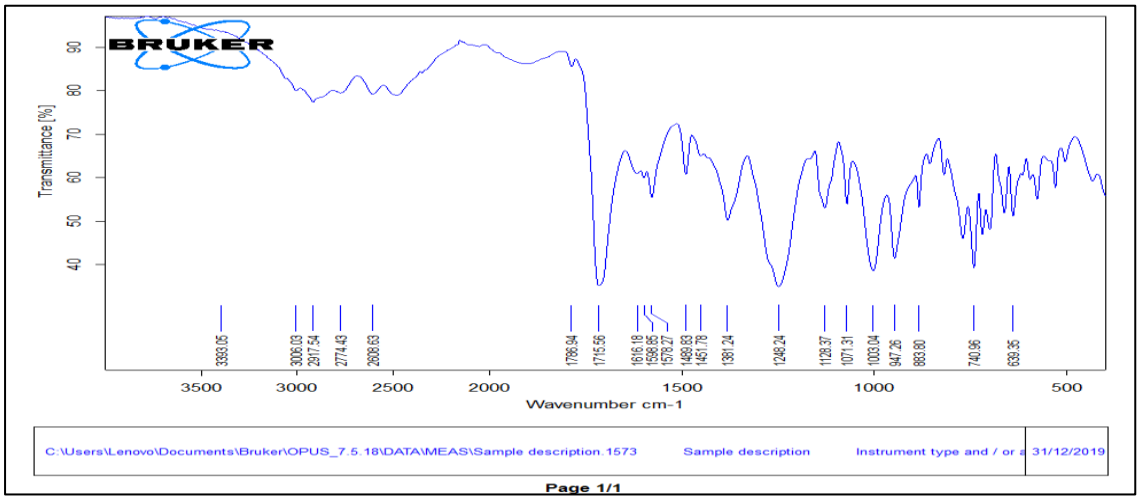


Figure (3-30): The FT-IR spectrum of compound (C17)

3.3 The Characteristic of Solubility

The solubility properties of polymer, in different solvents (H2O, Ethanol, Methanol, DMSO, Hexane, and Acetone) were studied. The solubility of the polymers was observed, some of which were completely dissolved (+) and some solids were partially dissolved (partial), and another has not been dissolved (-), as shown in Tables (3-4) for prepared nano co-polymers.

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

Polymer	H_2O	EtOH	MeOH	DMSO	Hexane	Acetone
C1	Partial	partial	partial	+	_	+
C2	Partial	+	+	+	_	+
C4	Partial	+	+	+	_	+
C5	Partial	+	+	+	_	+
C6	Partial	_	+	+	_	+
C7	Partial	+	+	+	_	+
C8	Partial	_	_	+	_	Partial
C11	Partial	+	+	+	_	+
C12	Partial	+	+	+	_	+
C13	Partial	_	_	+	_	+
C14	Partial	+	+	+	_	+
C15	Partial	_	_	+	_	+
C16	Partial	+	+	+	_	+
C17	Partial	_	_	+	_	+

3.4 Swelling Ratio

Tables (3-5) to (3-7) and Figures (3-35) to (3-40), represent the swelling ratio and the behavior curves of swelling in different time (hour and day) of prepared nano co-polymers **(Line 1)**.

Table (3-5): Swelling ratio % of prepared nano co-polymers at pH=2.2 and 310K

Time	**Swelling Ratio %**				
(Hour)	**Types of polymers**				
	C4	**C5**	**C6**	**C7**	**C8**
1	1.1557	0.6261	0.8236	0.1796	0.4022
2	1.3481	0.8236	1.0021	0.2432	0.6264
3	1.5680	1.0055	1.1992	0.4024	0.8236
4	1.8856	1.2195	1.5022	0.4344	1.0021
5	1.9555	1.3472	1.8221	0.4764	1.2281
6	1.9555	1.3472	1.8221	0.4764	1.2281
(Day)					
1	2.7237	2.1134	2.2233	0.5261	1.9331
2	2.9227	2.1667	2.3337	0.5442	2.005
3	3.1227	2.2443	2.5241	0.5663	2.074
4	3.2772	2.3312	2.7237	0.5863	2.2054

5	3.5052	2.6645	2.9965	0.6223	2.4554
6	3.8461	3.1003	3.4749	0.6421	2.9562
7	4.0307	3.1217	3.6608	0.6612	3.0072
8	4.0307	3.1217	3.6608	0.6612	3.0072

Table (3-6): Swelling ratio % of prepared nano co-polymers at pH=7 and 310K

Time	**Swelling Ratio %**				
(Hour)	**Types of polymers**				
	C4	**C5**	**C6**	**C7**	**C8**
1	1.3866	0.7935	0.9922	0.3784	0.6264
2	1.6633	0.9992	1.2233	0.5864	0.7936
3	1.9667	1.2215	1.4422	0.7736	0.9928
4	2.3399	1.3886	1.6775	0.9935	1.1875
5	2.5532	1.9266	2.218	1.1162	1.7683
6	2.5532	1.9266	2.218	1.1162	1.7683
(Day)					
1	2.9226	2.5223	2.7233	1.9617	2.1426
2	3.1027	2.6236	2.9326	2.1526	2.3435
3	3.3628	2.7732	3.1112	2.2061	2.4462

4	3.6425	3.1071	3.3942	2.3782	2.7061
5	4.0031	3.5532	3.8017	2.3983	3.0092
6	4.1145	3.7461	3.9271	2.523	3.2562
7	4.2233	3.7562	4.0307	2.5971	3.5560

Table (3-7): Swelling ratio % of prepared nano co-polymers at pH=8 and 310K

Time	**Swelling Ratio %**				
(Hour)	**Types of polymers**				
	C4	**C5**	**C6**	**C7**	**C8**
1	1.7981	0.9921	1.3826	0.5857	0.7646
2	1.9901	1.1891	1.5798	0.8735	0.9925
3	2.1627	1.5433	1.8848	1.2241	1.3726
4	2.5441	1.7932	2.1332	1.5652	1.6626
5	3.001	1.998	2.5051	1.5992	1.7662
6	3.001	1.998	2.5051	1.5992	1.7662
(Day)					
1	3.0033	2.7337	2.8832	2.1425	2.3437
2	3.2096	2.9626	3.1106	2.2237	2.5342
3	3.2995	3.1142	3.2211	2.5371	2.8844
4	3.6622	3.4883	3.5532	2.7335	3.1556

5	4.1231	3.8453	3.9933	3.1009	3.6034
6	4.4432	4.0994	4.3342	3.5522	3.8525
7	4.5622	4.3342	4.4432	3.6934	4.1008

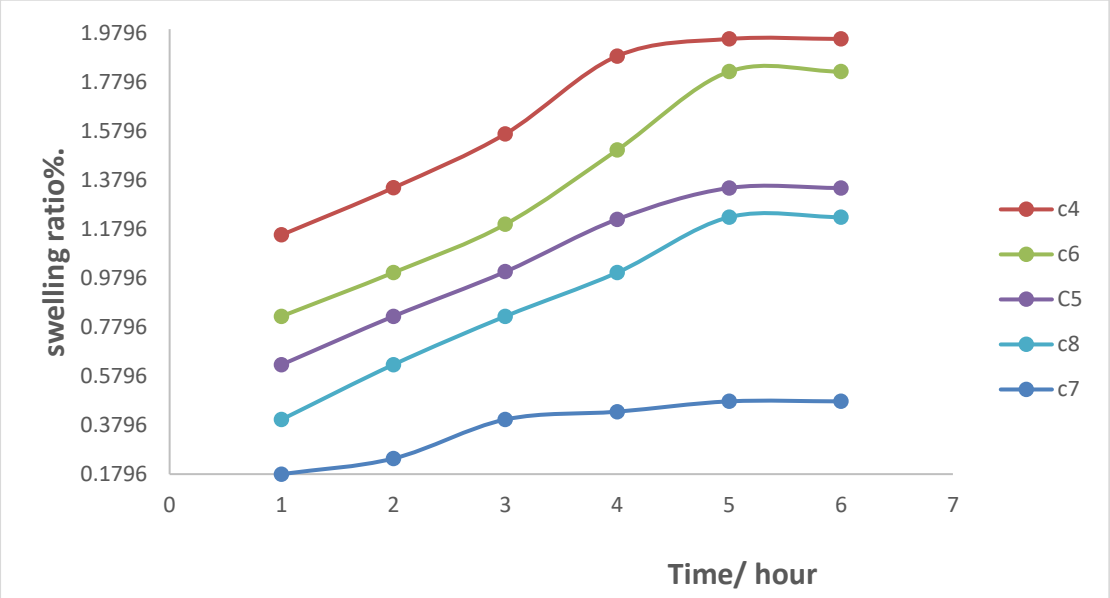


Figure (3-35): Swelling ratio (%) with time (hour) of prepared nano co-polymers in pH=2.2 at 310 K

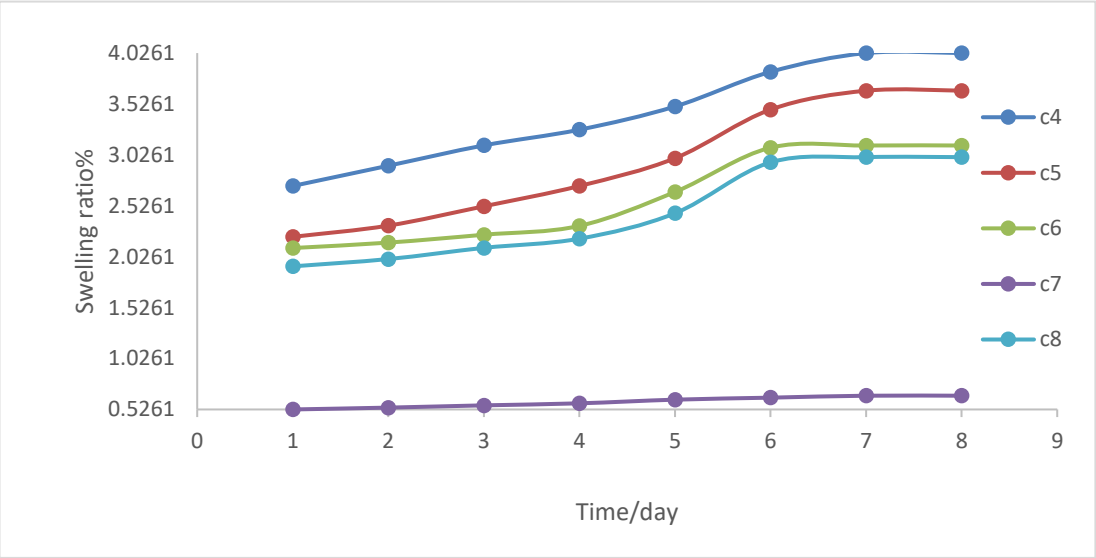


Figure (3-36): Swelling ratio (%) with time (day) of prepared nano co-polymers in pH=2.2 at 310 K

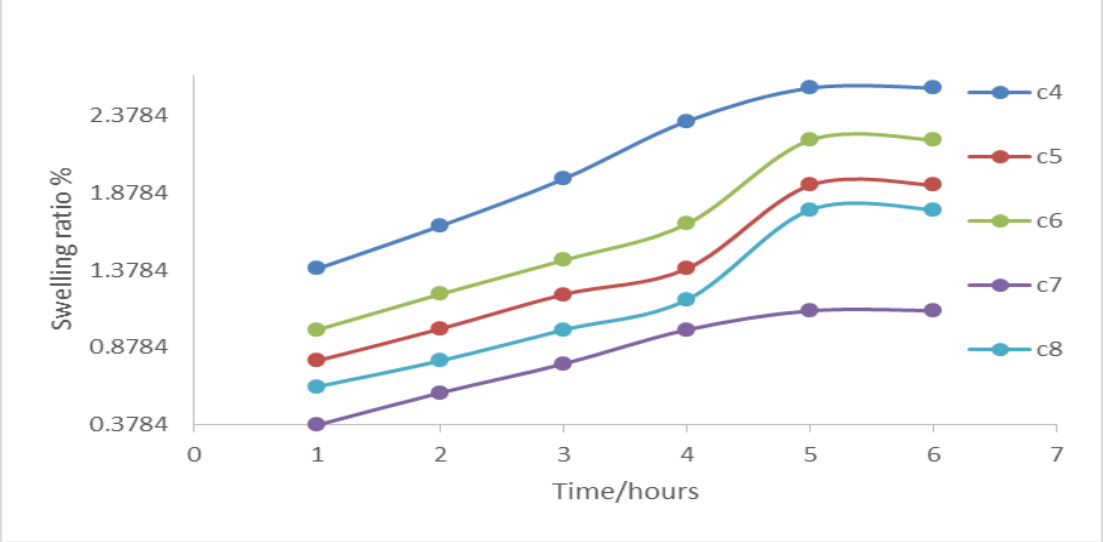


Figure (3-37): Swelling ratio (%) with time (hour) of prepared nano co-polymers in pH=7 at 310 K

