Republic of Iraq
Ministry of Higher Education
And Scientific Research
University of Karbala
College of Education for pure Science
Department of Chemistry

Synthesis of New Co-Polymers Based Maleimide As Drug delivery System and Study their Anti Cancer Activity

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

By

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2018 A.D. **1440 A.H.**

بِســـمالله الرحمـــنِ الرّحِيـــمِ

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

صدق الله العلي العظيم

سورة النساء:الآية (١١٣)

Supervisor Certification

We certify that this thesis (**Synthesis of New Co-Polymers Based Maleimide As Drug delivery System and Study their Anti Cancer Activity**)was papered under oursupervision in the Department of Chemistry-College of Education for Pure Sciences/University of Kerbala, in partial fulfillment of the requirements for the degree of Master in Chemistry Sciences by the student (**Fatimah Abdul RazzaqMageed**).

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Scientific Evaluation Report

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Acknowledgements

*All praise to **Allah** for giving me the inner strength and good health for completing thisthesis. I would like to express my sincere gratitude and appreciation to my supervisors Prof. Dr. **Mohammad Nadhum AL-Baiati** and Assist. Prof. Dr.**Mohanad Mousa Kareem AL-Hachamii** for putting in this research plan and their valuable guidance and help throughout the course of this study. In addition, I would especially like to express my deep appreciation to them for their kindness, patience and understanding through difficult times that I went through during the study period.*

*I would also like to express my deepest gratitude to the Head of Chemistry Department Prof.Dr.**Hamieda Edan Salman** for her kindness, interest, encouragement and guidance throughout the course of this project.I also express my deep appreciation and gratitude to the Deanery of the College of Education and Department of Chemistry, University of Karbala.*

I also express my deep appreciation and gratitude to the Deanery of the College of Science and Department of Chemistry, University of Babylon.

Special thanks to Dr. Saadon Abdullah, Dr. Faris H. Mohammad and Dr. NourAbdAlrazzak Department of Chemistry, University of Babylonfor their continuous help and faithful support and advice during my study.Also, I would like to express my gratitude to Assist.Prof.Dr.Majid Sakhi Jabir, Applied science department, University of technology for his assistance in the biological activity.

Furthermore, Iwould like to give my indebtedness to my wonderful family: My mother, father, brothers and sisters for their patience, support and enthusiastic encouragement during this research.

Last but not least, I would like to express my thanks to all my friends, colleagues who helped me in one way or another in the fulfillment of thiswork, to those who indirectly contributed in this research, your kindness means a lot to me. Thank you very much.

Fatima

Dedication

To the custodian of Grace and kindness…

For the life companion and the passionate one…

The owner of the AL- Zahra state and the aspect of generosity …

He, whobestows His Grace to the creation Imam al- Hajjah bin Al- Hassan " (aj) "……

Fatima

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Scientific Evaluation Report

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الخلاصة :

في هذا العمل ، تم تحضيرخمسة مونومرات دوائية معوضة جديدة وبوليمرات جديدة متجانسة وغير متجانسة محملة بالدواء حيث تكون ذات خواص طبية لغرض تنظيم تحرر الدواء.

تضمن البحث المسارات التالية :-

المسار الاول: تتضمن الخطـــوة الأولى تحضير حامض ماليميك (F1) عن طريق تفـاعل أنهيدريد ماليـك مع ٤- امينو حامض بنزويك. ثم تم تحويل المركب (F1) إلى مشتق كلوريد الأسيل (mF1) والذي فوعل مع ادوية أمينية مختلفة (سلفادزين، كلورورديازيبوكساید، باراسيتامول، ثيوفيلين ، سودافدرين) لتنتج المونومرات (F2-F6).

المسار الثاني:حضرت البوليمرات المتجانسة (F7-F11) من خلال تفاعل البلمرة للجذورالحرة للمونومرات (F2-F6) تحت النيتروجين باستخدام (MEKP) بادئاً للتفاعل.

المسار الثالث:حضرت البوليمرات غير المتجانسة (F12-F16) من خلال تفاعل البلمرة للجذور الحرة للمونومرات (F2-F6) بشكل منفصل مع حمض الأكريليك تحت النيتروجين باستخدام (MEKP) بادئاً للتفاعل.

المسار الرابع: جميع هذه المونيمرات والبوليمرات المحضرة شخصت بوساطة تقنيات TF-IR ، ^{1}H-NMR ، ^{13}C-NMR. تمت دراسة التحرر الدوائي المحكم والانتفاخ في قيم pH مختلفة في درجة حرارة ٣٧ درجة مئوية . تم قياس اللزوجة الجوهرية عند ٢٥ درجة مئوية باستخدام مقياس استوالد ودرست خاصية قابلية الذوبان لهذه البوليمرات، تمت دراسة بعض الخواص الفيزيائية للمونيمرات والبوليمرات المحضرة .

المسار الخامس: تحليلات السمية الخلوية والاكسدة

درست خصائص الفعالية البايولوجية لقسم من البوليمرات الدوائية المحضرة حيث تم تقييم تأثير مكافحة التكاثر للبوليمرات الدوائية المحضرة F7 ، F9 و F12 ضد خطوط الخلايا سرطان الثدي. استناداً إلى تحليلات السمية الخلوية ، يمكن الاستنتاج أنF7 ، F9 و F12 قد تكون استراتيجية مناسبة وواعدة لتطوير

Abstract

In this work, five new drug substituted monomers and their new homogenous and heterogeneous polymers were synthesized which loaded with medical properties to extended the controlled drug.

This work included following lines:

First line:

The first step includes preparing Maleimic acid (F1) via reaction of maleic anhydride with 4-aminobenzoic acid, then compound (F1) was converted to its corresponding acylchloride derivative(mF1) which reacted with different amino drugs such as (Theophylline, Chlorodizepoxide, Pseudoephedrine, Paracetamol , Sulfadizine) afforded (F2-F6) monomers.

Second line:

The homogeneous polymers (F7-F11) were synthesized through the polymerase reaction of the free radicals of the monomers (F2-F6) under the nitrogen using (MEKP) as initiator.

Third line:

The heterogeneous polymers (F12-F16) were introduced through the polymerase reaction of the free radicals of the monomers (F2-F6) separately with the acrylic acid under nitrogen using (MEKP) as initiator.

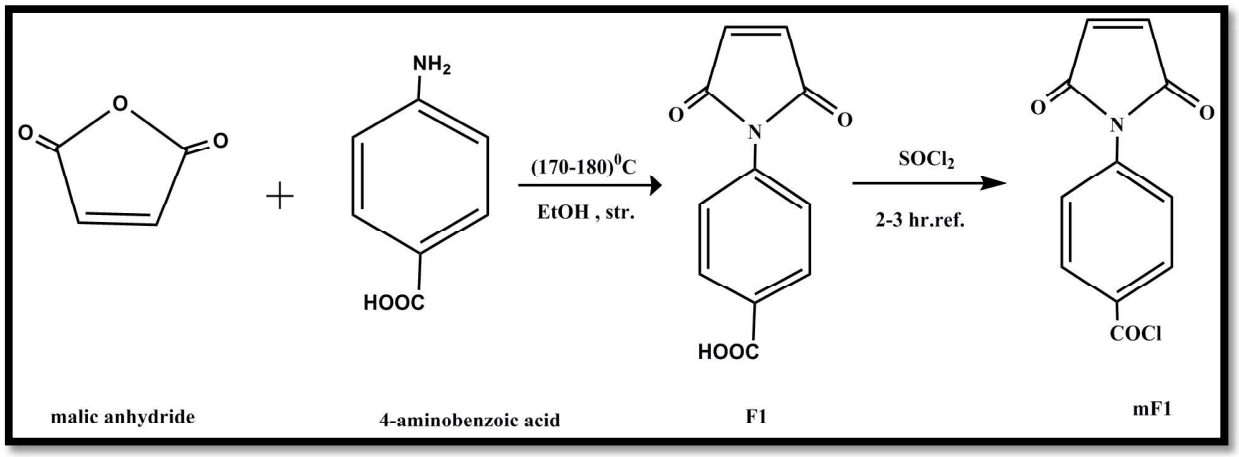
Forth line:

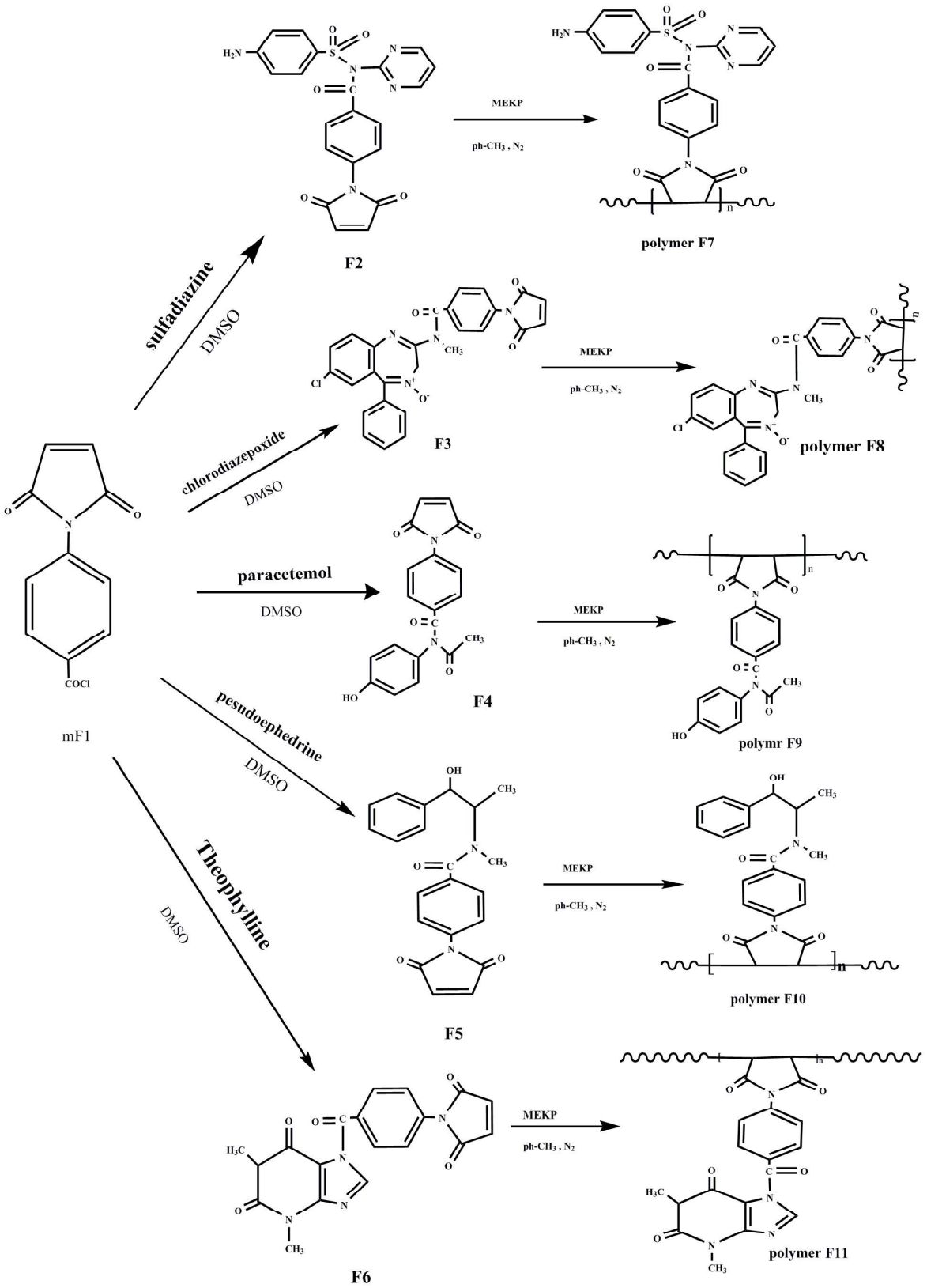
All of these monomers and polymers are characterized by FT-IR, ^{1} H-NMR and ^{13}C-NMR spectroscopies. Drug release under control and swelling were studied at different pH values at 37 °C. The viscosity was measured at 25 °C using the Ostwald viscosity scale and applied the solubility properties of these polymers. Some of the physical properties of all monomers and polymers were studied.