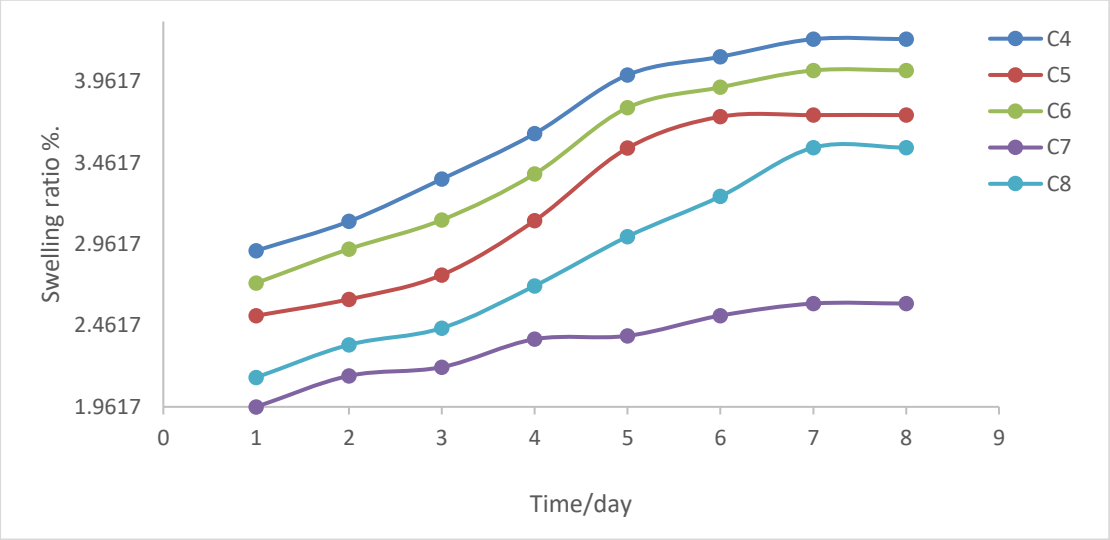


Figure (3-38): Swelling ratio (%) with time (day) of prepared nano co-polymers in pH=7 at 310 K

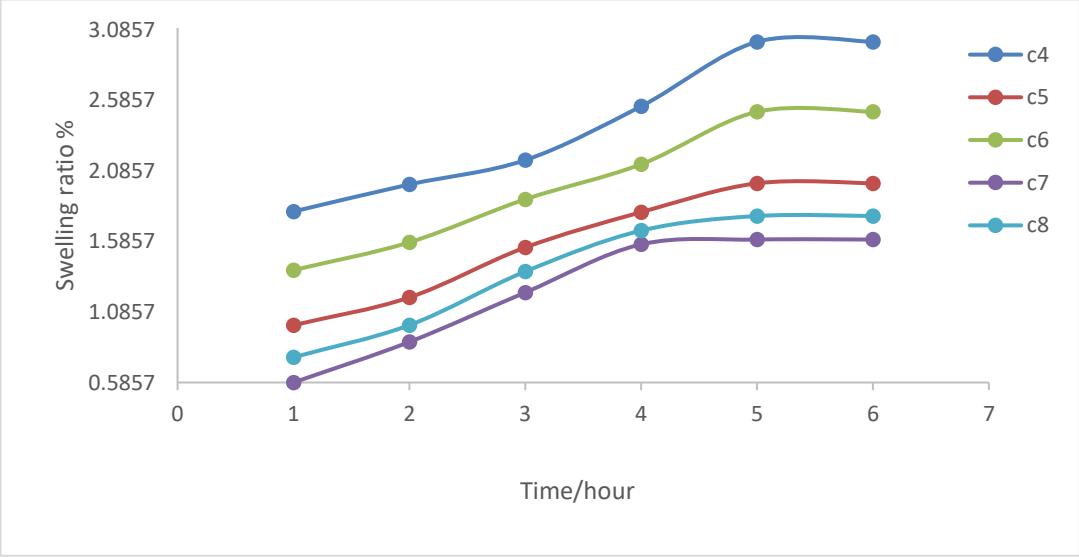


Figure (3-39): Swelling ratio (%) with time (hour) of prepared nano co-polymers in pH=8 at 310 K

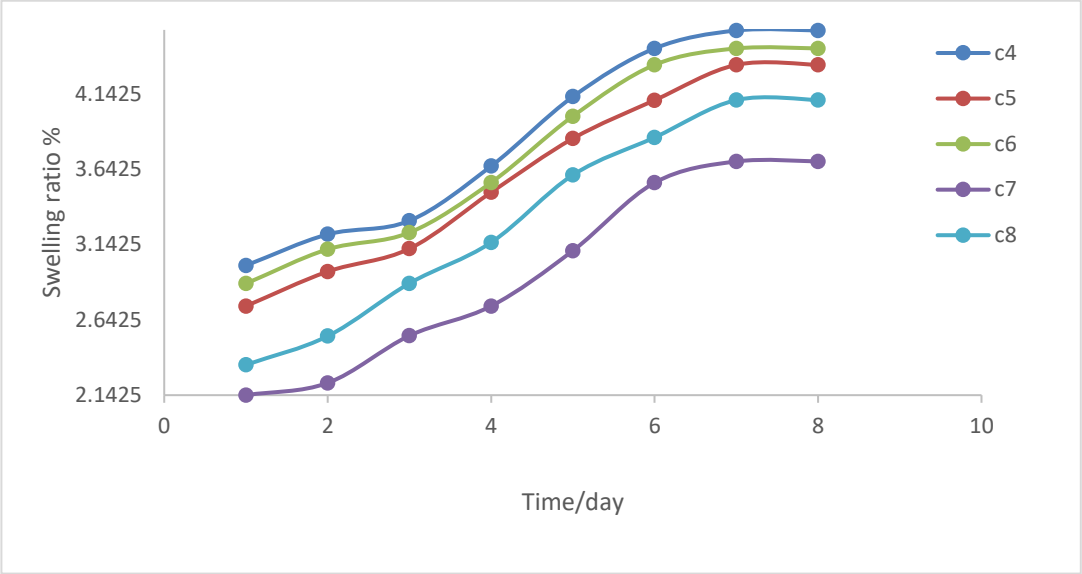


Figure (3-40): Swelling ratio (%) with time (day) of prepared nano co-polymers in pH=8 at 310 K

Tables (3-8) to (3-10) and Figures (2-41) to (2-46), 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 % of prepared nano co-polymers at pH=2.2 and 310K

Time	**Swelling Ratio %**						
(Hour)	**Types of polymers**						
	C11	**C12**	**C13**	**C14**	**C15**	**C16**	**C17**
1	1.3144	1.3766	1.2541	1.2844	1.4066	1.3451	1.2254
2	1.3566	1.4144	1.2944	1.3245	1.4477	1.3844	1.2644
3	1.3944	1.4566	1.3324	1.3644	1.4866	1.4288	1.3014
4	1.4366	1.4955	1.3778	1.4045	1.5244	1.4677	1.3455

5	1.4788	1.5344	1.4155	1.4466	1.5622	1.5066	1.3846
6	1.4788	1.5344	1.4155	1.4466	1.5622	1.5066	1.3846
(Day)							
1	1.5266	1.5844	1.4664	1.4977	1.6122	1.5588	1.4366
2	1.5788	1.6366	1.5152	1.5488	1.6644	1.6021	1.4844
3	1.6244	1.6877	1.5644	1.5972	1.7155	1.6544	1.5356
4	1.6733	1.7344	1.6172	1.6486	1.7644	1.7055	1.5844
5	1.7244	1.7855	1.6654	1.6955	1.8178	1.7563	1.6355
6	1.7744	1.8366	1.7142	1.7442	1.8644	1.8066	1.6833
7	1.8255	1.8776	1.7664	1.7966	1.9055	1.8577	1.7344

Table (3-9): Swelling ratio % of prepared nano co-polymers at pH=7.0 and 310K

Time	**Swelling Ratio %**						
(Hour)	**Types of polymers**						
	C11	**C12**	**C13**	**C14**	**C15**	**C16**	**C17**
1	1.3644	1.4588	1.2766	1.3088	1.3966	1.4277	1.3377
2	1.4162	1.4915	1.3177	1.3477	1.4377	1.4678	1.3744
3	1.4566	1.5344	1.3566	1.3866	1.4782	1.5088	1.4145
4	1.4992	1.5734	1.3944	1.4255	1.5156	1.5466	1.4566
5	1.5466	1.6033	1.4366	1.4667	1.5572	1.5892	1.5076
6	1.5466	1.6033	1.4366	1.4667	1.5572	1.5892	1.5076
(Day)							

1	1.5884	1.6698	1.4892	1.5192	1.6092	1.6388	1.5592
2	1.6377	1.7169	1.5366	1.5692	1.6582	1.6892	1.6064
3	1.6882	1.7685	1.5862	1.6172	1.7046	1.7382	1.6579
4	1.7369	1.8192	1.6379	1.6681	1.7565	1.7892	1.7089
5	1.7892	1.8695	1.6881	1.7162	1.8066	1.8366	1.7592
6	1.8392	1.9186	1.7382	1.7644	1.8569	1.8857	1.8096
7	1.8869	1.9554	1.7866	1.8166	1.9086	1.9366	1.8592

Table (3-10): Swelling ratio % of prepared nano co-polymers at pH=8.0 and 310K

Time	**Swelling Ratio %**						
(Hour)	**Types of polymers**						
	C11	**C12**	**C13**	**C14**	**C15**	**C16**	**C17**
1	1.3992	1.4925	1.4462	1.6462	1.5466	1.5962	1.3477
2	1.4392	1.5366	1.4862	1.6856	1.5862	1.6369	1.3882
3	1.4752	1.5782	1.5276	1.7211	1.6276	1.6782	1.4262
4	1.5111	1.6332	1.5669	1.7511	1.6652	1.7192	1.4668
5	1.5592	1.6576	1.604	1.7843	1.6921	1.7595	1.5082

6	1.5592	1.6576	1.604	1.7843	1.6921	1.7595	1.5082
(Day)							
1	1.5589	1.6093	1.6093	1.8332	1.7082	1.7982	1.6566
2	1.6072	1.9334	1.6596	1.8873	1.7592	1.8472	1.7072
3	1.6589	1.9774	1.7066	1.9244	1.8086	1.8982	1.7582
4	1.7085	2.0221	1.7569	1.9773	1.8592	1.9484	1.8092
5	1.7592	2.1553	1.8076	2.1145	1.9096	1.9966	1.8566
6	1.8522	1.9586	1.9072	2.2232	2.1006	2.1773	1.8095
7	1.9332	2.0052	1.9586	2.2441	2.1443	2.1996	1.8588

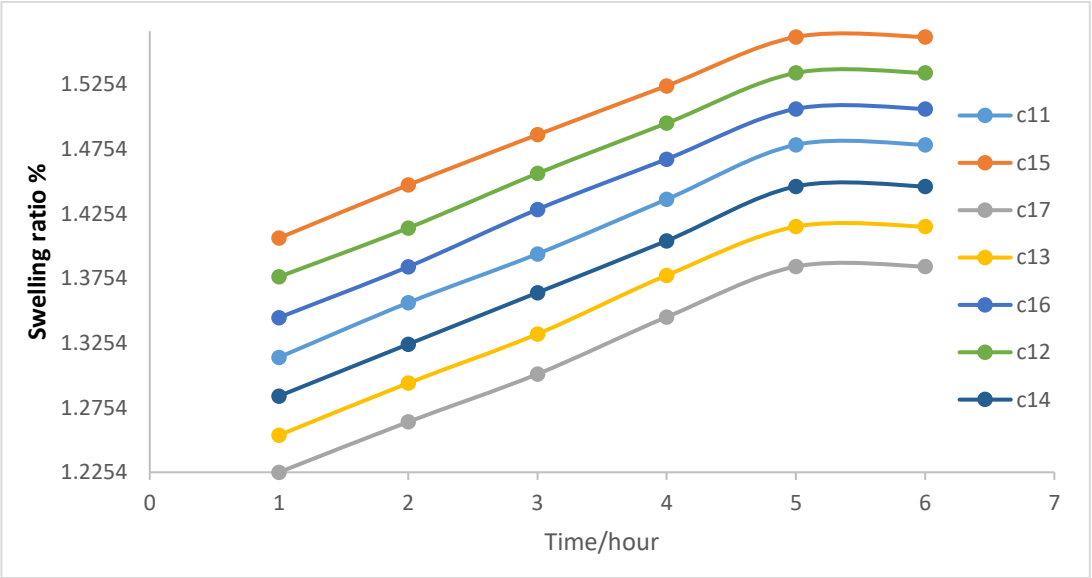


Figure (3-41): Swelling ratio (%) with time (hour) of prepared nano co-polymers at pH=2.2 and 310 K

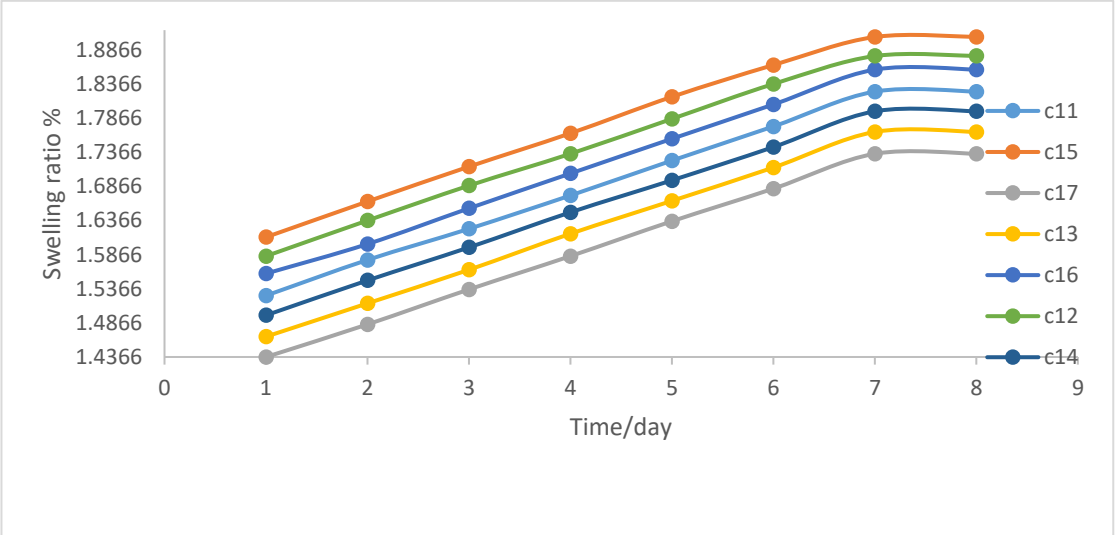


Figure (3-42): Swelling ratio (%) with time (day) of prepared nano co-polymers at pH=2.2 and 310 K

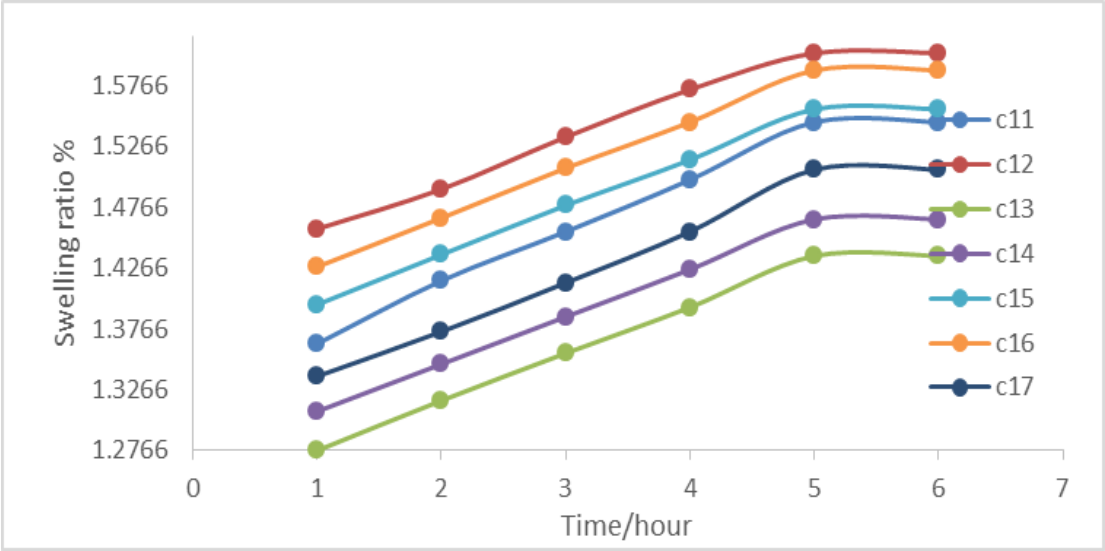


Figure (3-43): Swelling ratio (%) with time (hour) of prepared nano co-polymers at pH=7 and 310 K

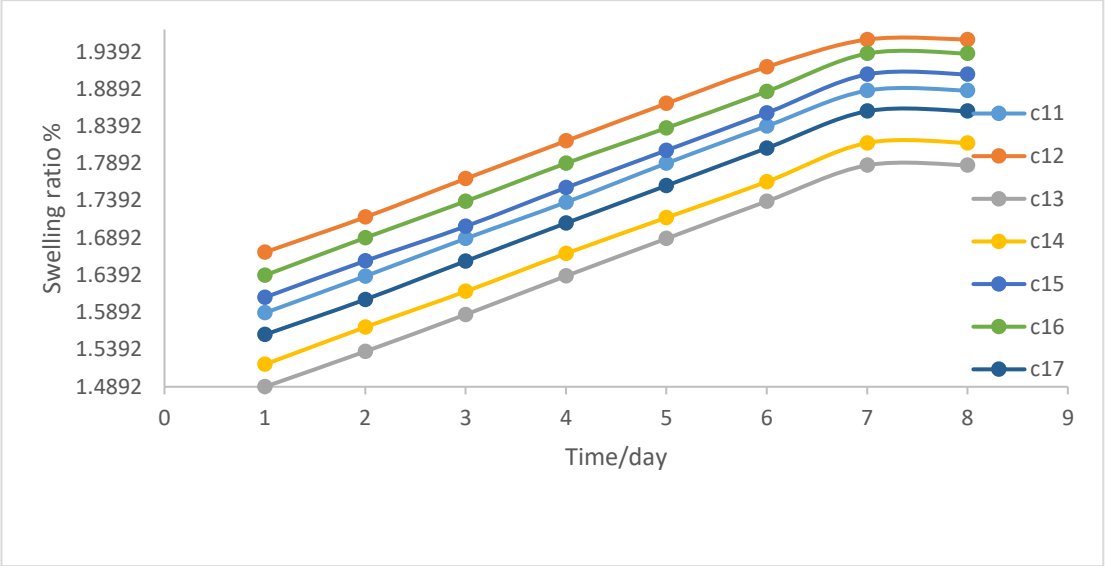


Figure (3-44): Swelling ratio (%) with time (day) of prepared nano co-polymers at pH=7.0 and 310 K

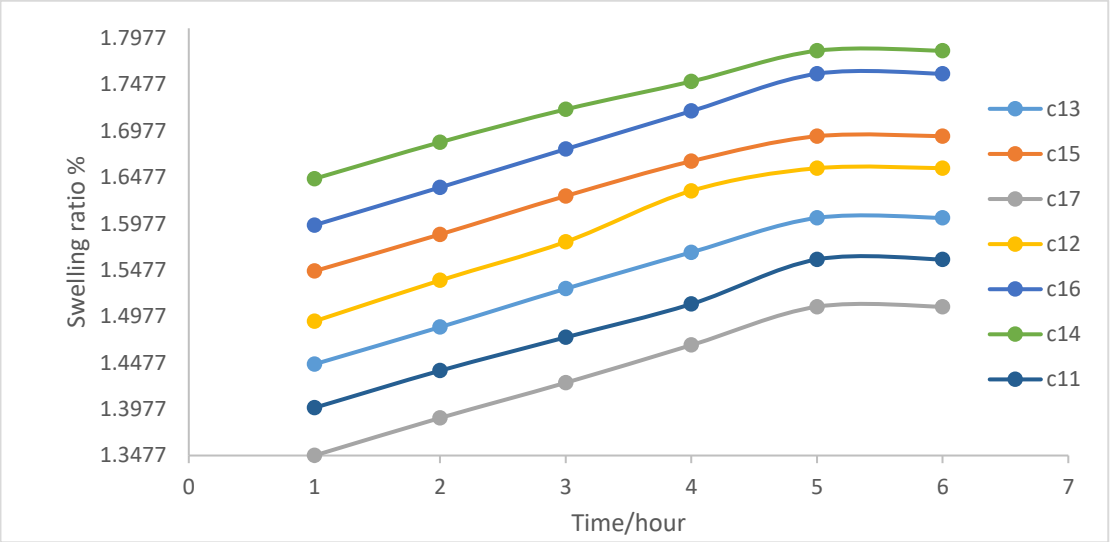


Figure (3-45): Swelling ratio (%) with time (hour) of prepared nano co-polymers at pH=8 and 310 K

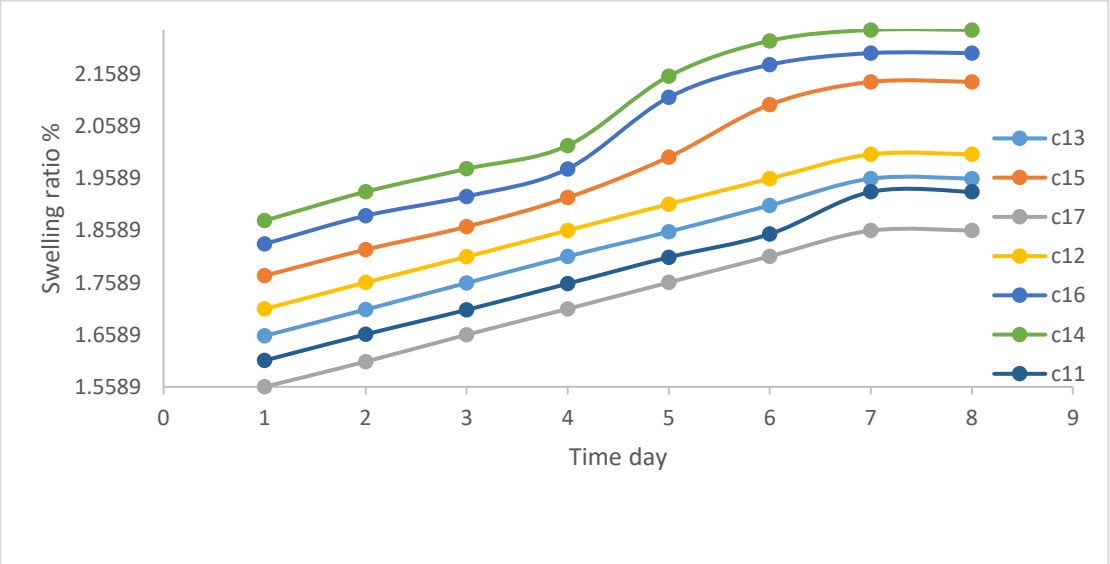


Figure (3-46): Swelling ratio (%) with time (day) of prepared nano co-polymers at pH=8 and 310 K

3.5 Release of drug

By using UV.-Vis. spectrophotometer, release the drug from the prepared nano co-polymers was determined in three different buffer solutions (2.2, 7.0 and 8.0) at constant temperature 310 K. Tables (3-11) to (3-13), represent the drug release from the prepared polymer and Figures (3-47) to (3-52), showed the behavior curves of the drug release.