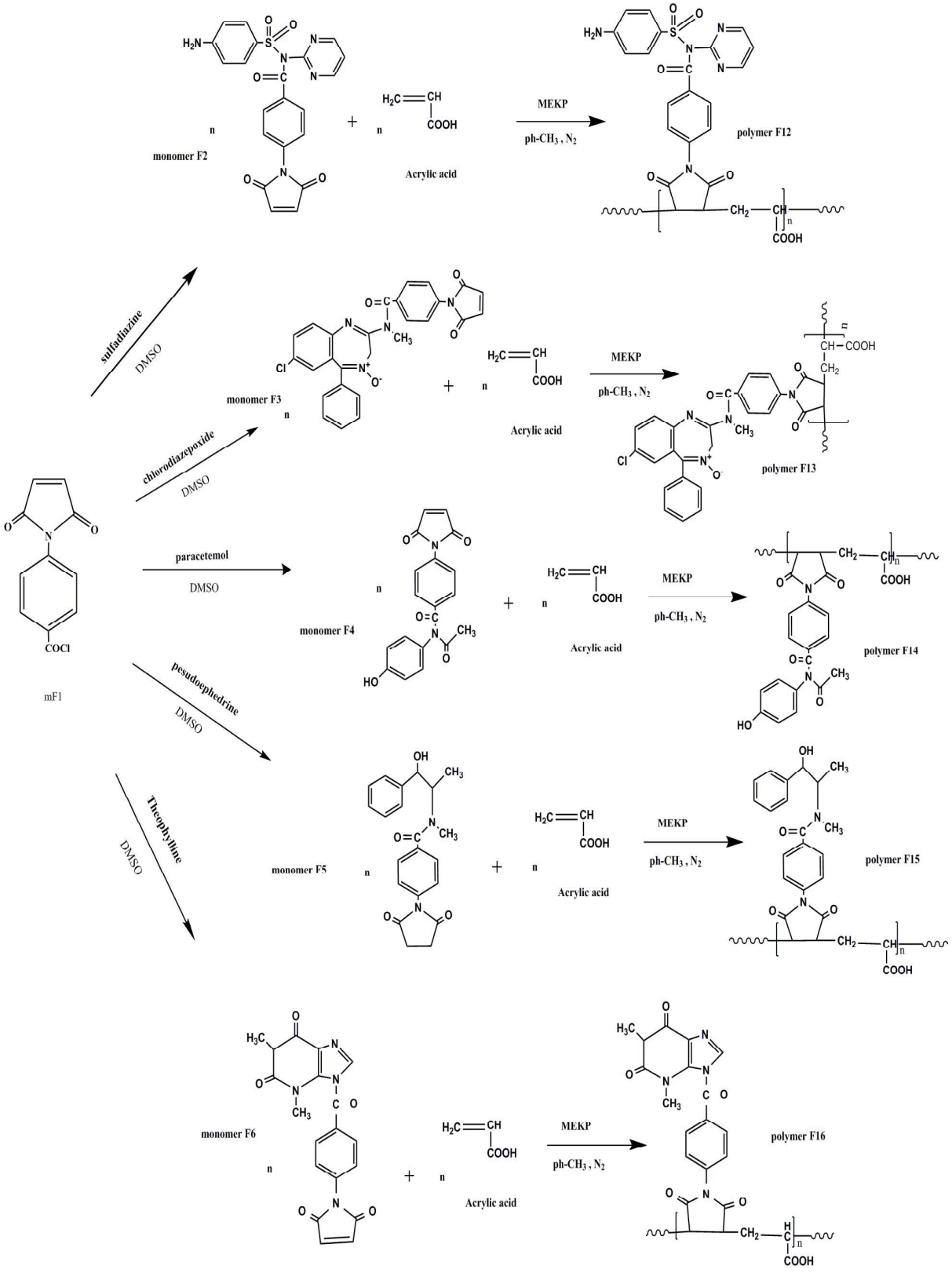
Fifth line: cytotoxicity and antioxidant analyses

The properties of biological activitywas studied.The anti-proliferating effect of drug-loading F7, F9 and F12 against the breast cancer cell lines was evaluated. Based on cytotoxicity analyses, it can be concluded that F7, F10 and F15 may be an appropriate and promising strategy for developing effective drug delivery system to clinical application against breast cancers.

The results of antioxidant agreed with the findings that indicated F10, F15, and F16 enhanced antioxidant activity of drugs. The enhanced antioxidant activity of modified drugs could be attributed to the enhanced solubility and dissolution rate.The following schemes were illustrated the summarized synthesis lines:-




sulfadiazine
DMSO
chlorodiazepoxide
DMSO
paracetemol
DMSO
pesudoephedrine
DMSO
Theophylline
DMSO
mF1
COCl
F2
F3
F4
F5
F6
MEKP
ph-CH3 , N2
polymer F7
polymer F8
polymr F9
polymer F10
polymer F11


monomer F2
Acrylic acid
MEKP
ph-CH3 , N2
polymer F12
sulfadiazine
DMSO
monomer F3
chlorodiazepoxide
DMSO
Acrylic acid
MEKP
ph-CH3 , N2
polymer F13
mF1
paracetemol
DMSO
monomer F4
Acrylic acid
MEKP
ph-CH3 , N2
polymer F14
pesudoephedrine
DMSO
monomer F5
Acrylic acid
MEKP
ph-CH3 , N2
polymer F15
Theophylline
DMSO
monomer F6
Acrylic acid
MEKP
ph-CH3 , N2
polymer F16

List of Abbreviations	
Symbol	**Description**
EtOH	Ethanol absolute
FT-IR	Fourier Transform Infra red
Et_3N	Triethyl ammine
m.p	Melting points
$\eta_{pol.}$	Viscosity of polymer
$\eta_{d.w}$	Viscosity of water
T	Temperature
$d_{pol.}$	Density of polymer
$d_{D.W}$	Density of water
UV-Vis	Ultraviolet-visible
^{1}H-NMR	Proton nuclear magnetic resonance
^{13}C-NMR	Carbon nuclear magnetic resonance
DMSO	Dimethyl sulfoxide
MEKP	Methyl ethyl ketone peroxide
MCF-7	Michigan Cancer Foundation
RPMI	Roswell Park Memorial Intitute
DPPH	2,2-diphenyl-1-picryl hydrazyl
Vit:C	Ascorbic acid
MTT	3-(4,5-dimethylthyazol-2-yl)-2,5-diphenyltetrazoliumbromid

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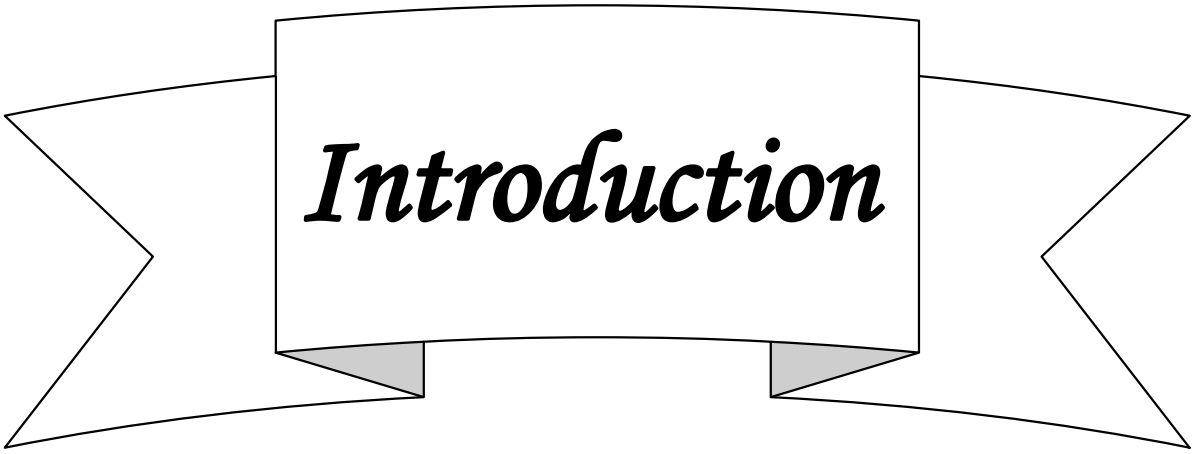
Chapter one



Many drugs have different problems such as poor solubility, low stability, shorted time of circulation, and non-specific toxicity limiting their therapeutic efficacy. Biopharmaceuticals such as nucleic acids, peptides, and proteins are often limited by poor stability and rapid clearance from the body. The materials and strategies of drug delivery aren't wide obtainable to those outside the field of polymer synthesis.The purpose of effective drug delivery is improving the pharmacokinetics and therapeutic to enable drug delivery to the proper place. Drug polymers techniques such as encapsulation, compression, spray and immerse coating, have been used in the pharmaceutical industry as bioactive agents with polymers [1].

1.1. The drug polymers

Functional polymers used in medicine and has been attract attention through the past two decades. Polymers as biomaterials have different applications such as artificial organs, components of medical devices, tissue engineering and dentistry. 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 (eg. proteins, genetic materials, etc) pharmaceutical agents [2].The synthetic polymers with biological materials can also be positive and desirable, the Increasing attention has been growing to development of systems to deliver drugs for long time period at controlled rates [3].

Some characteristics paid attention on the synthesis of bioactive polymeric materials, where the drug bounding to a polymer via covalent linking. For example , chlorompheniсol was attached to a methacrylic by an acetal function group and then by heteropolymerization with 2-hydroxyl methacrylate give the copolymer [4] .Restriction of a drug to polymer may prolong the activity of the drug. The purpose of various polymeric drug systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time, by traditional tablets or injections, the drug stage in the blood follows the profile shown in Figure (1-1).The drug stage rises after each administration of the drug and then decreases until the next administration.

Controlled drug delivery systems are designed for long period administration, the drug stage in the blood follows the profile remaining constant between the desired maximum and minimum, for an extended period of time as shown in Figure (1-2) [5].

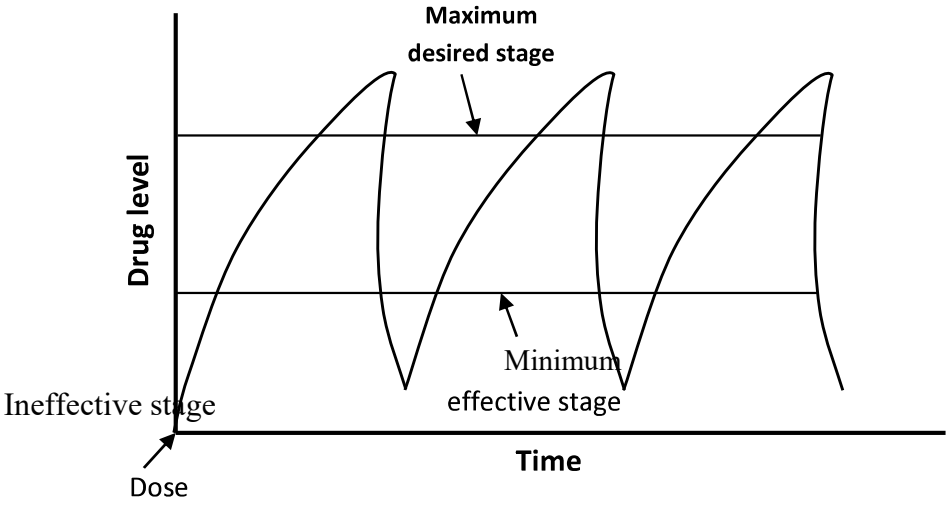


Figure (1-1): Drug level in blood with traditional drug doses.

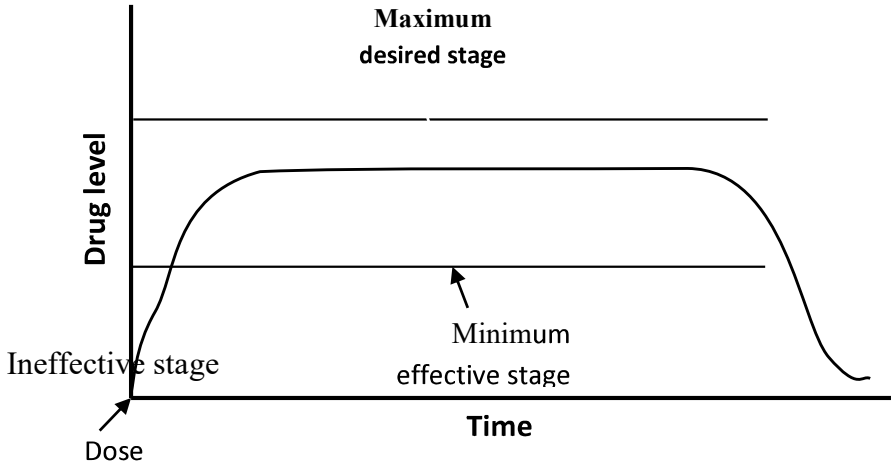


Figure (1-2): Drug level in blood with controlled delivery doses.

delivery of drugs at a sustained rate, targeted delivery of drugs at specific sites to minimize toxicity and enhance selectivity for certain antitumor agents, as well as macromolecular pro-drugs with polymers acting as carrier molecules [6,7].There have been important advancements in the area of polymeric drug delivery system including commercial products. The important point is that blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value where the drug is no longer effective [8].

1.2. Drug carriers

Desirable properties such as sustained therapy, prolonged activity, slow drug release, as well as decreased drug metabolism and excretion are the main reasons for the development of polymeric-drug carriers. Ringsdorf had been developed a model for pharmacologically active polymer-drug carriers [9] , Figure (1-3).

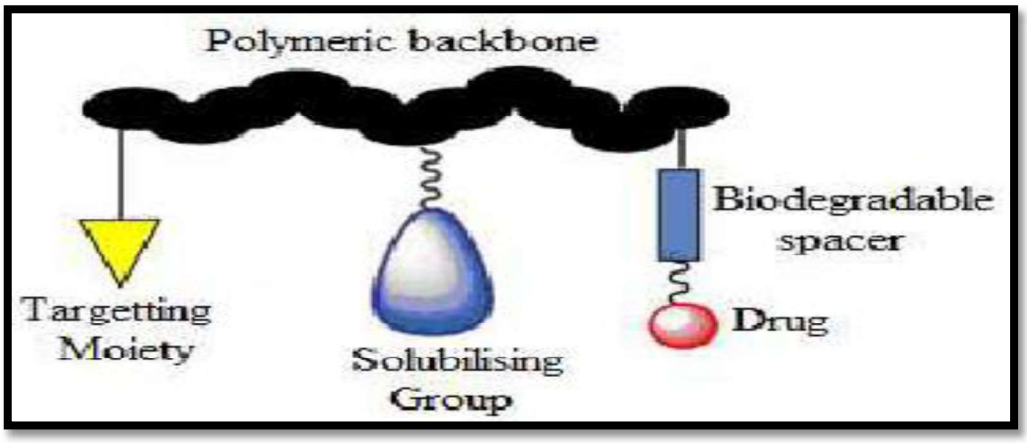
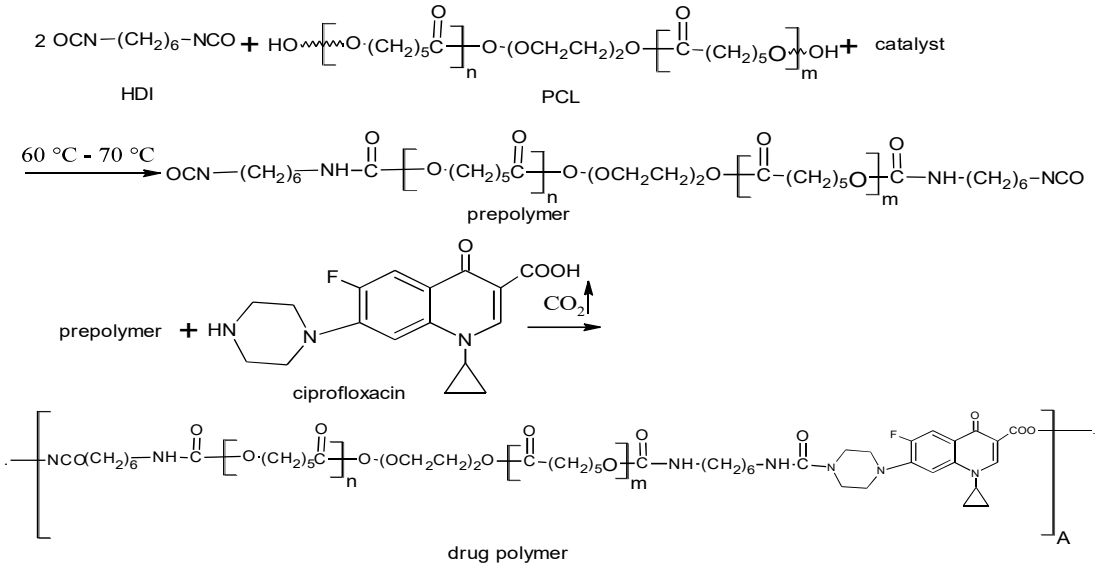


Figure (1-3): Ringsdorf's model of polymer drug carrier

Four different groups were attached to a biostable or biodegradable polymer backbone. This system includes, one group is the drug, the second is a spacing group, the third is a transport system, and the fourth is a group to solubilize the entire biopolymer system. The drug is the agent that appears the physiological response in the living system. It can be attached permanently by a stable bond between the drug and the polymer, or it can be temporarily attached and removed by enzymatic or by hydrolysis process. The delivery systems for these soluble polymer-drug carriers can be made specific for certain tissue cells. Solubilizing groups, such as amines,carboxylates, and sulfonates, are added to increase the hydrophilicity of the polymer system in aqueous media. while large alkyl groups adjust the solubility in lipid regions. Another important role for a polymer-drug carrier is to move the drug away from the polymer backbone of other group so that there is a minimal structural interference with the pharmacological action of the drug [10,11] . Scheme (1-1) show a model of drug polymer was synthesized using 1,6-hexanediisocyanate (HDI) , polycaprolactonediol (PCL) , and afluoroquinolone antibiotic, Ciprofloxacin [12].



Scheme (1-1): drug polymer carrier model

various agents have been bound via degradable linkages to many different polymeric systems is to increase the therapeutic efficiency of bioactive agents, while decreasing their toxicity, It involved their chemical attachment to synthetic or naturally occurring macromolecular[13]. That systems could be designed that they would undergo hydrolysis or enzyme-catalyzed cleavages when placed in the body, so as to release the agent at a predetermined rate [14].

Two different synthetic routes have been employed in the preparation of polymers that contain drug pendent substituent. At first the active agent is converted to a polymerization able derivative that is subsequently polymerized to afford the macromolecular combination. Second bioactive agents have also been chemically bound to performed synthetic or naturally occurring polymers by allowing them, or one of their derivatives, to react with polymers functional groups. An alternative to the direct drug-polymer linkage is the incorporation of a spacer group between the drug and polymer chain, which in general is oxyalkyl segments. The use of suitable spacer arms can increase the mobility of drug on the polymer chain and enhance the sensitivity of conjugates to undergo chemical or enzymatic hydrolysis [14,15].

DDS used to improve the therapeutic efficiency and safety of drugs by delivering them at a rate dictated by the needs of the body over the period of treatment, and to the site of action, which may reduce size and number of doses, side-effects, and biological inactivation and/or elimination [16].Both biodegradable no degradable polymers used as drug carriers basically in two different forms; namely, inject able systems and implants [17].An ideal

polymeric carrier system for use in intravascular systems is expected to be[18]:

(1) blood-compatible (does not cause undesirable events e.g., thrombus or emboli formation, complement activation);

(2) Circulate in the blood stream without causing embolization at capillaries.

(3) Escape from excretion in the kidneys.

(4) Release the drug, preferentially at the target area and a desired rate.

(5) Degrade in vivo during or after drug release.

Bioactive polymers which active pharmaceutical ingredients are relatively development [19]. These polymers offers many advantages over low molecular weight agents as potential therapeutic agents. The benefits may include greater specificity of action,lower toxicity, and enhanced activity due to multiple interactions. Some of the underlying concerns include the polydispersity in molecular weight, and compositional heterogeneity that could development to fcomplicate process. The high molecular weight characteristics of polymers, these potentially limiting pharmacological characteristics of polymers can in fact be exploited to design and develop therapeutic agents for disease conditions where low molecular weight drugs have either failed or produced inadequate therapeutic profiles [20,21].

Delivery of drugs as controlled release technology started in the 1970 Polymers have played aimportant role in the improvement of controlled release systems on the application of biocompatible and biodegradable polymers [22].These applications requiredfor development of new technologies to prepare nano-sized biodegradable polymeric particles for providing a new function to drug delivery systems [23-28]. Microspheres with DL-lactide/glycolide copolymer (PLGA) and poly(lactic acid) (PLA) have been already developed to extend the therapeutic effect of peptide drug [29-31]. However, their sizes were too large to direct the drug to target tissues across the mucosal membrane or via systemic circulation. Block or graft copolymers can form micelles in selective solvents. The good solvent for one component of the block or graft copolymer and a precipitant for the other component, amphiphilic

copolymers will aggregate to form micelles, i.e. particles with an insoluble swollen core surrounded and stabilized by a sheath of soluble chains [32-38]. For the preparation of micelles in water, PEG is often used as the hydrophilic block in block copolymer.

Cerraietal.[39], prepared tri block copolymers of PEG capro lacton due to di block copolymers form micelles are easier than the triblockcopolymers.Cerrai et al. have also proved the improved efficiencies of non-catalyzed di block copolymeric nano spheres composed of MePEG and poly(caprolactone) [39]. Poly(caprolactone) is also crystallisable due to the stereo regular. Poly(caprolactone) chains have been studied for biodegradable and biocompatible nano-spheres with controlled hydrophilic/hydrophobic balance [40,41].Catalysts used to activate the reaction in the synthesis of most biodegradable polymers, many researchers [42,43]. For the application of biomedical polymers in contact with body, a small amount of the catalysts remained they could cause a lot of complications in the physiological environments.

To achieve a long blood circulation half-life, Poly(lactic acid) (PLA) and a poly(ethylene glycol) (PEG) areknown to be biodegradable and meets the requirement for this purpose [44,45]. They are chosen as the hydrophilic segment, It is known to impart protein and cellular stealth properties to surfaces and interfaces, and has a nontoxic nature [46]. Moreover, the biodegradability of PLA might be enhanced by copolymerization of PEG and DL-lactide. The molecular weight of PEG is important, PEG with low molecular weight (i.e. less than 3.0×10^3g/mole) is known to be cytotoxic in the body[47] Therefore ,MePEG with a molecular weight of 5.0×10^3used which is different from the previous study of Tanodekaew et al.[40]. On the prepared diblock copolymer using DL-lactide and EO monomers and the remaining EO monomer has a potential harm for human beings because of its toxicity.This is a continuing study[40,41] on biodegradable nano-spheres prepared using block copolymer synthesized without catalysts [48].

A variety of functional polymers have been used to conjugate therapeutic proteins, with the selection of polymers requiring stringent criteria. The polymers need to be nonantigenic, biocompatible, and intrinsically non denaturing to the ward the therapeutic protein. A

number of reactive polymers including copolymers of maleic anhydride with divinylether and styrene, poly(vinyl alcohol), poly (vinylpyrrolidinone) , and poly(ethylene glycol)(PEG) have been utilized for this purpose [49].

Veronese et al. have prepaerd novel drug-containing polymeric devices with; degradation times appropriate for pulmonary drug delivery(thereby reducing polymer build-up in the lung upon repeat administration);improved surface chemistries to optimize aerodynamic performance (thereby increasing delivery efficiency); and properties that reduce particle clearance rates in the deep lung (thereby increasing drug delivery duration).A countless number of drugs could potentially benefit from controlled delivery via the lung, including many hormones, cytokines, asthma medications, insulin, vaccines, genes and more [50].

1.3. The pro-drug concept

Albert [51] was the first one suggested the concept of pro-drug approach for increasing the efficiency of drug. He described pro-drugs as pharmacologically inactive chemical derivatives that could be used to alter the physicochemical properties of drugs, in a temporary manner, to increase their usefulness or to decrease associated toxicity. Therefore, pro-drug can be defined as a drug derivative that undergoes biotransformation enzymatically or no enzymatically, inside the body before exhibiting its therapeutic effect. The pro-drug is converted to the original drug as soon as the derivative reaches the site of action, followed by the rapid elimination of the released derivative group without causing side effects in the process (Figure 1.4)[52].

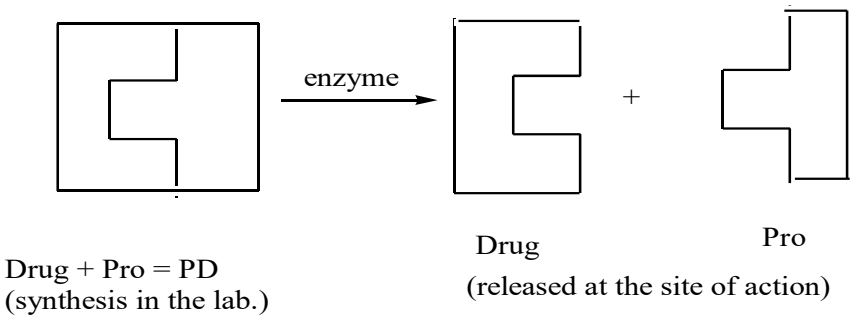
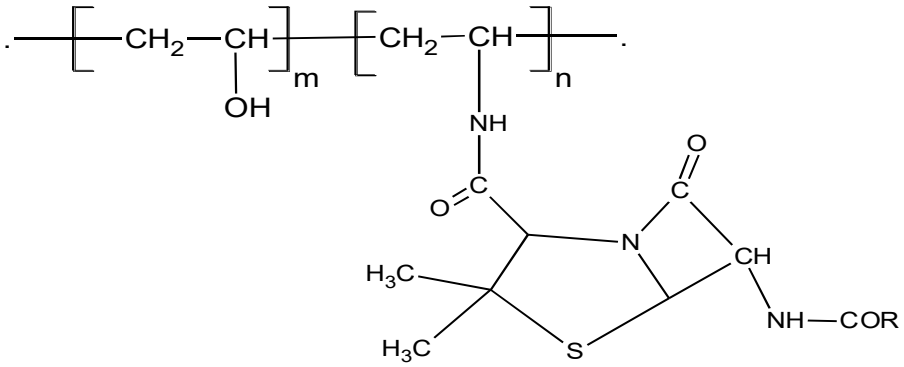
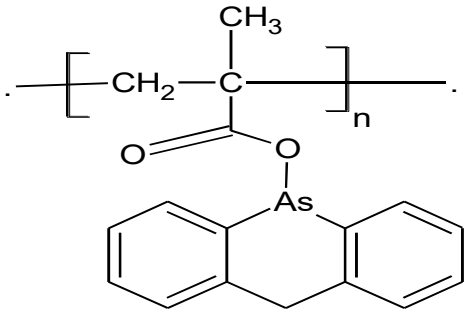


Figure (1-4): Enzymatic or chemical transformation of inactive pro-drug (PD)to active drug(D) at the site of action.

Methacrylic derivatives proposed as a carrier monomer for salicylic acid[53]. Antibacterial agents bound to polymeric carrier investigated early as 1968 by Ushakov and Panarin [54]. Elucidate that derivatives of penicillin bound to a copolymer of vinyl alcohol and vinyl amine (2%) units, shows an activity which is 30-40 times longer lasting in comparison of the free penicillin.



Poly(methacryloyloxyphenoarsine)is a type of series of examples of the in vitro activity of polymeric antibacterial, since such preparations are also applied as protection of polymeric materials against bacterial attack or as pesticides [55].



Mori [56] synthesized two acrylamides containing proline and hydroxyprolinemoieties.The acrylamides were polymerized by reversible addition fragmentation chain transfer polymerization to yield amino acid based polymer with thermo-responsive properties.

1.4. Biomedical polymers

To choose a polymer for use in biomedical application, the physical properties are requiredmust specified by the scientist. Design parameters are based on athorough understanding of the physiological functions and

conditions under which the device must operate. [57].polymer that be used in biomedical device, it must have the appropriate mechanical properties, can be consulted to identify potential commercial materials that have a minimum of the required physical properties [58].

A reliable and reproducible source of polymer must be assured before a material is selected for a device. Quality control in biomedical manufacturing is more critical than in other fields. Especially, for materials that will have direct contact with body tissue and fluids. Biomedical polymers should not be adversely affected by the normal physiological environment. No biodegradation that could compromise function over the short or long term should occur, and no process should release toxic products to the environment. No changes should take place in the bulk polymer that would alter its mechanical properties; for example, crystallization, embrittlement, or plasticizing may result from oxidation, absorption of biological compounds (eg, proteins, lipids),deposition of inorganic material or in growth of tissue, resulting in impaired function. Surface morphology should be stable; this is particularly important in inter facially sensitive applications, as in blood. The physiological temperature, ie, 37°C, may accelerate these effects over what is seen at room temperature[59].

Adverse biological responses to an implanted biomedical polymer include excessive foreign-body response, thrombogenicity, and immunogenic, anti-leukotactic (predisposition toward infection), and mutagenic or carcinogenic responses [60] .Several biomedical applications require polymer systems with unique properties, such as diffusion properties in membranes for dialysis, oxygenators,drug-delivery, and contact-lens applications. Also, biodegradation properties for long-term implants and biodegradable applications, including sutures and some drug-delivery system. Metabolic and Digestive Diseases(NIAMDD) has suggested test methods membranes and dialyzer evaluation[59].

The design and preparation of novel bio erodible hydrogels shown in Figure (1-5) developed by free radical polymerization of acrylamide and acrylic acid and some formulations with bis-acrylamide, in the presence of a corn starch/ethylene-co-vinyl alcohol copolymer blend (SEVA-C), is reported for drug delivery[59]. Elvira et al.[61]performed

swelling studies as a function of pH in different buffer solutions to determine the water-transport mechanism that governs the swelling behavior. They performed degradation studies of the polymers in simulated physiological solutions for times up to 90 days, determining the respective weight-loss.