Table (3-11): Release of drug of prepared nano co-polymers at pH=2.2 and 310K

Time	**Absorbance ($\lambda_{max.}$)**				
(Hour)	**Types of polymers**				
	C4	**C5**	**C6**	**C7**	**C8**
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
(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

Table (3-12): Release of drug of prepared nano co-polymers at pH=7.0 and 310K

Time	**Absorbance ($\lambda_{max.}$)**				
(Hour)	**Types of polymers**				
	C4	**C5**	**C6**	**C7**	**C8**
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

Table (3-13): Release of drug of prepared nano co-polymers at pH=8.0 and 310K.

Time	**Absorbance ($\lambda_{max.}$)**				
(Hour)	**Types of polymers**				
	C4	**C5**	**C6**	**C7**	**C8**
1	1.001	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
(Day)					
1	2.106	0.668	1.199	0.341	0.442
2	2.241	0.798	1.491	0.362	0.599
3	3.051	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	1.028
6	4.121	1.788	2.777	0.488	1.441
7	4.199	2.131	3.199	0.502	2.009

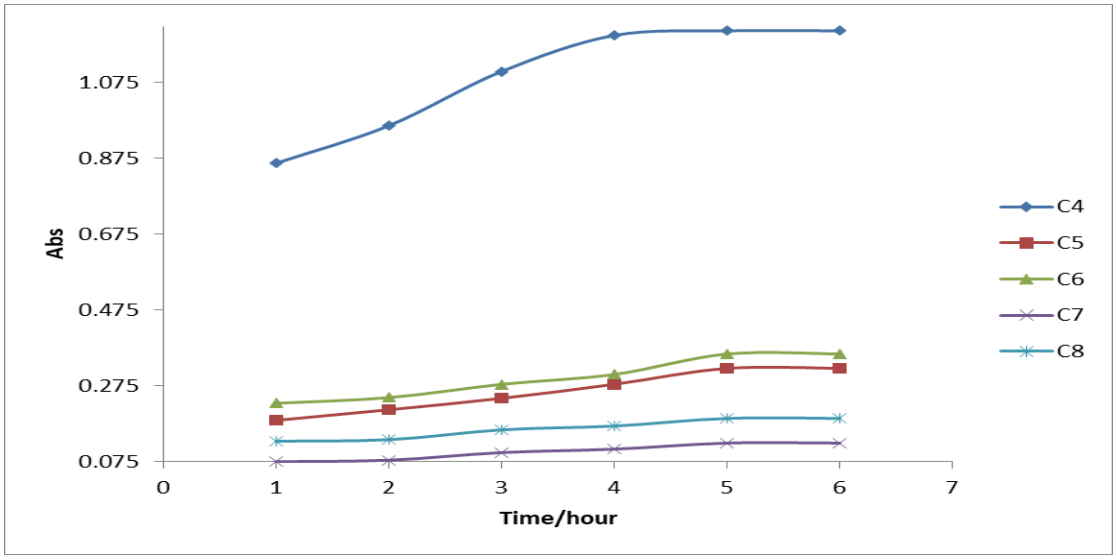


Figure (3-47): Release of drug (Abs) with time (hour) of prepared nano co-polymers at pH=2.2 and 310 K

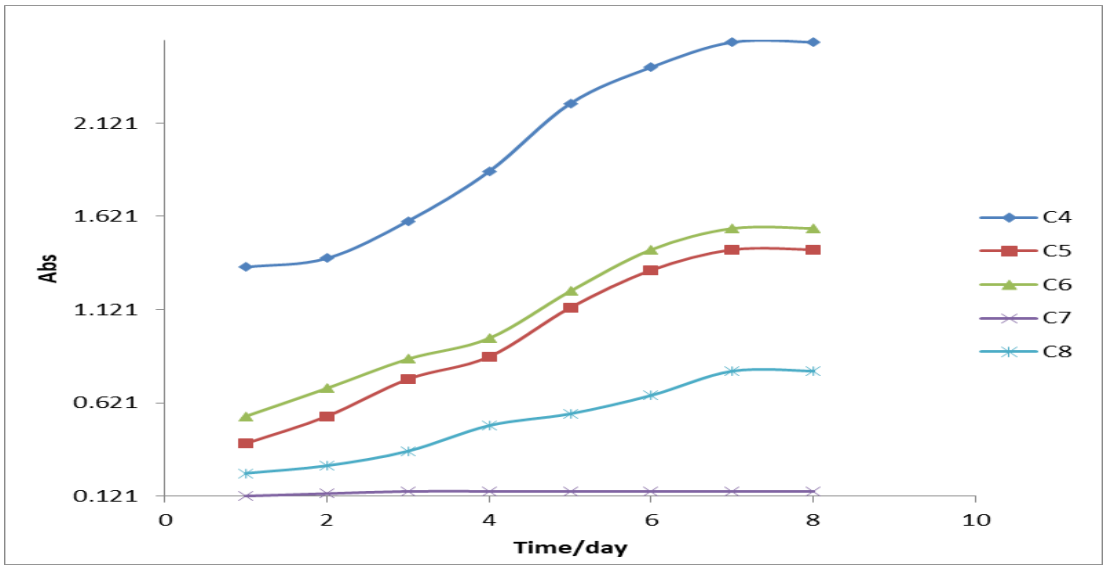


Figure (3-48): Release of drug (Abs) with time (day) of prepared nano co-polymers at pH=2.2 and 310 K

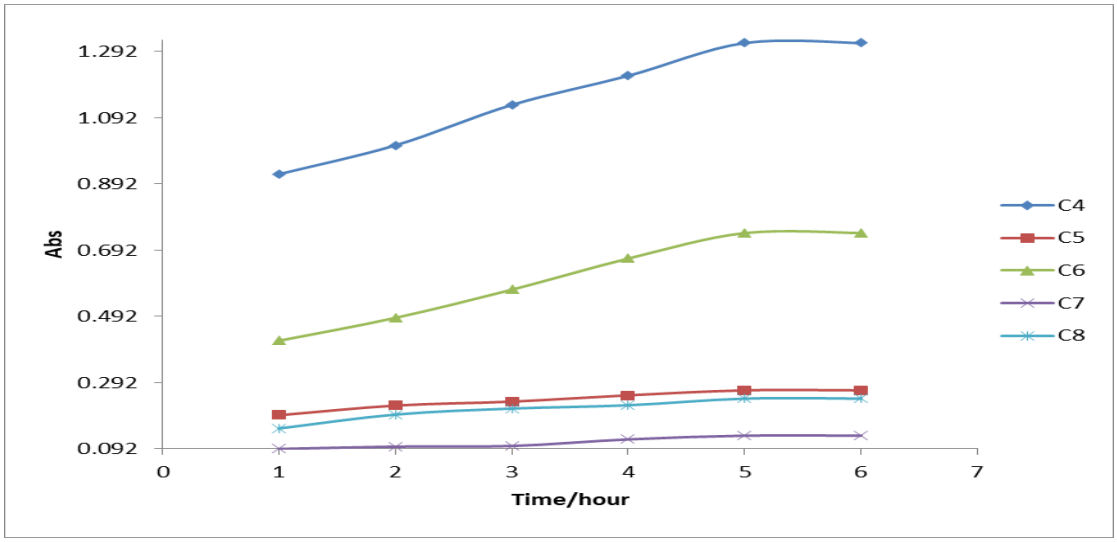


Figure (3-49): Release of drug (Abs) with time (hour) of prepared nano co-polymers at pH=7.0 and 310 K

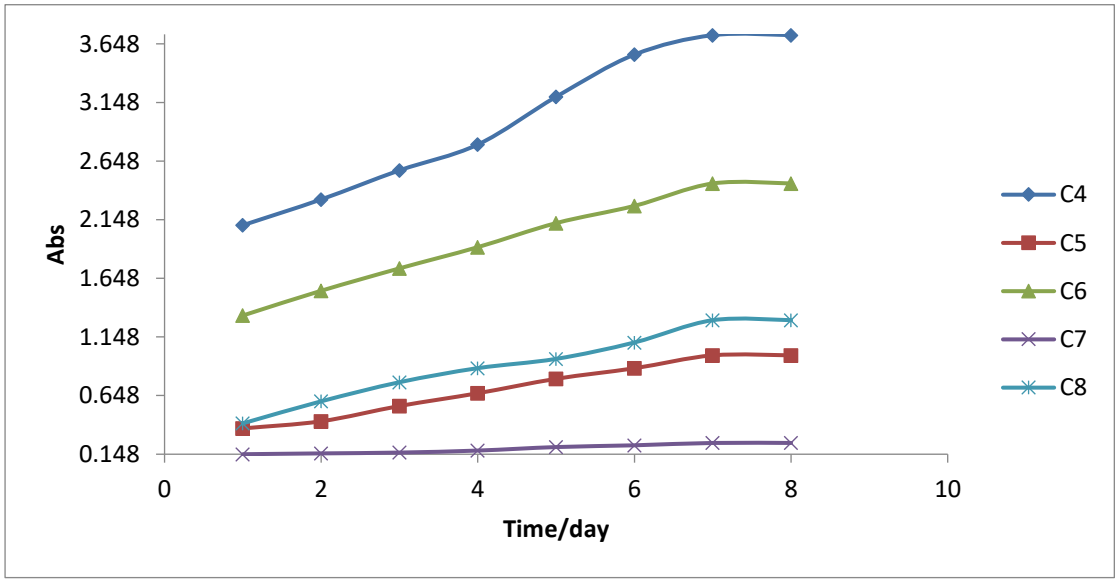


Figure (3-50): Release of drug (Abs) with time (day) of prepared nano co-polymers at pH=7.0 and 310 K

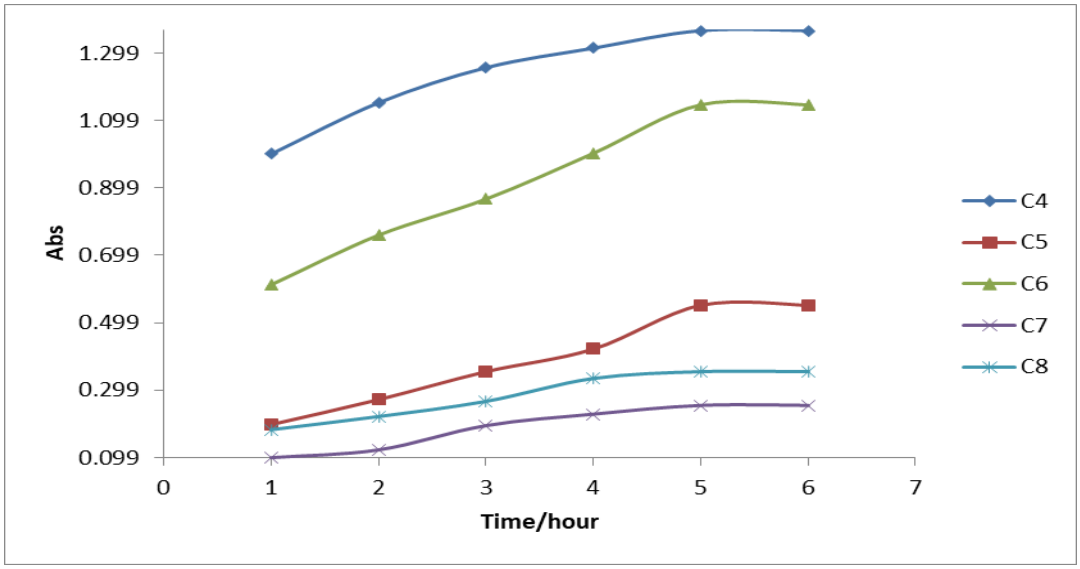


Figure (3-51): Release of drug (Abs) with time (hour) of prepared nano co-polymers at pH=8.0 and 310 K