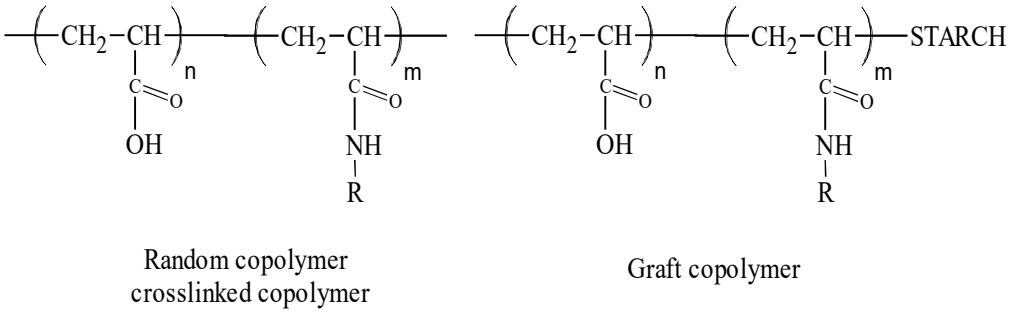
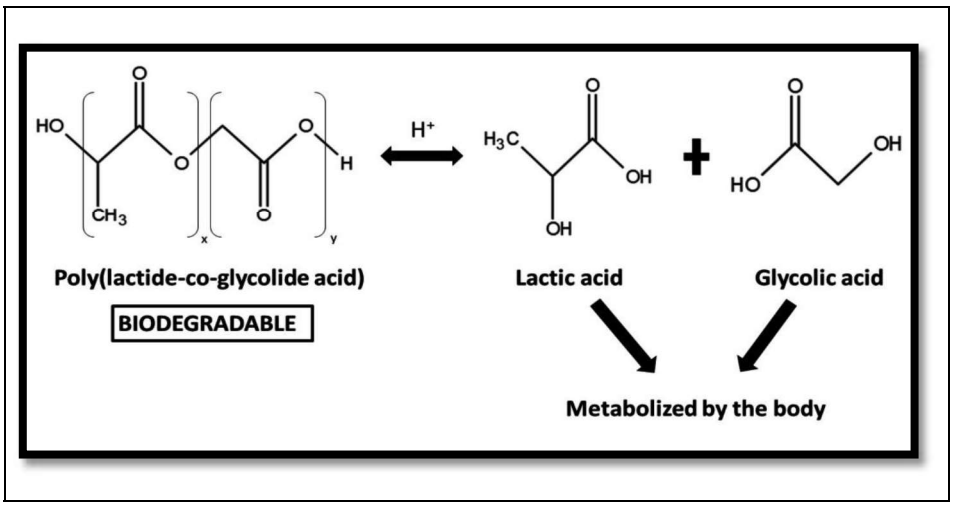


Figure (1-5): corn starch/ethylene-co-vinyl alcohol copolymer blend (SEVA-C)formulations.

The polymer must be designed into the desired form without being degraded or adversely affected in a way that could influence biological performance. The polymer and its surface must not be chemically altered,(eg.oxidized), contaminatedor physically altered(eg. Crystallinity, bulk or surface morphology, or the creation of fabrication-induced stresses) in any adverse manner. For reproducible biological performance, the fabrication technique must allow for process control to obtain reproducible polymer morphology and properties. Biomedical polymers including additives and degradation products should not exhibit toxic or irritant qualities, or elicit adverse physiological responses locally or systemically. The rate of release of the substance, the biological processing and removal of the substance can be affected by toxicity [62,63].

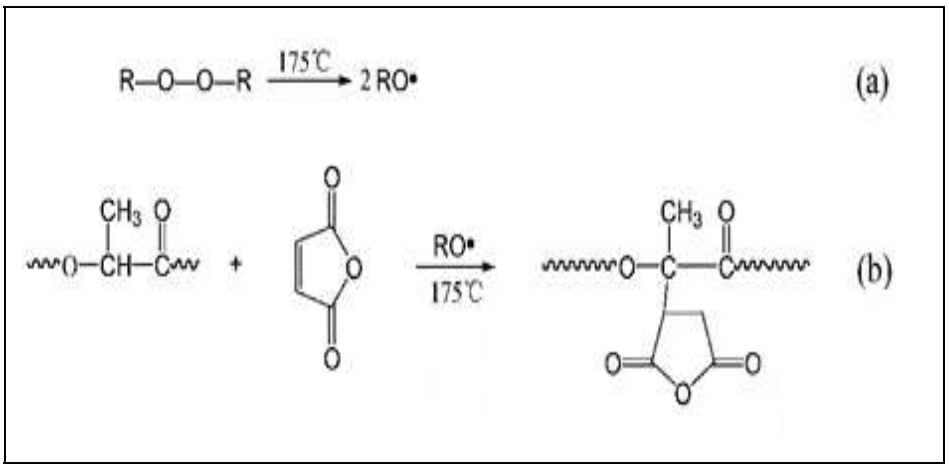
1.5. Synthetic polymer

Synthetic polymers are resistant to biological attack due to their hard structure, low moisture absorption, soft surface, and lack of susceptibility to enzymatic systems. Poly-L-lactic (PLLA) is widely used in tissue engineering, it is synthetic degradable polymer, with good biocompatible properties, PLLA has excellent mechanical character; it is used in the fixation of fractured bones in orthopedic and oral surgeries in the form of plates Equation (1-1).[62].



Equation (1-1) Chemical structure of poly(lactic-co-glycolic acid)

(PLA) is both bio-based and biocompatible, and several favourable properties such as high strength and stiffness at room temperature, PLA is hydrophobic polyester whereas natural materials, such as celluloses, starch, protein, lignin and inorganic fillers, are generally hydrophilic. Blends of PLA with natural additives usually exhibit coarse morphology and poor mechanical performances, due to the lack of affinity .The affinity improved by using a compatibilizer or by the functionalization of PLA chains such as grafting. Maleic anhydride (MA), amide glycidyl methacrylate, *N*-vinylpyrrolidone, PEG and chitosan were grafted onto PLA. MA is popular among these grafting pendants due to its difficulty in homo polymerization and the benefit of cell attachment and proliferation Equation (1-2) [64].



Equation (1-2) Grafting reactions of MA onto PLA chains in the presence of Decimal peroxide.

Biocompatible amphiphilic poly(ethyleneoxide) (PEO) and poly(propylene oxide) (PPO) block structures are in focus for biomedical applications doxorubicin was conjugated to a water-soluble synthetic polymer, *N*-(2-hydroxypropyl) methacrylamide (HMPA) methacylic acid copolymers through a tetrapeptide linker (Gly-Phe-Leu-Gly) . The tetrapeptide linker allowed selective release of the active drug in the tumors through the action of Lysosomal enzymes Fig. (1-6) [65].

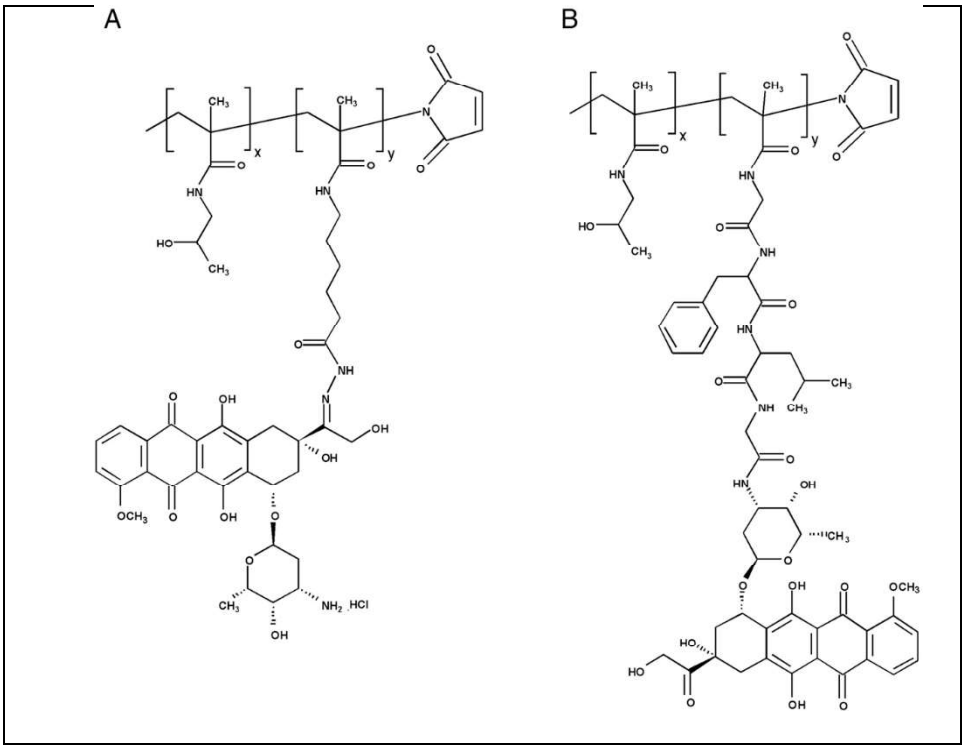


Figure (1-6) Structure of semitelechelic polymer–DOX precursors. (A) Semi telechelic precursor containing DOX attached via amide bond to GFLG spacer.

1.6. Antibiotics:

In 1928, Alexander Fleming made one of modern day medicine's most important discoveries, when he noticed a strange mold present in some old bacteria cultures that had an area surrounding the mold that was bacteria free. He was able to culture the mold and to extract a liquid that was effective at killing a variety of bacteria [66]. He called the compound penicillin since the mold was of the genus Penicillium.After that, Howard Walter Florey and his team abled to show promising clinical results for

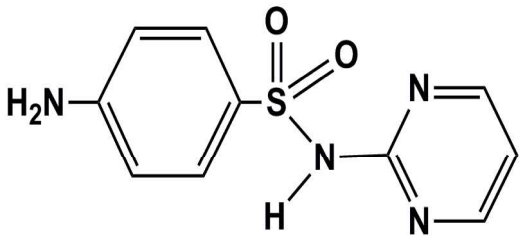
using penicillin in treating infections. In 1942 the new medicine was available for clinical use, with most of the penicillin production occurring in the United States. There are now over 12,000 known antibiotics, 160 of which have been used for human clinical use [66]. Most of classes of antibiotics, their mechanisms against bacteria, and their synthetic methods will be briefly reviewed.

Antibiotics can be categorized based on their mechanisms for killing or slowing down the growth of bacteria. Six major classes have been identified and include: β-lactam, macrolide, quinolones, tetracyclines, aminoglycosides, and glycopeptides [67].β-Lactams kill bacteria by blocking transpeptidase and transglycosylase enzymes. These enzymes play a role in providing a strong peptidoglycan layer in the cell wall of bacteria.A large number of antibiotic-producing strains of streptomycetes have been developed. Other key microorganisms for antibiotic fermentation include : the bacteria, Saccharopoly spores, the mold , Penicilliumchrysogenum.[68],and the fungus, Cephalosporiumacremonium .

The manufacture of some antibiotics, such as cephalosporins, can be accomplished by chemical synthesis. Some of these processes start with an initial reagent from a fermentation broth and the resulting products are called semi-synthetic antibiotics [69].The enzymatic synthetic routes are considered environmentally friendly alternatives to traditional synthesis, because the use of toxic solvents is eliminated. The enzyme penicillin G acylase is used often for the synthesis of β-lactam antibiotics [70].

1.6.1. Sulfadiazine drug.

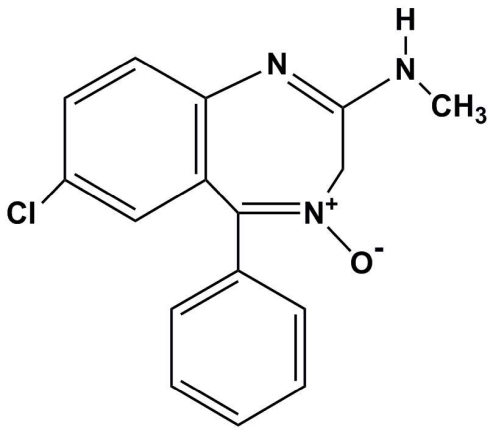
Sulfadiazine is an antibiotic [71], chemistry formula $C_{10}H_{10}N_4O_2S$. It is a second line treatment for otitis media , prevention of rheumatic fever, chancroid , chlamydia and infections by Haemophilusinfluenzae [72].



Sulfadiazine works by inhibiting the enzyme dihydropteroatesynthetase, in combination with pyrimethamine (a dihydrofolatereductase inhibitor), sulfadiazine is used to treat active toxoplasmosis [73].It eliminates bacteria that cause infections by stopping the production of folate inside the bacterial cell, and is commonly used to treat urinary tract infections , and burns.In combination, sulfadiazine and pyrimethamine , can be used to treat toxoplasmosis , a disease caused by Toxoplasma gondii.

1.6.2. Chlorodiazepoxide drug.

Chlordiazepoxide, trade name Librium,chemistry formula$C_{16}H_{14}Cl$ N_3O, is a sedative and hypnotic medication of the benzodiazepine class; it is used to treat anxiety, insomnia and withdrawal symptoms from alcohol and/or drug abuse.

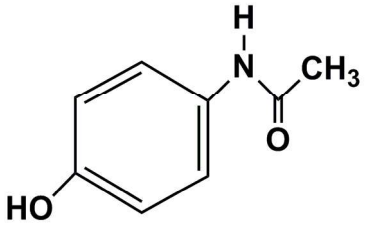


Chlordiazepoxide has a medium to long half-life but its active metabolite has a very long half-life. The drug has amnesic, anticonvulsant, anxiolytic, hypnotic, sedative and skeletal muscle relaxant properties[74].Chlordiazepoxide was discovered in 1959[75]. it was the first benzodiazepine to be synthesized and the discovery of chlordiazepoxide was by pure chance. Chlordiazepoxide is indicated for the short-term (2-4 weeks) treatment of anxiety that is severe and disabling or subjecting the person to unacceptable distress. It is also indicated as a treatment for the management of acute alcohol withdrawal syndrome [76-78]. It can sometimes be prescribed to ease symptoms of irritable bowel syndrome combined with clidinium bromide as a fixed dose medication, Librax[79].

Chlordiazepoxide acts on benzodiazepine allosteric sites that are part of the GABA A receptor/ion-channel complex and this results in an increased binding of the inhibitory neurotransmitter GABA to the GABA A receptor thereby producing inhibitory effects on the central nervous system and body similar to the effects of other benzodiazepines [80-82]. Benzodiazepines act via micromolar benzodiazepine binding sites as Ca2+ channel blockers and significantly inhibit depolarization-sensitive Calcium uptake in animal nerve terminal preparations[83]. Chlordiazepoxide inhibits acetylcholine release in mouse hippocampal synaptosomes in vivo. This has been found by measuring sodium-dependent high affinity choline uptake in vitro after pretreatment of the mice in vivo with chlordiazepoxide. This may play a role in chlordiazepoxide's anticonvulsant properties[84] .

1.6.3. Paracetemol

Paracetamol consists of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the *para* (1,4) pattern [85]. The amide group is acetamide (ethanamide). It is an extensively conjugated system, as the lone pair on the hydroxyl oxygen, the benzene pi cloud, the nitrogen lone pair, the p orbital on the carbonyl carbon, and the lone pair on the carbonyl oxygen is all conjugated.

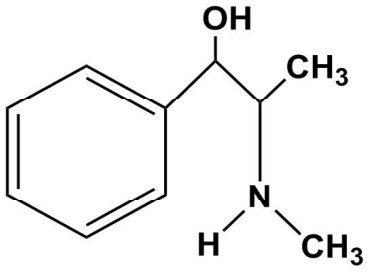


The presence of two activating groups also makes the benzene ring highly reactive toward electrophilic aromatic substitution. As the substituents are ortho, para-directing and para with respect to each other, all positions on the ring are more or less equally activated. The conjugation also greatly reduces the basicity of the oxygens and the nitrogen, while making the hydroxyl acidic through delocalization of charge developed on the phenoxideanion[86].

Paracetemol is a widely used over-the-counteranalgesic (pain reliever) and antipyretic (fever reducer). It is commonly used for the relief of headaches, other minor aches and pains, and is a major ingredient in numerous cold and flu remedies. In combination with opioid analgesics, paracetamol can also be used in the management of more severe pain such as postsurgical pain and providing palliative care in advanced cancer patients The onset of analgesia is approximately 11 minutes after oral administration of paracetamol ,and its half-life is 1-4 hours[87,89].While generally safe for use at recommended doses (1,000 mg per single dose and up to 4,000 mg per day for adults, up to 2,000 mg per day if drinking alcohol) [89,90].

1.6.4. Pseudoephedrine drug.

Pseudoephedrine is a diastereomer of ephedrine and is readily reduced into methamphetamine or oxidized into methcathinone. Pseudoephedrine is a sympathomimetic drug of the phenethylamine and amphetamine chemical classes, chemistry formula$C_{10}H_{15}NO$, It may be used as a nasal/sinus decongestant , as a stimulant , or as a wakefulness-promoting agent in higher doses[91].

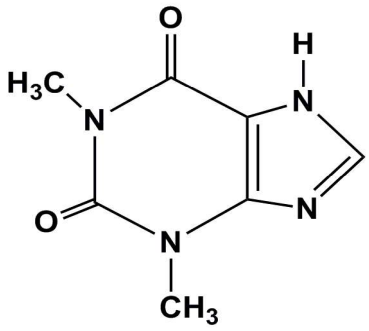


Pseudoephedrine is a sympathomimetic amine. Its principal mechanism of action relies on its direct action on the adrenergic receptor system [92,93]. The vasoconstriction that pseudoephedrine produces is believed to be principally α-adrenergic receptor response [94]. Pseudoephedrine acts on α- and β2-adrenergic receptors, to cause vasoconstriction and relaxation of smooth muscle in the bronchi, respectively [92-94] α-adrenergic receptors are located on the muscles lining the walls of blood vessels. When these receptors are activated, the muscles contract, causing the blood vessels to constrict (vaso-constriction). Thus, by constriction of blood vessels, mainly those located

in the nasal passages, pseudoephedrine causes a decrease in the symptoms of nasal congestion. Activation of β2-adrenergic receptors produces relaxation of smooth muscle of the bronchi [92], causing bronchial dilation and in turn decreasing congestion (although not fluid) and difficulty breathing.

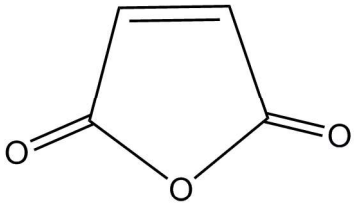
1.6.5. Theophylline drug.

Theophylline, also known as 1,3-dimethylxanthine, is a methylxanthine drug. Chemistry formula $C_7H_8N_4O_2$, 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 (Camellia sinensis) and cocoa (Theobroma cacao). A small amount of theophylline is one of the products of caffeine metabolic processing in the liver[95].



1.7 . Malic anhydride

Malic anhydride is an organic compound with the formula $C_2H_2(CO)_2O$. It is the acid anhydride of maleic acid. It is a colorless or white solid with an acrid odor ,it is produced industrially on a large scale for applications in coatings and polymers [96].Maleic anhydride has very rich chemistry, reflecting its ready availability and bi-functional reactivity. It hydrolyzes, producing malic acid ,cis -HOOC–CH=CH–COOH. With alcohols, the half-ester is generated, eg, cis -HOOC–CH=CH–$COOCH_3$.



Maleic anhydride is a classic substrate for Diels-Alder reactions[97],it was used for work in 1928.The Nobel Prize were awarded in 1950for Otto Paul Hermann Diels and Kurt Alderdue to the reaction between maleic anhydride and 1,3-butadiene, through this reaction that maleic anhydride converted to different pesticides and pharmaceuticals.

Maleic anhydride with active methylene or methine compounds such as malonate or acetoacetate esters in existence of sodium acetate catalyst called Michael reaction .These intermediates were subsequently used for the generation of the Krebs cycle intermediates aconitic and isocitric acids[98].Also**,** Maleic anhydride dimerizes in a photochemical reaction to form cyclobutanetetracarboxylicdianhydride (CBTA). Maleic anhydride is used in the production of polyimides and as an alignment film for liquid crystal displays[99].A number of smaller applications for maleic anhydride,The food industry uses malic anhydride in artificial sweeteners and flavor enhancements. Personal care products consuming malic anhydride include hair sprays, adhesives and floor polishes. Malic anhydride is also a precursor to compounds used for water treatment detergents, insecticides and fungicides, pharmaceuticals, and other copolymers[100].

MA grafted PE is importance for application as a copolymer precursor in polymer blends. The graft of MA onto linear PE poly(PE-*g*-MA) initiated by dicumyl peroxide. Major MA monomers were attracted onto PE chains as branched graft at higher MA content. Also, MA grafted PA, the formation MA copolymer/PA graft by reaction of end amine groups with the anhydride moiety via formation of an imide linkage (Figure 1-7).

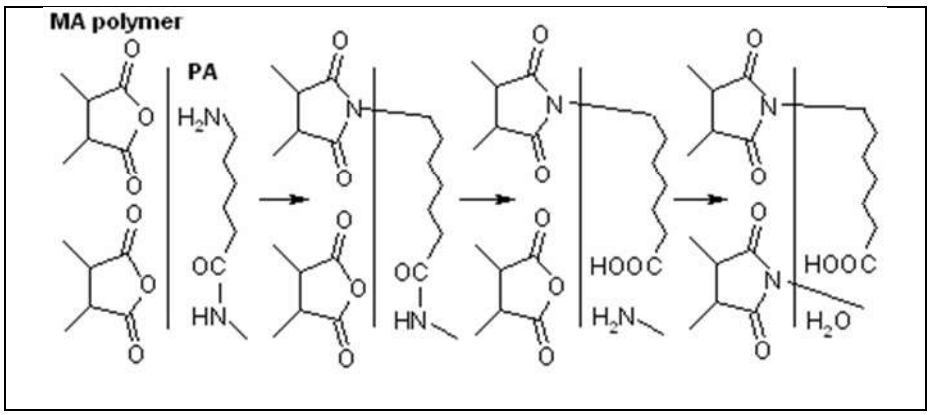


Figure (1-7). The formation MA copolymer/PA graft.

Amic acid formation due to the nucleophilic attack of the amino group on the carbonyl carbon of the anhydride group a reversible reaction leading to opening of the anhydride ring to form an amic acid group the forward rate constant for the reaction is several orders of magnitude larger than the reverse reaction and thus the reaction often appears irreversible if pure reagents are utilized [Fig. 1-8].

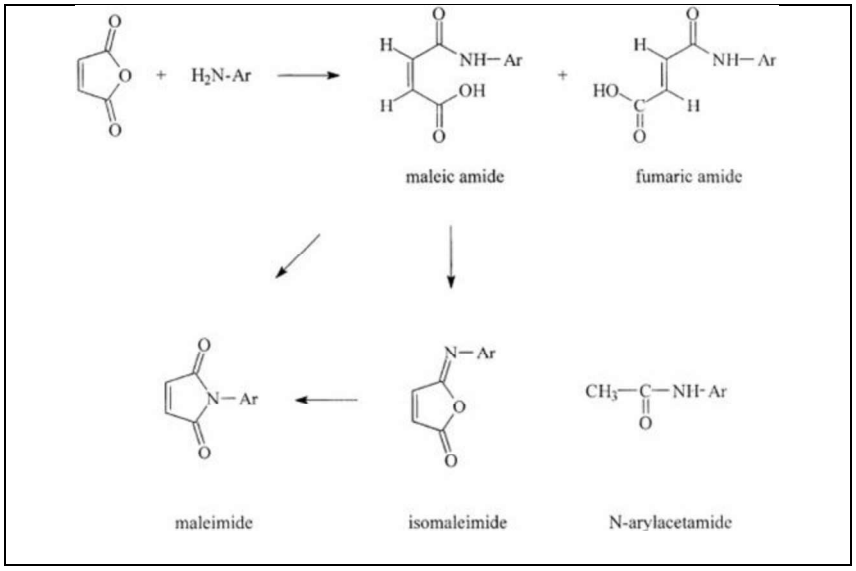
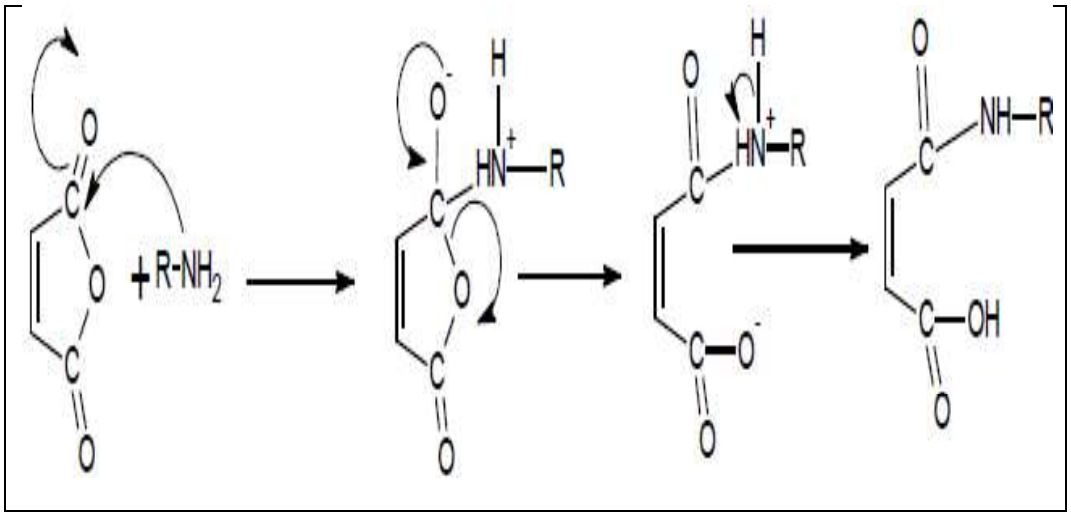


Figure (1-8). Reactions which take place during the maleimide synthesis

Maleic anhydride (MA) was grafted onto polymer backbones in a homogeneous medium using APS as radical initiator. A general reaction mechanism for polymer-maleic anhydride is shown in Scheme 1-4 . At the first step, the thermally dissociating initiator, i.e., APS is decomposed under heating to produce sulphate anion-radical. Then, the anion-radical

abstracts hydrogen from one of the functional groups in side chains (i.e. COOH, NH_2) of the substrate to form corresponding radical these macroradicals initiated monomers grafting onto polymer backbones led to a graft copolymer. Presence of $–NH_2$ group in the antibiotic, which is a strong nucleophile, which attack the C=O group in the cyclic of maleic anhydride. The mechanism of the reaction this reaction was described as a nucleophilic attack of NH_2 group on C=O group, which explained as in[101,102].



Scheme (1-4) ring opening reaction of acid anhydride by nucleophilic reaction.

1.8.Swelling:

1.8.1. Unlimited swelling[103]

It is that process which leads to spontaneous dissolution Figure (1-9). 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”.

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.

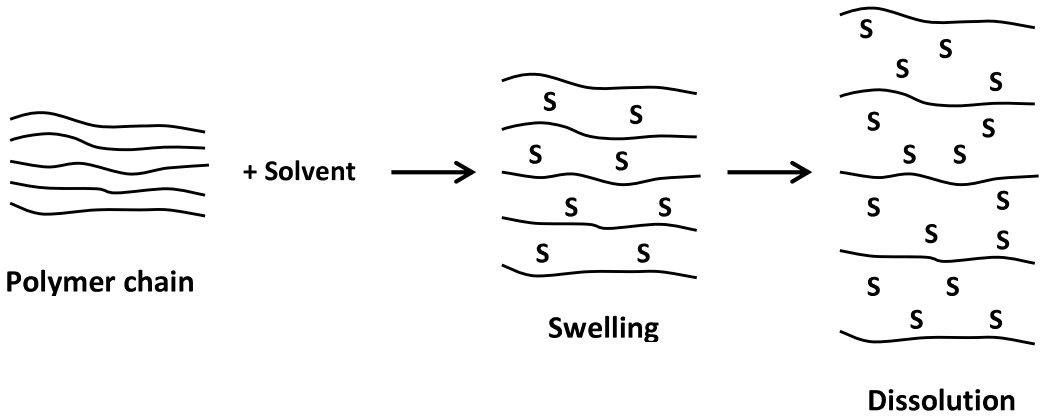


Figure (1-9): Swelling unlimited for some polymers

1.8.2 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 (1-10). Thus two phases are formed, one separated from the solute in the swelling polymer and the other from the pure solute.