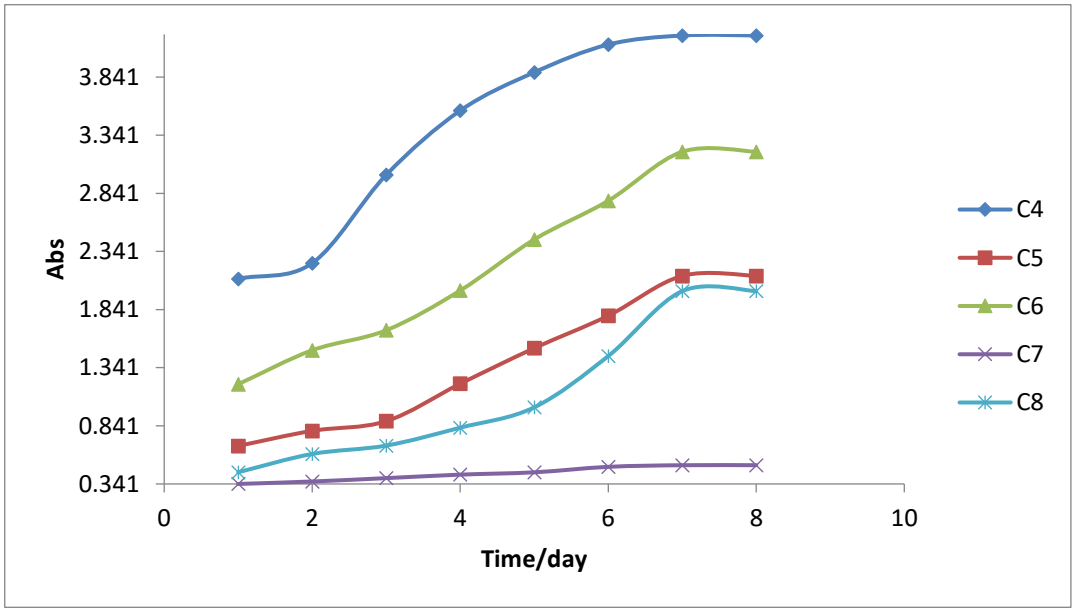


Figure (3-52): Release of drug (Abs) with time (day) of prepared nano co-polymers at pH=8.0 and 310 K

Tables (3-14) to (3-16) and Figures (2-53) to (2-58), represent the release of drug and the behavior curves of release of drug in different time (hour and day) of prepared nano co-polymers **(Line 2)**.

Table (3-14): Release of drug of prepared nano co-polymers at pH=2.2 and 310K.

Time	**Absorbance (λ max.)**						
(Hour)	**Types of polymers**						
	C11	**C12**	**C13**	**C14**	**C15**	**C16**	**C17**
1	1.231	1.432	1.033	1.211	1.572	1.254	1.001
2	1.252	1.454	1.122	1.241	1.615	1.279	1.112
3	1.279	1.477	1.144	1.262	1.653	1.298	1.133
4	1.299	1.496	1.162	1.282	1.692	1.317	1.151
5	1.318	1.518	1.185	1.309	1.734	1.339	1.172
(Day)							
1	1.693	1.752	1.512	1.661	1.782	1.721	1.572
2	1.742	1.802	1.562	1.712	1.824	1.773	1.621
3	1.793	1.853	1.611	1.763	1.873	1.821	1.671
4	1.844	1.902	1.662	1.812	1.924	1.873	1.721
5	1.892	1.952	1.712	1.863	1.984	1.921	1.762
6	1.942	2.084	1.762	1.912	2.132	1.994	1.802
7	1.992	2.133	1.811	1.962	2.193	2.091	1.842

Table (3-15): Release of drug of prepared nano co-polymers at pH=7 and 310K

Time	Absorbance (λ max.)						
(Hour)	Types of polymers						
	C11	C12	C13	C14	C15	C16	C17
1	1.242	1.334	1.152	1.182	1.272	1.304	1.212
2	1.284	1.372	1.193	1.225	1.314	1.344	1.254
3	1.321	1.412	1.234	1.264	1.354	1.382	1.292
4	1.364	1.453	1.273	1.299	1.393	1.424	1.334
5	1.401	1.484	1.314	1.334	1.445	1.463	1.372
(Day)							
1	1.452	1.542	1.402	1.382	1.396	1.514	1.425
2	1.502	1.592	1.451	1.431	1.441	1.562	1.472
3	1.552	1.641	1.502	1.482	1.492	1.612	1.522
4	1.603	1.692	1.553	1.531	1.542	1.663	1.572
5	1.652	1.741	1.602	1.581	1.591	1.711	1.622
6	1.702	1.792	1.651	1.631	1.641	1.762	1.673
7	1.751	1.841	1.701	1.682	1.692	1.812	1.724

Table (3-16): Release of drug of prepared nano co-polymers at pH=8.0 and 310K

Time	Absorbance (λ max.)						
(Hour)	Types of polymers						
	C11	C12	C13	C14	C15	C16	C17
1	1.321	1.421	1.371	1.571	1.471	1.521	1.271
2	1.361	1.461	1.421	1.611	1.511	1.561	1.311
3	1.401	1.501	1.471	1.651	1.551	1.601	1.351
4	1.441	1.541	1.521	1.691	1.591	1.641	1.391
5	1.481	1.581	1.561	1.724	1.631	1.681	1.431
(Day)							
1	1.531	1.631	1.611	1.781	1.681	1.731	1.481
2	1.58	1.681	1.661	1.831	1.731	1.781	1.531
3	1.632	1.731	1.711	1.881	1.781	1.831	1.581
4	1.682	1.781	1.761	1.931	1.821	1.881	1.631
5	1.731	1.831	1.811	1.981	1.871	1.932	1.681
6	1.781	1.881	1.862	2.028	1.921	1.982	1.731
7	1.830	1.931	1.911	2.077	1.971	2.008	1.781

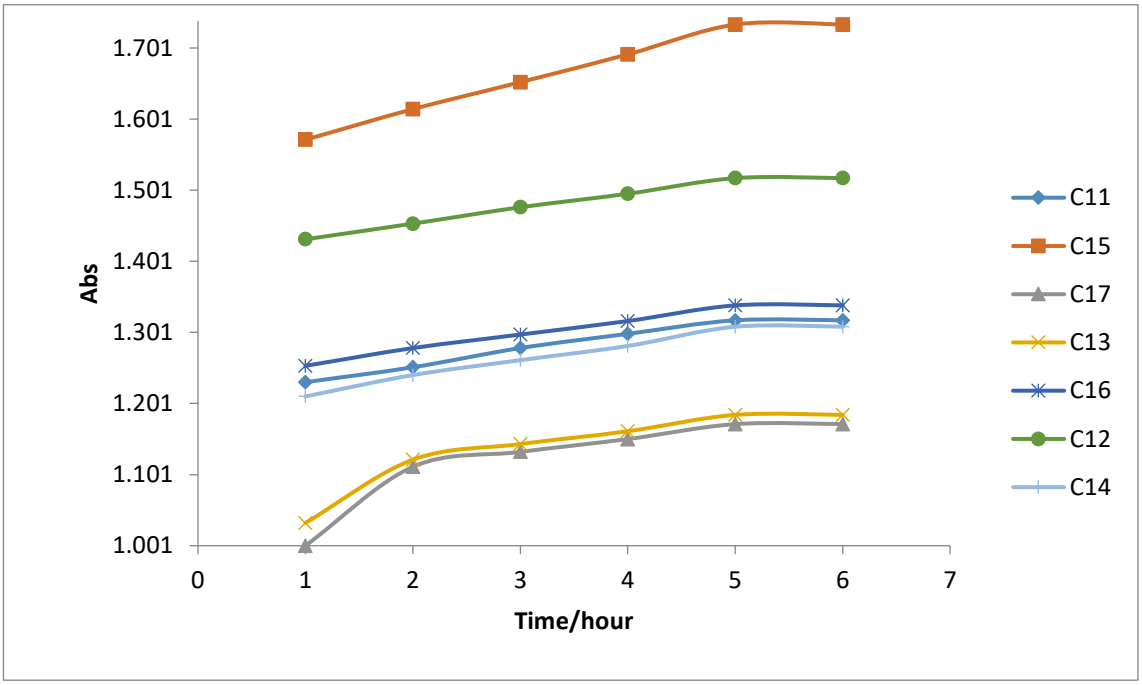


Figure (3-53): Release of drug (Abs) with time (hour) of prepared nano co-polymers at pH=2.2 and 310 K

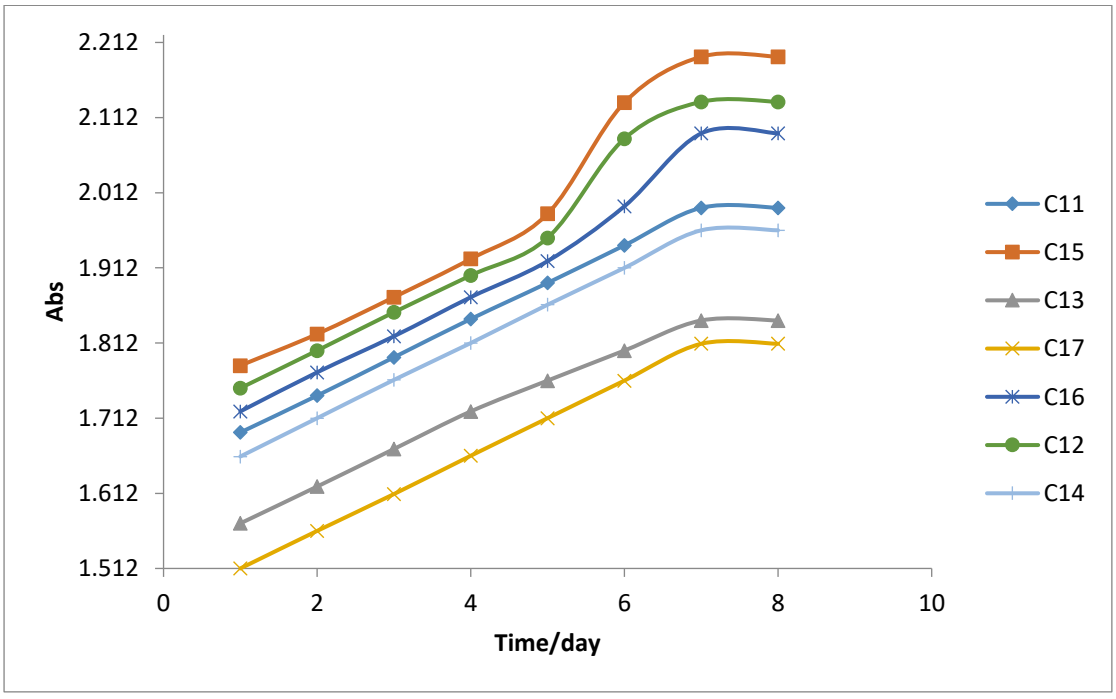


Figure (3-54): Release of drug (Abs) with time (day) of prepared nano co-polymers at pH=2.2 and 310 K