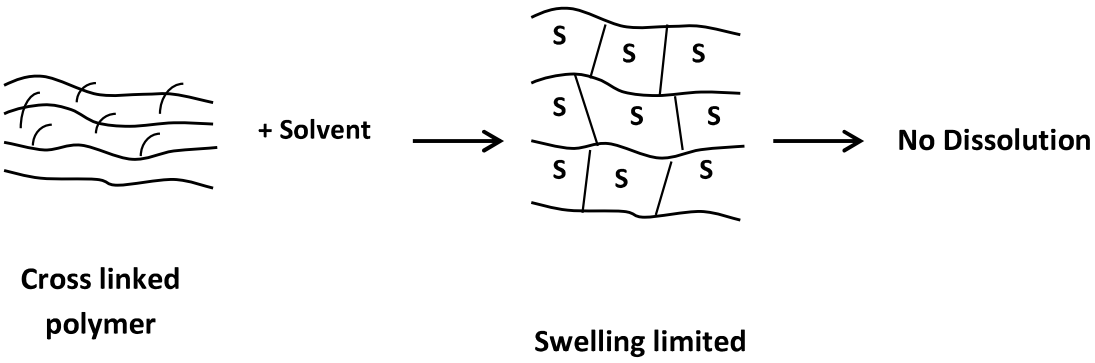


Figure (1-10): Swelling limited for some polymers

1.8.3 Rate and kinetics of swelling[104]

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:

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

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.

From the figure (1-11) 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 (1-11) is greater than the second sample.

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, 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 [104].

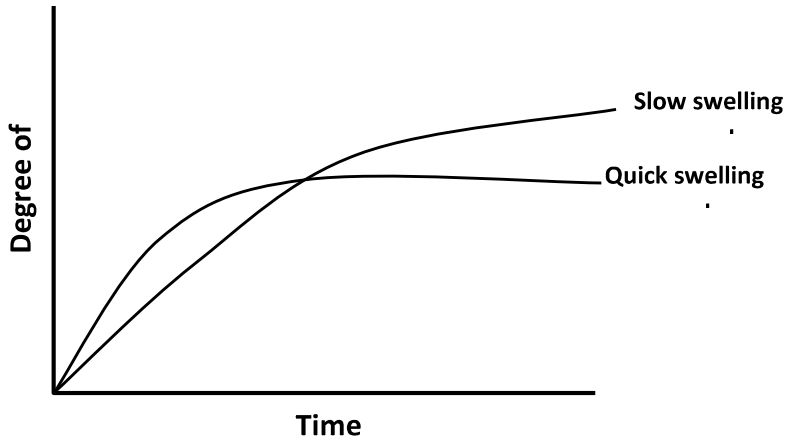


Figure (1-11): Kinetic of swelling

1.9 Biological activity[105,106].

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.

1.10 Anticancer.

Cancer is a "range of diseases characterized by abnormal growth and spread of abnormal cells "and is considered one of the most serious diseases in the world, where it represents the second most cause of death in the united States and Europe after cardiovascular diseases according to the facts of cancer numbers 2016[107].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[108]. 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 . 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, 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[109]

1.11. Aim of the work

Synthesis of a new various drug delivery systems (DDS) could be developed to provides the modifications and improve the therapeutic efficiency and safety of drugs. These may be cause reduce size and number of doses, side effect and biological inactivation and elimination. Also, the benefits may include lower toxicity and greater specificity of action. The aim of this work:

1 - Preparation of new monomers of the type of maleimide loaded with different drugs by the reaction of the maleic anhydride with 4–aminobenzoic acid and then loaded several drugs including (sulfadiazine, Chlorodiazepoxide, Paracetemol, Pseudoephdrine, Theophylline).

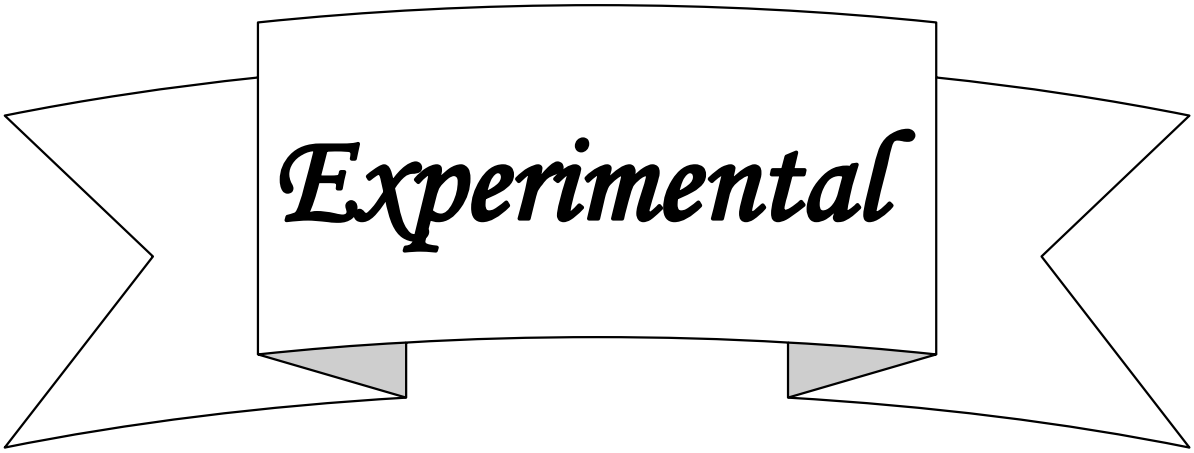
2 - Polymerization the prepared monomers by free radical polymerization to produce homo and hetero polymers .

3 - Identification of prepared monomers and (homo and hetero) polymers by FT-IR,^{1}HNMR, ^{13}C-NMR .

4- Study the solubility, density and viscosity of the prepared monomers and polymers, and measuring the speed of medical release of polymers prepared.

5 - Study of the effectiveness of the biological activity of some of the prepared polymers.

Chapter tow



2-1- Chemical and Techniques:

2-1-1 Chemicals

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

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

Materials	Company	Purities%
4-aminobenzoic acid	Fluka	98.5
Malic anhydride	Fluka	95.5
Thionylchloride	Fluka	99.9
Triethylamine	Fluka	99.5
Methylethylketoneperoxide	Fluka	98.9
Ethanol absolute	BDH	99.9
Acetone	BDH	99.8
Hexane	BDH	99.7
Dimethyl sulphxide	BDH	98.9
Borax	BDH	99
KCl	BDH	99
Acrylic Acid	BDH	99.8
MTT stain	Bio-world/USA	99.9
Trypsin-EDTA	Capricorn/Germany	99.9
RPMI 1640	Capricorn/Germany	99.9
Fetal bovine serum	Capricorn/Germany	99.9
Sulfadizine	Samarra Company	99.9
Chlorodiazepoxide	Samarra Company	99.9
Paracetamol	Samarra Company	99.9
Pseudoephedrine	Samarra Company	99.9
Theophylline	Samarra Company	99.9

2.1.2 Techniques:

1- Melting points were determined using SMP30 melting point; college of science, university of Babylon.

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

3- ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker AC 400 NMR spectrometer; DMSO solvent , operating at 300 MHz for H-NMR and 75 MHz for C-NMR. All chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) as reference (δ=0.0 ppm); University of Al-albayt , Jordon.

4- UV- Visb Spectrophotometer, UV-1800 PC –Shimadzu / College of Education for pure Sciences, University of Karbala**.**

5- Density of polymers was recorded on a Denstiu 30px Instrument/ College of Education for pure Sciences, University of Karbala.

6- Viscosity Measurement, Viscosity of polymers was recorded on Capillary Viscosity type Ostwald/ College of Education for pure Sciences, University of Karbala.

7- Thin layer chromatography (TLC) was performed on aluminum plates coated with 0.25mm layer of silica-gel (Fluka); measured in College of Sciences, university of Babylon.

8- Micro titer reader; Gennex Lap (USA), Cell culture plates ; Santa Cruz Biotechnology (USA).

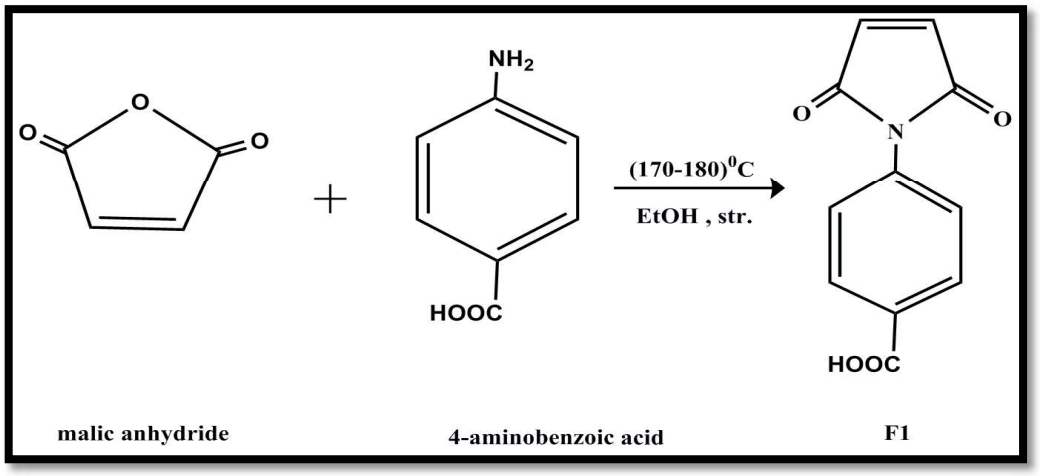
9- Micropipette , CO_2 incubator ;Cypress Diagnostics (Belgium).

10 - Laminar flow hood ; K & K Scientific Supplier (Korea).

2.2 Synthesis of the compound (F1)[110]

About (0.7 gm, 0.005 mmol) of 4-aminobenzoic acid and (1.0 gm, 0.002 mmol) malice anhydride, these materials were placed in beaker (75 mL) and heat the mixture with stirrer (using glass stirrer), in oil bath at

(170-180) ºC, for 10 min. until all the materials were fusion to dark yellow liquid, then the mixture was allowed to cool for 5 min., and re-crystallization by ethanol. The reaction was monitored by TLC.

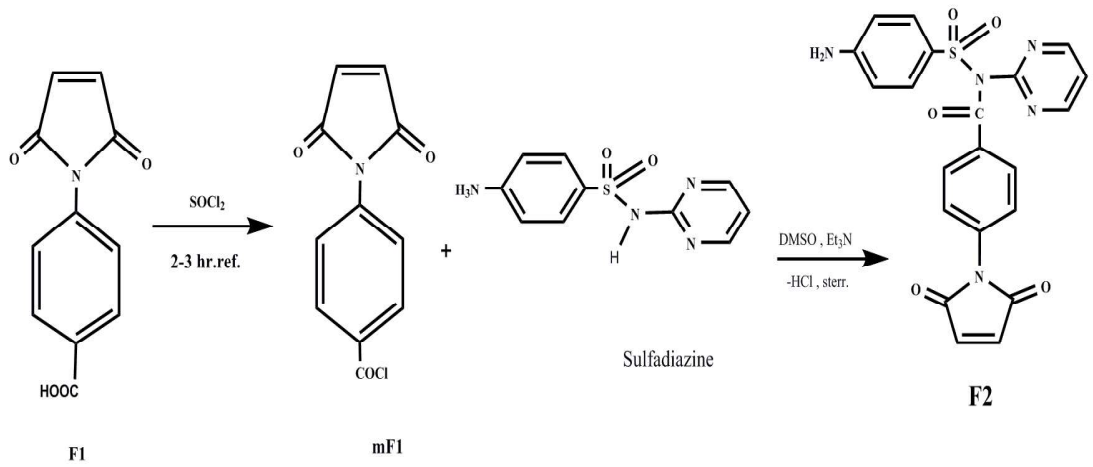


Equation (2-1): synthesis the compound F1

2.3 Synthesis of the monomers[111]

2.3.1 Synthesis of monomer (F2)

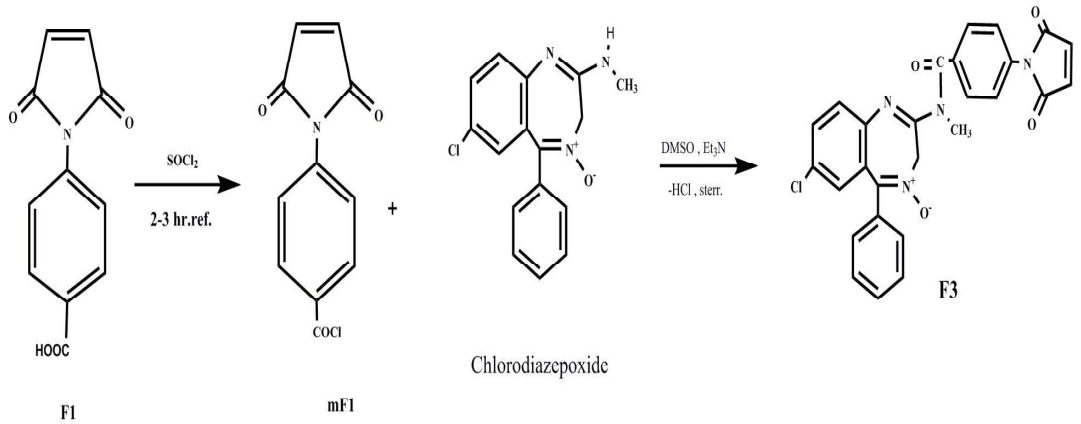
In the beaker (150 ml), (0.5 gm, 0.0023 mmole) of compound (F1) and added 20 ml of dimethylsulfoxide (DMSO) then add (4.1gm, 0.034mmole) of thionylchloride ($SOCl_2$), were mixed together and heating by sensitive hot plat magnetic stirrer at (60-70) ºC , and then added (1.815gm, 0.0179 mmole) of triethylamine (Et_3N), after 2 hr., add the drug of Sulfadiazine (0.575 gm, 0.0023 mmole) and stirrer at 30 ºC to 30 min. The mixtures were cooled by ice bath and left until the precipitate was formed, filtered and dried the product. The reaction process was followed using TLC technique.



Equation (2-2): synthesis the monomer (F2)

2.3.2 Synthesis of monomer (F3)

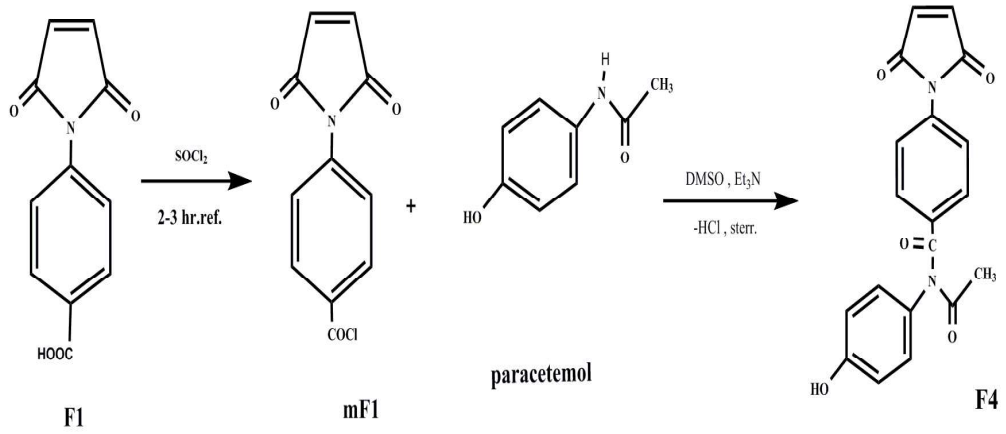
In the beaker (150 mL), (0.5 gm, 0.0023 mmole) of compound (F1) and added 20 mL of dimethylsulfoxide (DMSO) then add (4.1gm, 0.034 mmole) of thionylchloride ($SOCl_2$), were mixed together and heating by sensitive hot plat magnetic stirrer at (60-70) ^oC , and then added (1.815gm, 0.0179 mmole) of triethylamine (Et_3N), after 2hr. add the drug of Chlorodizepoxide (0.688 gm, 0.0023 mmole) and stirrer at 30 ^oC for 30 min. . The mixtures were cooled by ice bath and left until the precipitate was formed, filtered and dried the product. The reaction process was followed using TLC technique.



Equation (2-3): synthesis the monomer (F3)

2.3.3 Synthesis of monomer (F4)

In the beaker (150 mL), (0.5 gm, 0.0023 mmole) of compound (F1) and added 20 mL of dimethylsulfoxide (DMSO) then add (4.1gm, 0.034mmole) of thionylchloride ($SOCl_2$), were mixed together and heating by sensitive hot plat magnetic stirrer at (60-70) ^oC, and then added (1.815gm, 0.0179 mmole) of triethylamine (Et_3N) , after 2 hr., add the drug of Paracetamol (0.347 gm, 0.0023 mmole) and stirrer at 30 ^oC to 30 min. The mixtures were cooled by ice bath and left until the precipitate was formed, filtered and dried the product. The reaction process was followed using TLC technique.

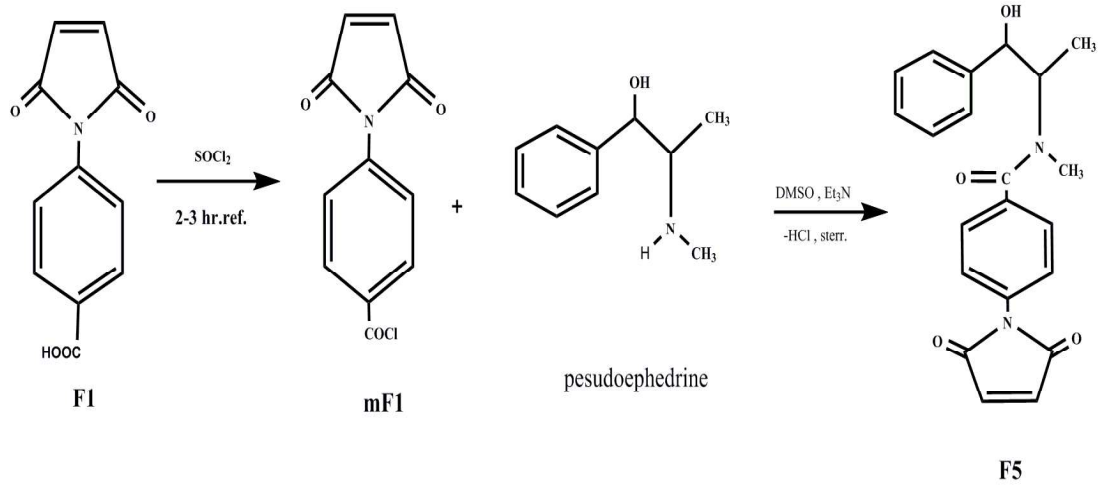


Equation (2-4): synthesis the monomer (F4)

2.3.4 Synthesis of monomer (F5)

About (0.5 gm, 0.0023 mmole) of compound (F1) and 20 mL of dimethylsulfoxide (DMSO) was add in the beaker (150 mL), then add (4.1gm, 0.034mmole) of thionylchloride($SOCl_2$), were mixed together and heating by sensitive hot plat magnetic stirrer at (60-70) ^oC, and then added (1.815gm, 0.0179 mmole) of triethylamine (Et_3N) , after 2 hr., add the drug of Pseudoephedrine(0.38 gm, 0.0023 mmole) and stirrer at 30 ^oC to 30 min.

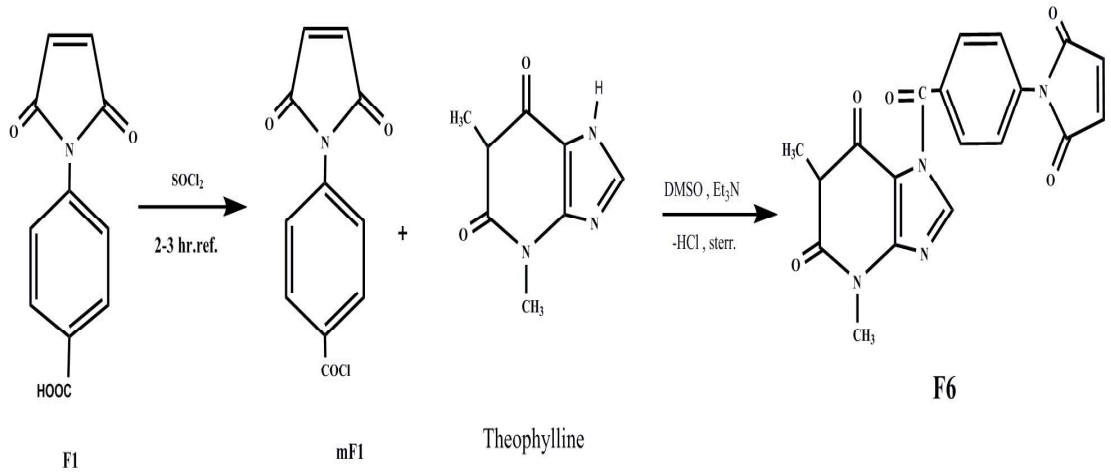
The mixtures were cooled by ice bath and left until the precipitate was formed, filtered and dried the product. The reaction process was followed using TLC technology.



Equation (2-5): synthesis the monomer (F5)

2.3.5 Synthesis of monomer (F6)

About (0.5 gm, 0.0023 mmole) of compound (F1) and 20 ml of dimethylsulfoxide (DMSO) was add in the beaker (150 mL), then add (4.1gm, 0.034mmole) of thionylchloride ($SOCl_2$), were mixed together and heating by sensitive hot plat magnetic stirrer at (60-70) ^oC, and then added (1.815gm, 0.0179 mmole) of triethylamine(Et_3N), after 2hr., add the drug of Theophylline (0.38 gm, 0.0023 mmole) and stirrer at 30 ^oC to 30 Min. The mixtures were cooled by ice bath and left until the precipitate was formed, filtered and dry the product. The reaction process was followed using TLC technique.Table (3-1) shows the physical properties synthesis of monomers(page58).



Equation (2-6):Represent synthesis of monomer (F6)

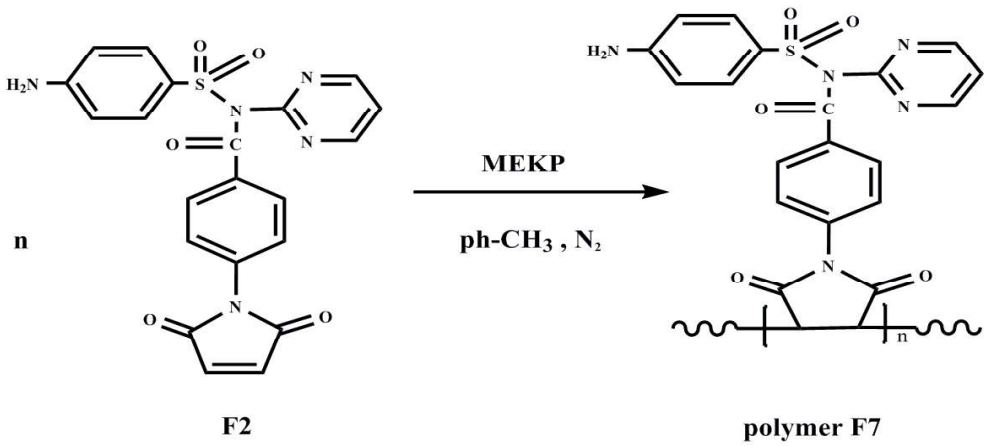
2.4 . Synthesis of polymers [112]

The polymerization process was done in both homogeneous and heterogeneous forms, as shown below:

2.4.1 Synthesis of homo-polymer

2.4.1.1 Synthesis of polymer (F7)

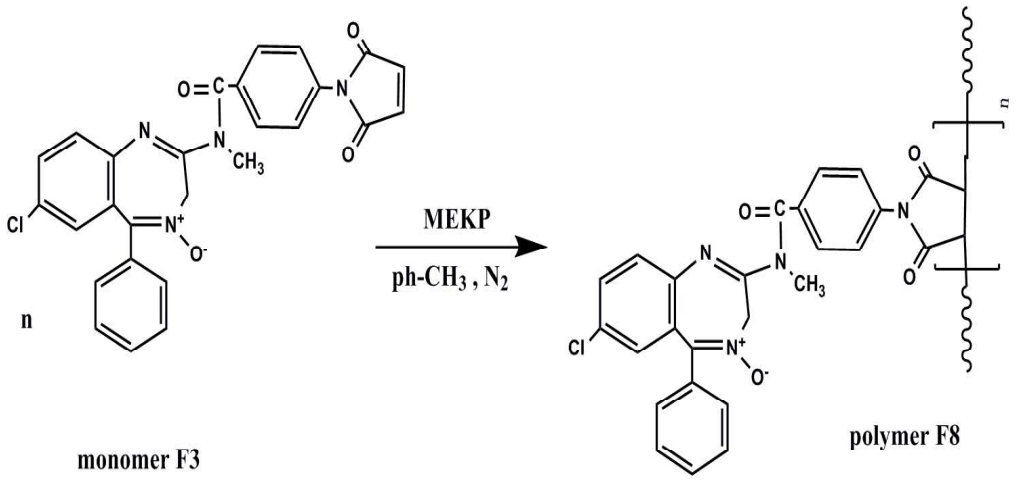
In a (50 ml) round bottom flask two neck,(0.2 gm, 0.00045 mmole) of monomer (F2) with 10 mL of toluene was then sealed with a tight seal and placed in a water bath at 90 °C, and added two drops of methylethylketoneperoxide (MEKP), then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2hr. and at the end of the polymerization, Evaporated of the solvent and filtered the precipitate and washing by using ether then dried up in an oven at 50 °C.



Equation (2-7): synthesis of homo-polymer (F7)

2.4.1.2 Synthesis of polymer (F8)

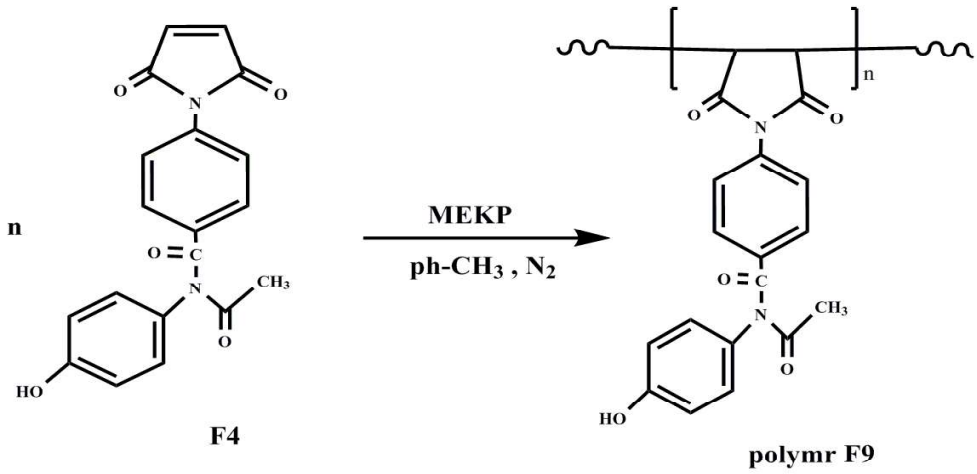
In a (50 ml) round bottom flask two neck,(0.2 gm, 0.0004 mmole) of monomer (F3) with 10mLof toluene was then sealed with a tight seal and placed in a water bath at 90 °C, and added two drops of methyl ethyl ketone peroxide (MEKP), then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2hr. and at the end of the polymerization, Evaporated of the solvent and filtered the precipitate and washing by using ether then dried up in an oven at 50 °C.