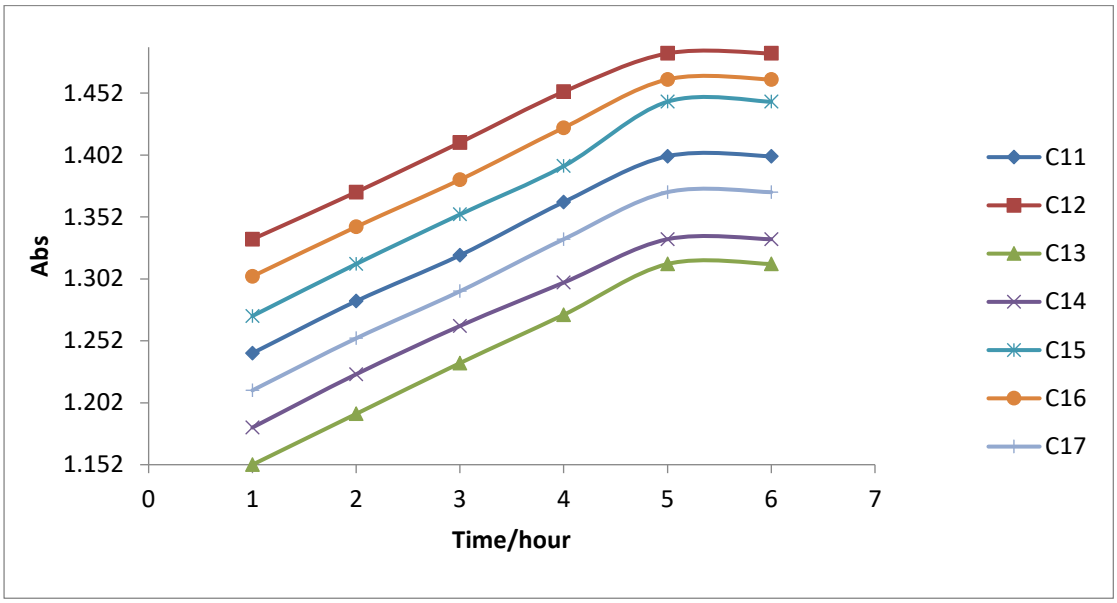


Figure (3-55): Release of drug (Abs) with time (hour) of prepared nano co-polymers at pH=7 and 310 K

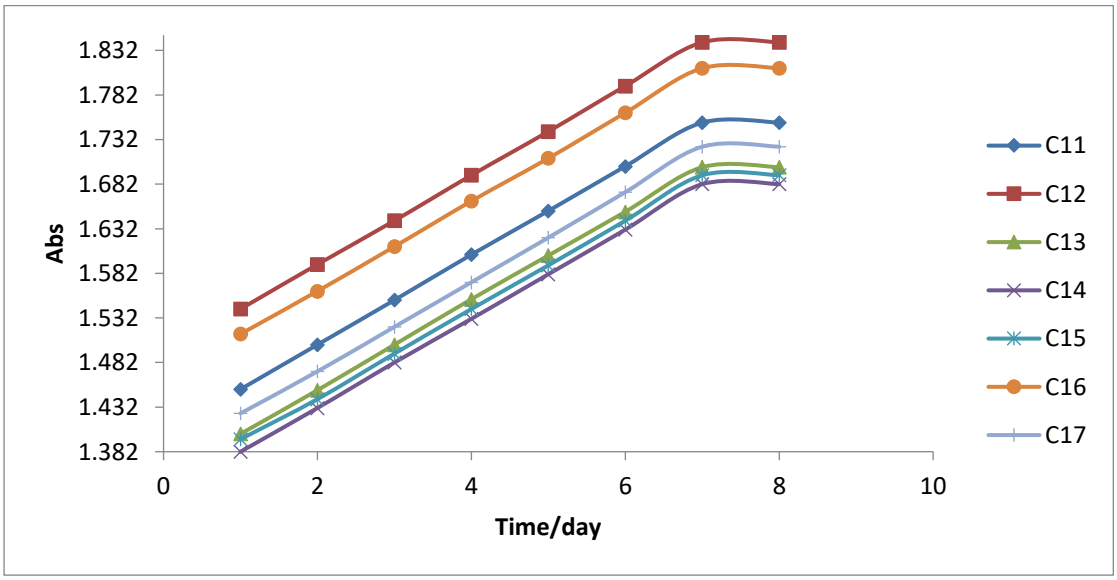


Figure (3-56): Release of drug (Abs) with time (day) of prepared nano co-polymers at pH=7 and 310 K

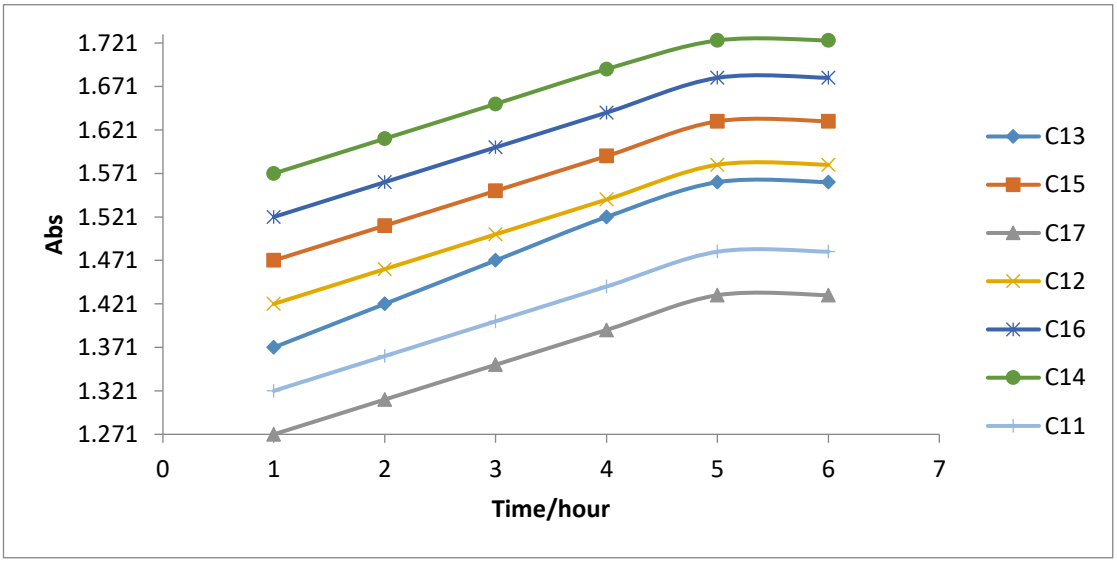


Figure (3-57): Release of drug (Abs) with time (hour) of prepared nano co-polymers at pH=8 and 310 K

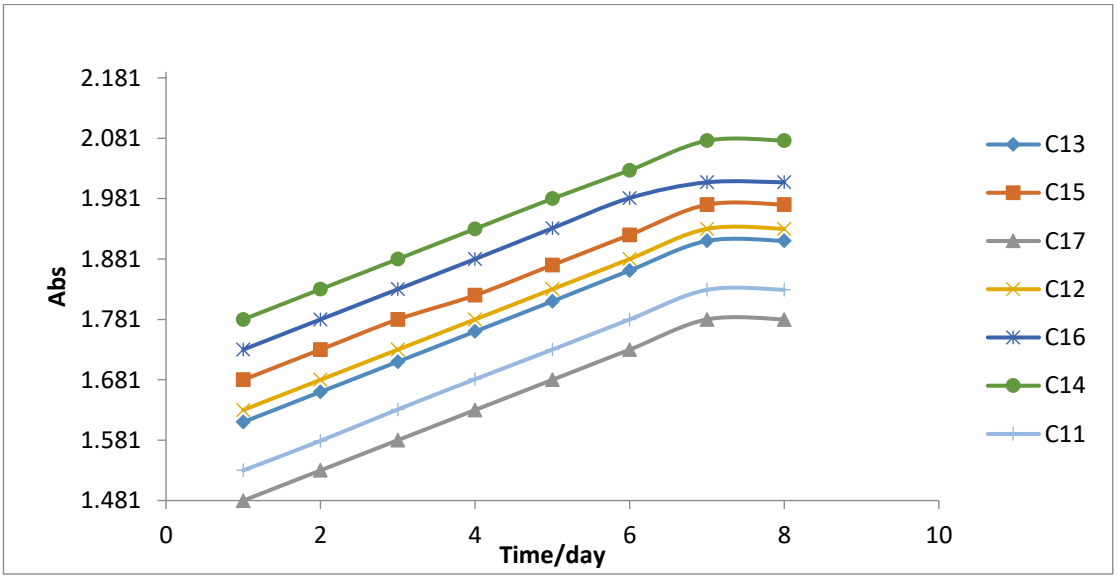


Figure (3-58): Release of drug (Abs) with time (day) of prepared nano co-polymers at pH=8 and310 K

3.6 Biological activity

MCF-7 is a breast cancer cell line discovered in 1970, MCF-7 is the acronym of Michigan Cancer Foundation-7. In this present work, we evaluated the anti-proliferating effect of drug-loading (C5, C6, C7, C8, C11, C13 and C17), against the breast cancer cell lines. Based on cytotoxicity analyses, it can be concluded that C5, C6, C7, C8, C11, C13 and C17, may be an appropriate and promising strategy for developing effective drug delivery system to clinical application against breast cancers.

IC50 value was significantly decreased in C8 (IC50=16.83) in comparison with pure drugs and induced apoptotic cell death pathway. The results of this study suggest that the C8 might be used for medical applications and offer a beneficial formulation for chemotherapy. The IC50 value of C5, C6, C7, C11, C13 and C17 are (33.21, 41.25, 63.14, 21.42, 29.81 and 79.08 µg/ml), respectively; as shown in Figures (3-59) to (3-65).

The synthesis nano co-polymer-drug, showed efficacy in the following order against the spread of breast cancer:

C8 > C11> C13> C5 > C6 > C7 > C17

← The trend of increasing efficacy

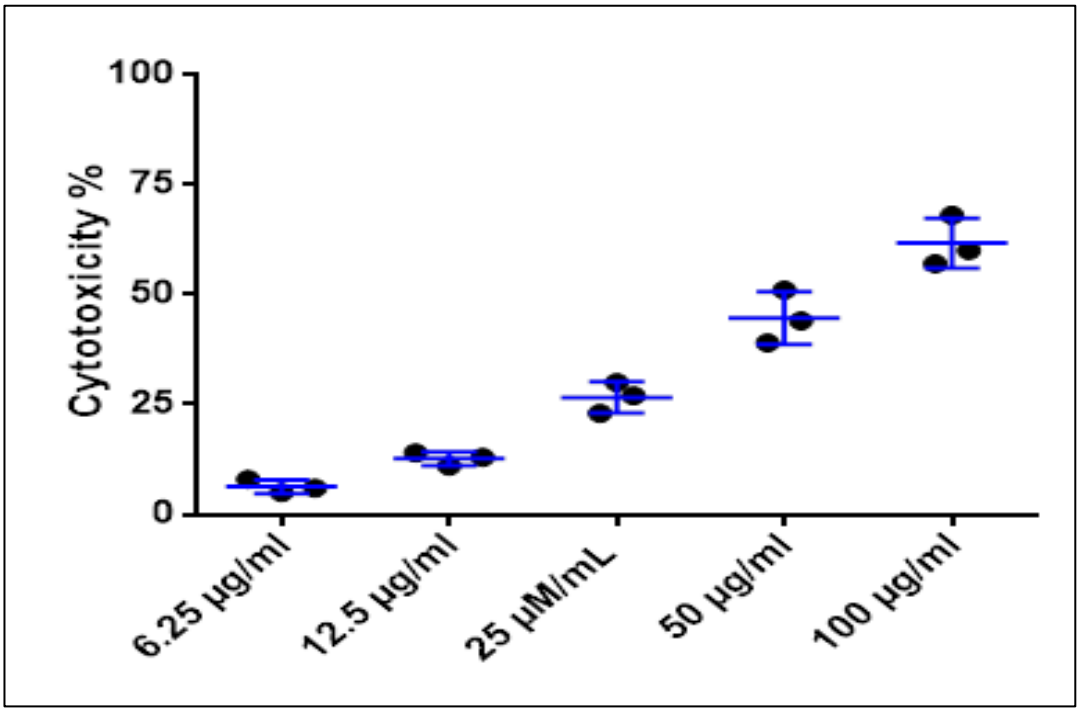


Figure (3-59): Cytotoxic effect of C5 in MCF-7cells. IC50=33.21 µg/ml

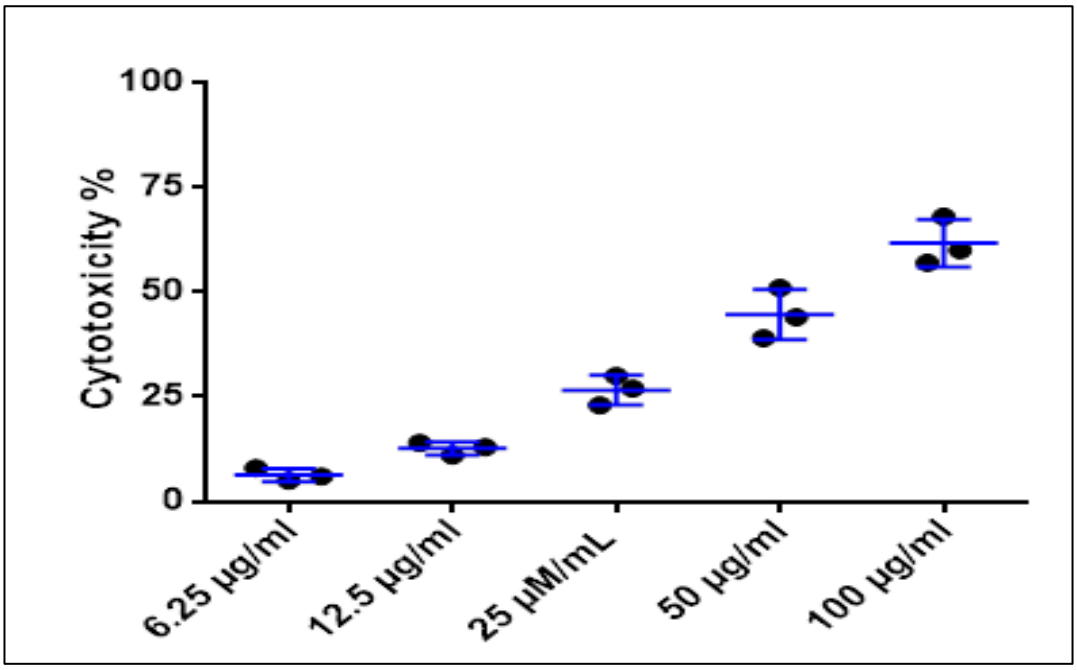


Figure (3-60): Cytotoxic effect of C6 in MCF-7 cells. IC50=41.25 µg/ml

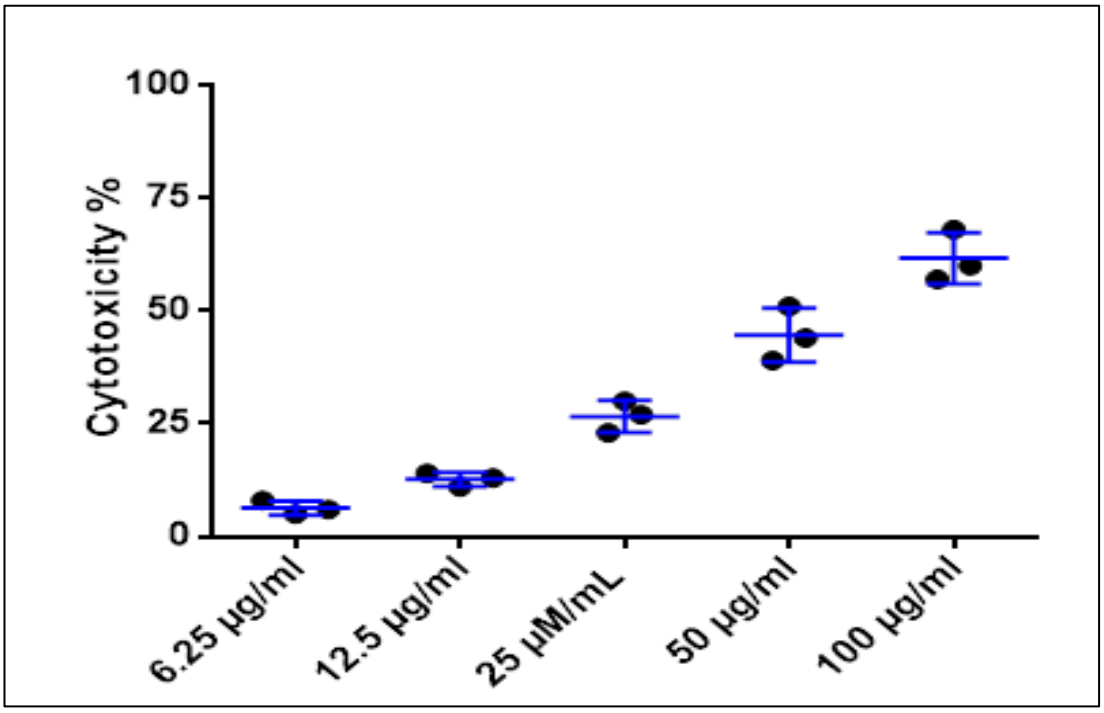


Figure (3-61): Cytotoxic effect of C7 in MCF-7 cells. IC50=63.14 µg/ml

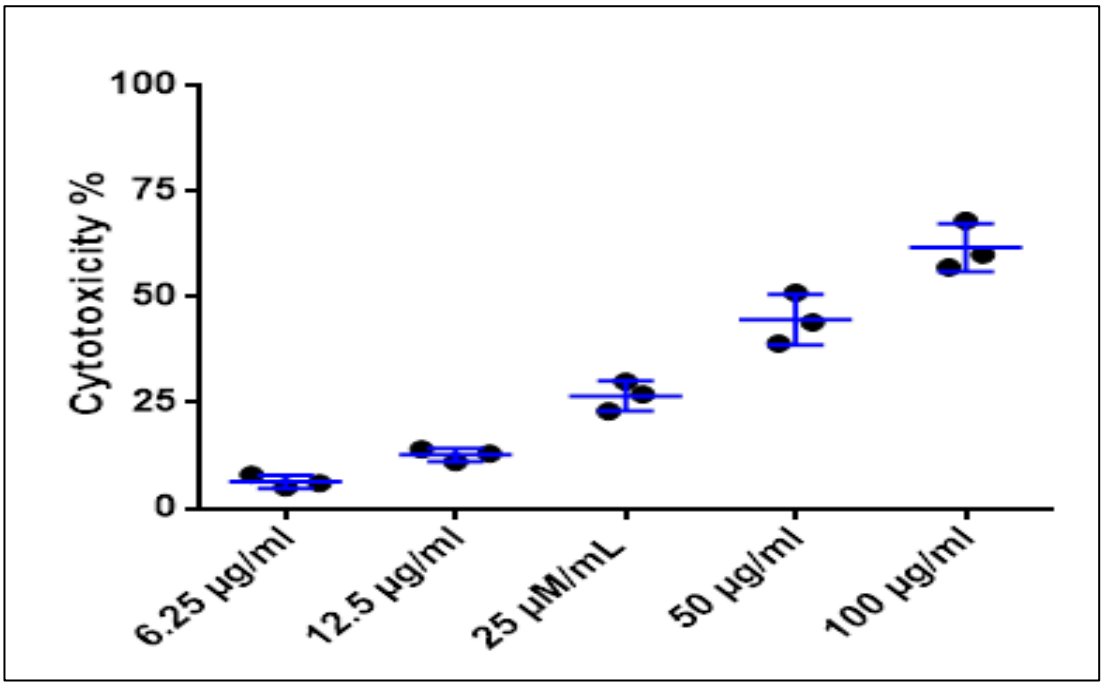


Figure (3-62): Cytotoxic effect of C8 in MCF-7 cells. IC50=16.83 µg/ml

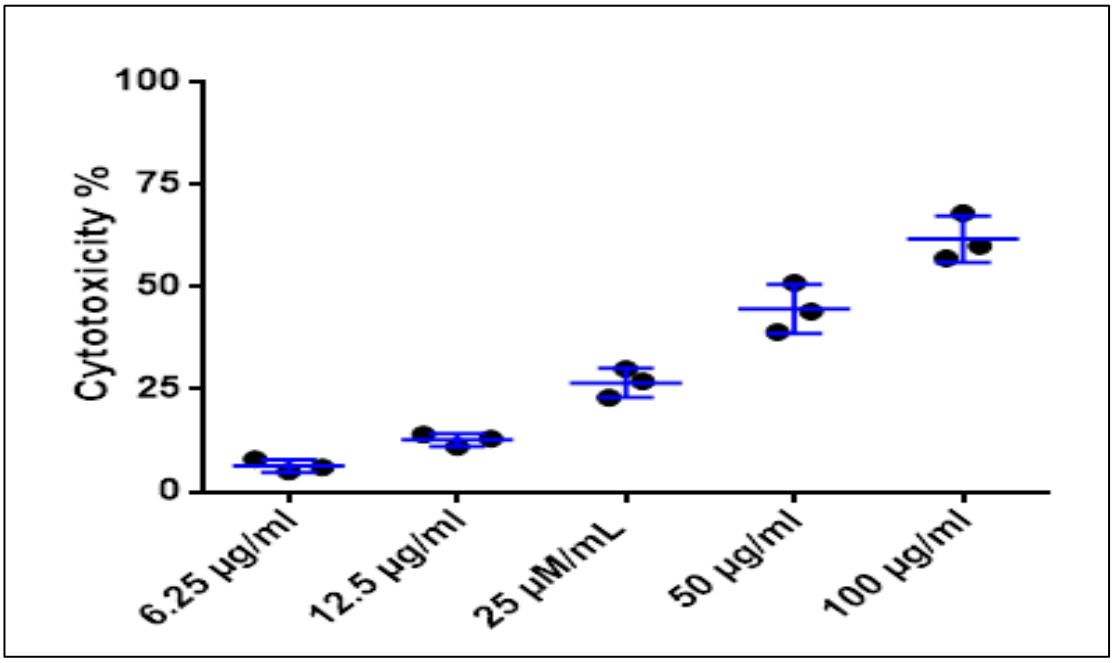


Figure (3-63): Cytotoxic effect of C11 in MCF-7 cells. IC50=21.42µg/ml

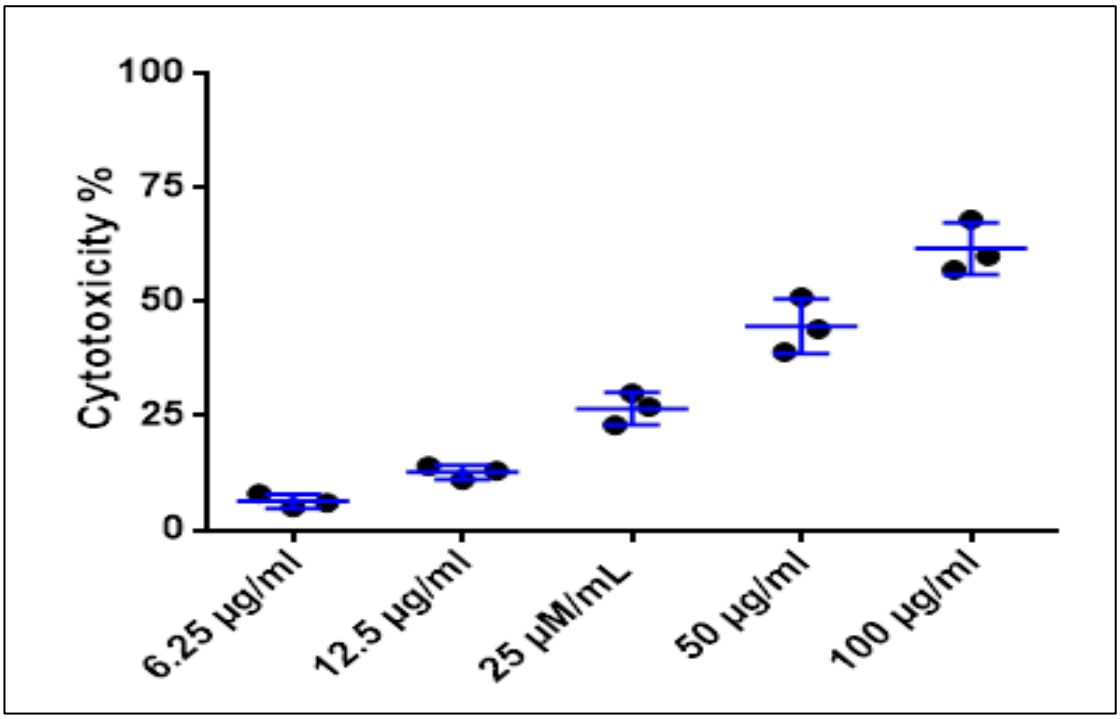


Figure (3-64): Cytotoxic effect of C13 in MCF-7 cells. IC50=29.81µg/ml

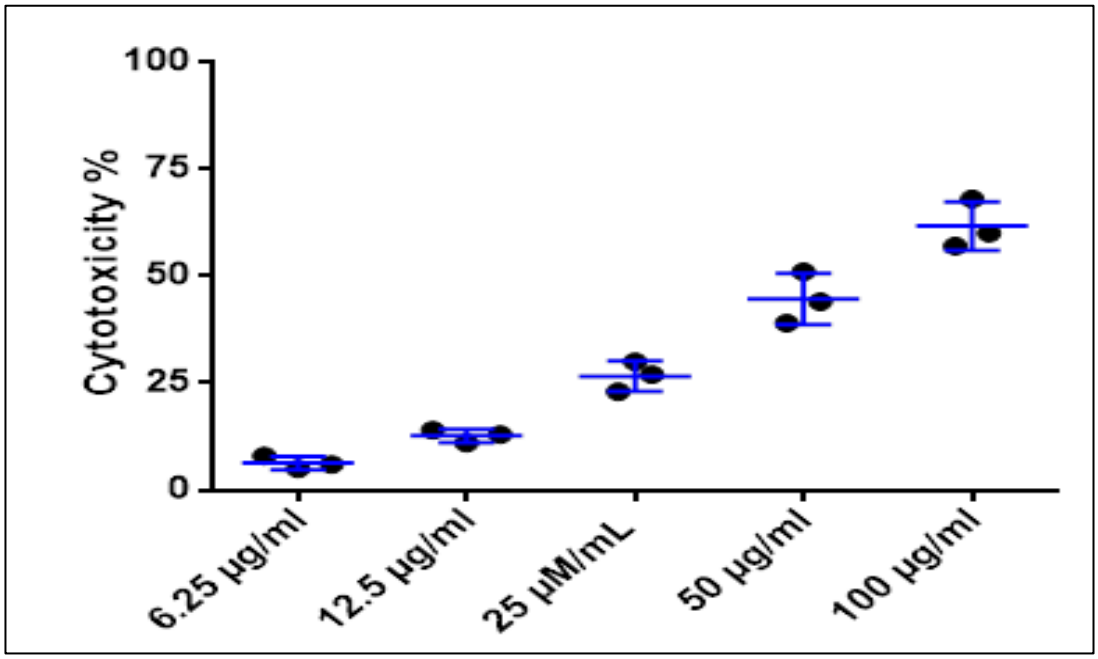


Figure (3-65): Cytotoxic effect of C17 in MCF-7 cells. IC50=79.08µg/ml

Conclusions

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

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

3- The solubility of these nano co-polymer-drugs was determined in deferent solvents.

4- Swelling behavior of these nano co-polymer-drugs were determined in deferent acid value (pH= 2.2, 7.0 and 8.0).

5- The biological effectiveness of the prepared compounds was studied by studying their effectiveness in the direction of inhibition of the spread of breast cancer.

6- The drugs that were used in this work are known and used on a daily basis by humans in treating specific diseases, the great thing about this work is that these drugs have been linked with a novel nano co-polymer and used in the treatment of breast cancer, and they gave amazing results in inhibiting the spread of breast cancer and Treating and healing the affected cells. The most effective in inhibiting the spread and treatment of breast cancer in infected cells was obtained by the drugs bound with the nano co-polymer as shown below.

C8>C11>C13>C5>C6>C7>C17

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 the 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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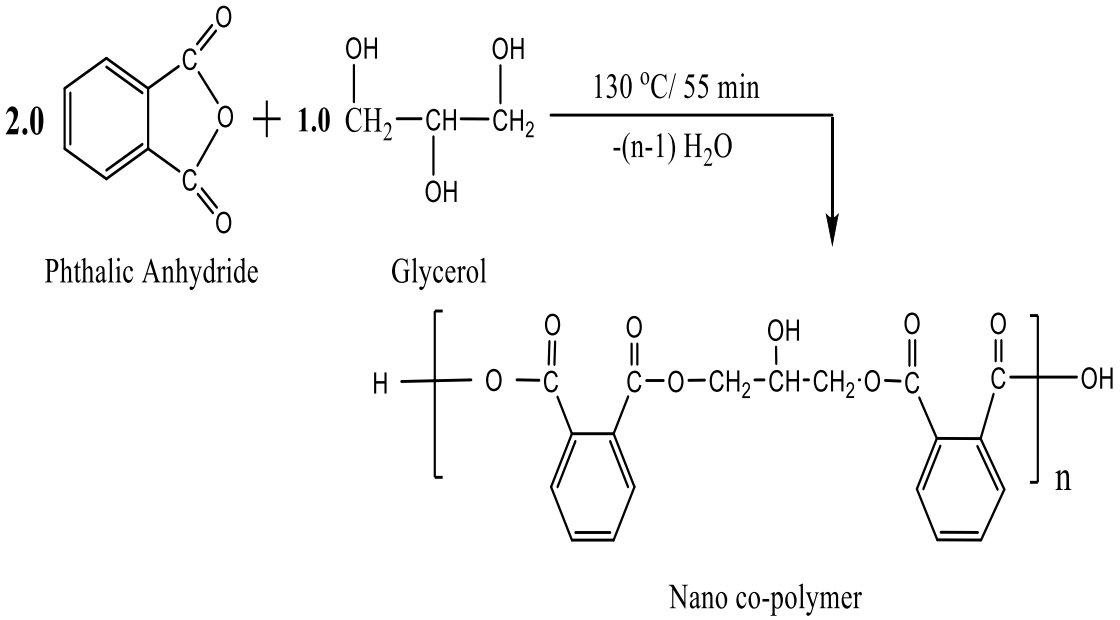
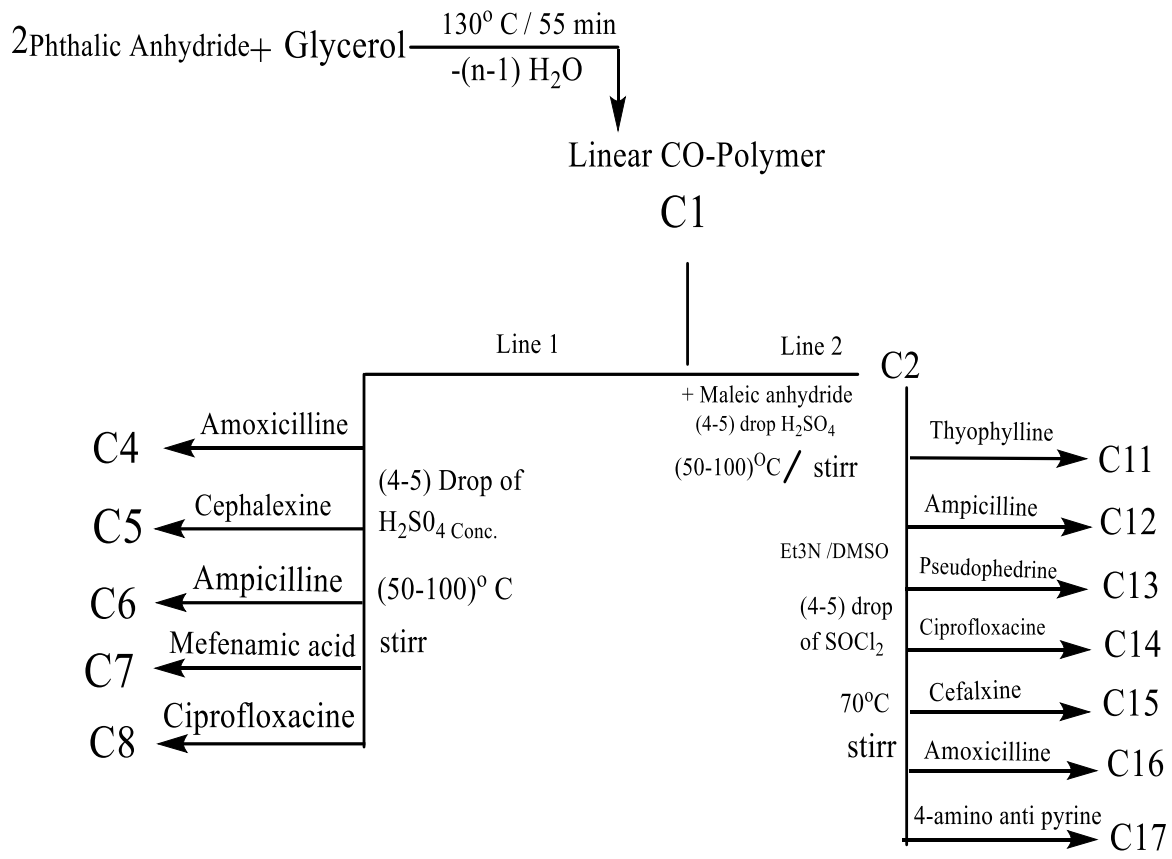
الخلاصة

في هذا العمل ، تم تصنيع بوليمر مشترك نانوي جديد من تفاعل أنهيدريد الفثاليك مع الكليسرول لتحضير البوليمر الخطي عند ١٣٠ درجة مئوية ، كما في المخطط التالي . تم تشخيص البوليمر المشترك النانوي الجديد بواسطة التقنيات التالية (FT-IR ، DSC ، AFM ، XRD و TEM.(



(البوليمر المشترك النانوي الخطي)

تم تحضير عدة عقاقير نانو بوليمرية باستخدام أدوية مختلفة (أموكسيسيلين ، سيفاليكسين ، أمبيسيلين ، حمض الميفيناميك 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 ، ٧,٠ و ٨,٠) عند درجة حرارة ثابتة ٣١٠ كلفن كدالة للوقت (الساعة واليوم).

في ثلاثة أوساط UV-Vis باستخدام مقياس الطيف الضوئي (.Abs) تم قياس إطلاق الأدوية حامضية مختلفة (٢,٢ ، ٧,٠ و ٨,٠) عند درجة حرارة ثابتة ٣١٠ كلفن كدالة للوقت (الساعة واليوم).

تمت دراسة النشاط البيولوجي لبعض البوليمرات المشتركة النانوية المرتبط بها الدواء (C5 ، C6، C7 ، C8 ، C11 ، C13 و C17) من خلال دراسة تأثيرها في تثبيط انتشار سرطان الثدي. و قد لوحظ انخفاض قيمة IC50 بشكل ملحوظ في (C8 IC50 = 16.83) مقارنة بالعقاقير النقية ومسار قتل الخلايا المبرمج المستحدث.

جمهورية العراق
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قسم الكيمياء

تحضير بوليمرات مشتـــــركة نانوية واستعمالها كنظام ناقل للدواء

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

من قبل

امل فليح حسن الشمري

بكالوريوس كيمياء / جامعة كربلاء (2013)

إشـــــراف

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2020م **1442 هـ**