Equation (2-8): synthesis of homo-polymer (F8)

2.4.1.3 Synthesis of polymer (F9)

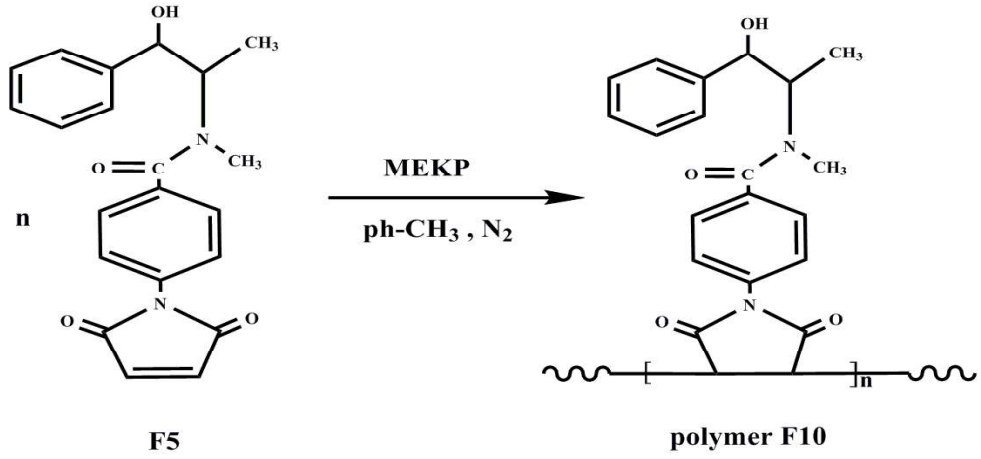
In a (50 mL) round bottom flask two neck, (0.2 gm, 0.00057 mmole) of monomer (F4) with 10mL of toluene was then sealed with a tight seal and placed in a water bath at 90 °C, and added two drops of methylethylketoneperoxide (MEKP), then pass the nitrogen gas from one of the flask nozzle.The reaction continued for 2hr. and at the end of the polymerization, Evaporated of the solvent and filtered the precipitate and washing by using ether then dried up in an oven at 50 °C.



Equation (2-9): synthesis of homo-polymer (F9)

2.4.1.4 Synthesis of polymer (F10)

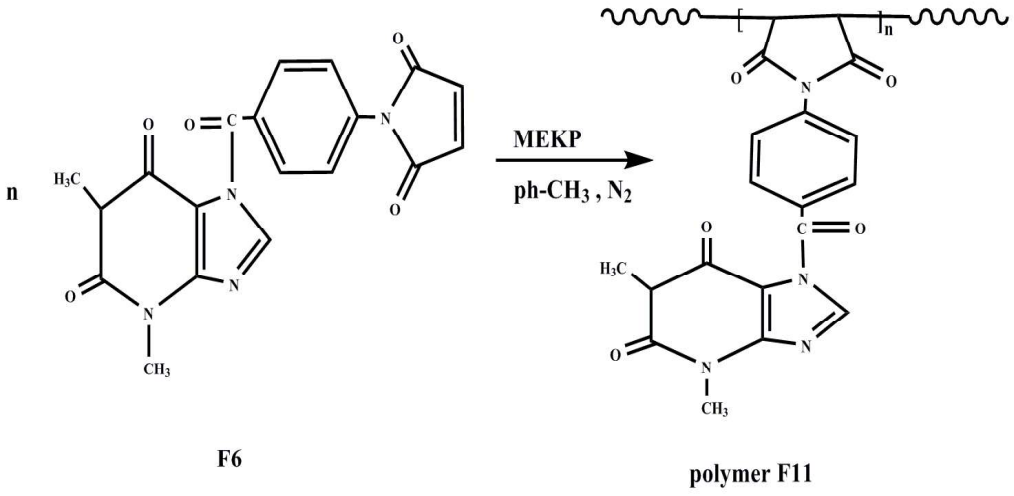
In a (50 mL) round bottom flask two neck, (0.2 gm, 0.00055 mmole) of monomer (F5) with 10mL of toluene was then sealed with a tight seal and placed in a water bath at 90 °C, and added two drops of methylethylketoneperoxide (MEKP), then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2 hr. and at the end of the polymerization, Evaporated of the solvent and filtered the precipitate and washing by using ether then dried up in an oven at 50 °C.



Equation (2-10): synthesis of homo-polymer (F10)

2.4.1.5 Synthesis of polymer (F11)

In a (50 mL) round bottom flask two neck, (0.2 gm, 0.00053 mmole) of monomer (F6) with 10mL of toluene was then sealed with a tight seal and placed in a water bath at 90 °C, and added two drops of methylethylketoneperoxide (MEKP), then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2hr. and at the end of the polymerization, Evaporated of the solvent and filtered the precipitate and washing by using ether then dried up in an oven at 50 °C.

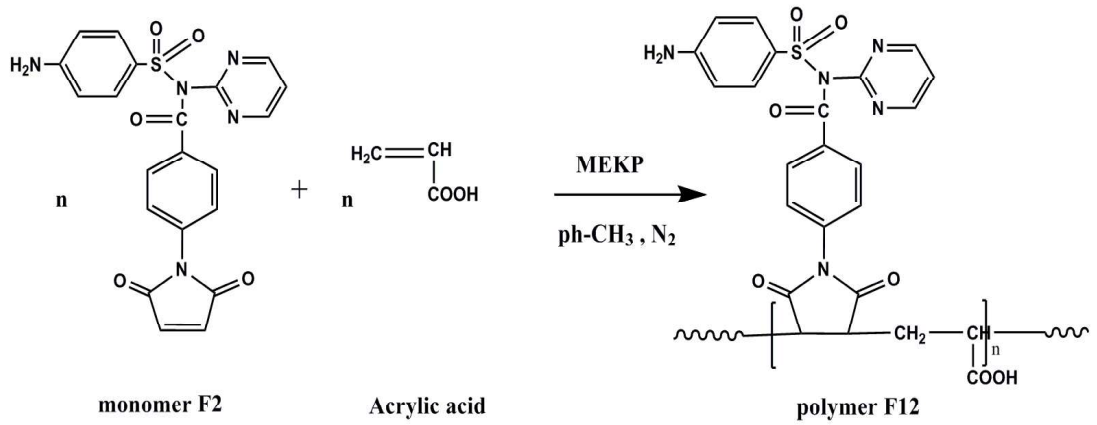


Equation (2-11): synthesis of homo-polymer (F11)

2.4.2 Synthesis of hetero-polymer

2.4.2.1 Synthesis of polymer (F12)

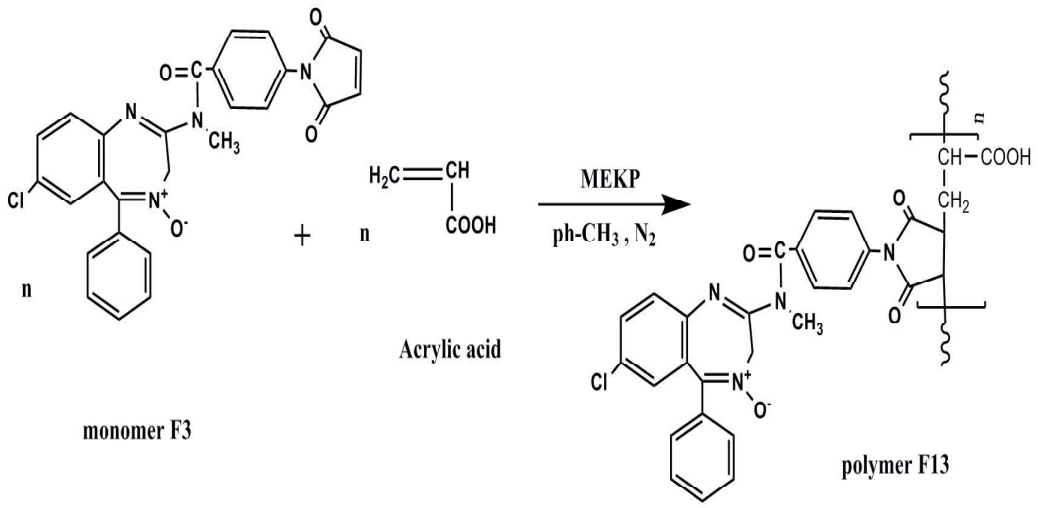
In a (50 mL) round bottom flask two neck, (0.2 gm, 0.00045 mmole) of monomer (F2) with 10mL of toluene and (0.033 g, 0.00045 mmole) of acrylic acid monomer ,was then sealed with a tight seal and placed in a water bath at 90 °C, and added two drops of methylethylketoneperoxide (MEKP), then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2hr. and at the end of the polymerization, Evaporated of the solvent and filtered the precipitate and washing by using ether then dried up in an oven at 50 °C.



Equation (2-12):synthesis of hetero-polymer (F12)

2.4.2.2 Synthesis of polymer (F13)

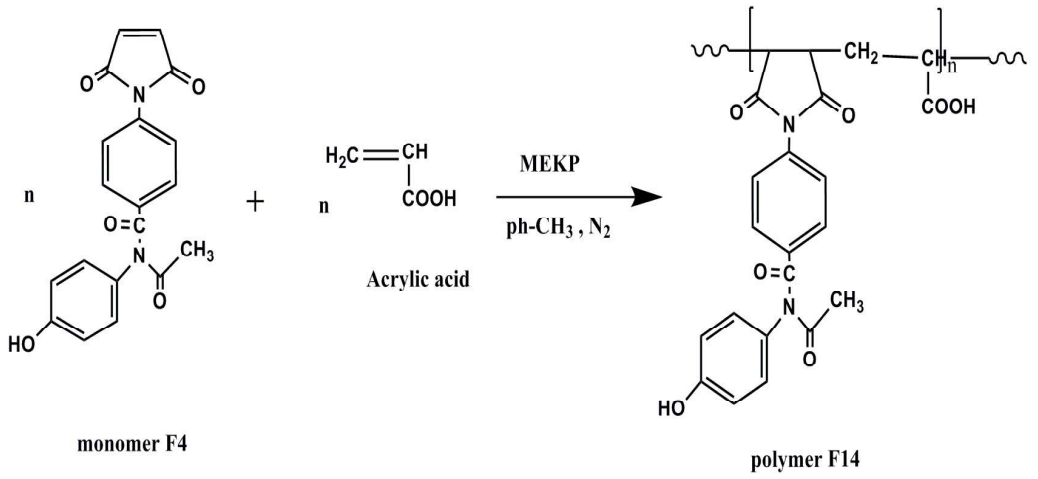
In a (50 mL) round bottom flask two neck, (0.2 gm, 0.0004 mmole) of monomer (F3) with 10mL of toluene and (0.0288 g, 0.0004 mmole) of acrylic acid monomer, was then sealed with a tight seal and placed in a water bath at 90 °C, and added two drops of methylethylketoneperoxide (MEKP), then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2 hr. and at the end of the polymerization, Evaporated of the solvent and filtered the precipitate and washing by using ether then dried up in an oven at 50 °C.



Equation (2-13):synthesis of hetero-polymer (F13)

2.4.2.3 Synthesis of polymer (F14)

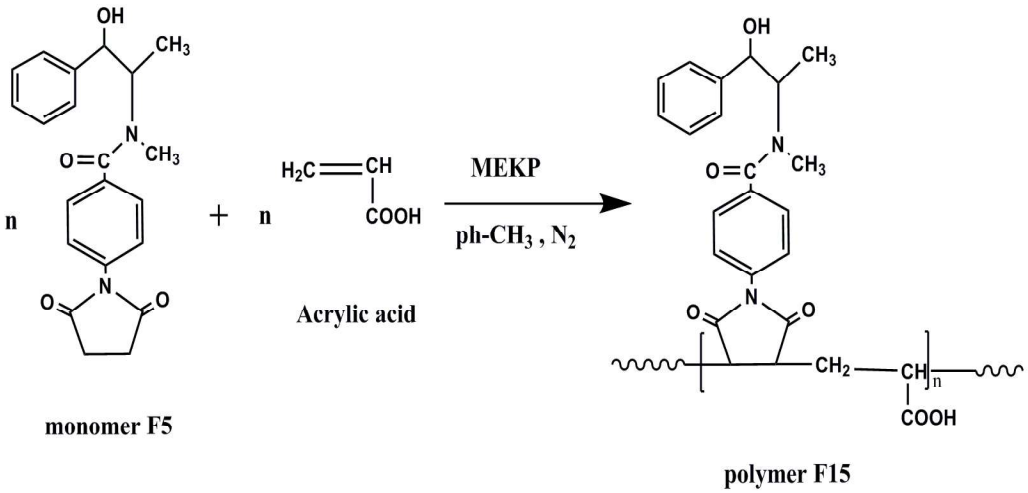
In a (50 mL) round bottom flask two neck, (0.2 gm, 0.00057 mmole) of monomer (F4) with 10ml of toluene and (0.041 g, 0.00057 mmol) of acrylic acid monomer, was then sealed with a tight seal and placed in a water bath at 90 ºC, and added two drops of methylethylketoneperoxide (MEKP), then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2hr. and at the end of the polymerization, Evaporated of the solvent and filtered the precipitate and washing by using ether then dried up in an oven at 50 ºC.



Equation (2-14):synthesis of hetero-polymer (F14)

2.4.2.4 Synthesis of polymer (F15)

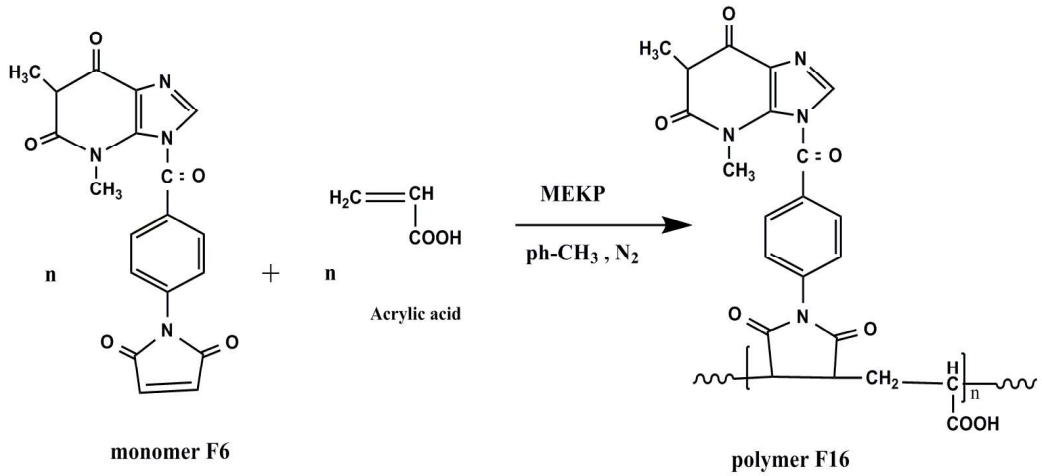
In a (50 mL) round bottom flask two neck, (0.2 gm, 0.00055 mmole) of monomer (F5) with 10mL of toluene and (0.0396 g, 0.00055 mmol) of acrylic acid monomer ,was then sealed with a tight seal and placed in a water bath at 90 °C, and added two drops of methylethylketoneperoxide (MEKP), then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2hr. and at the end of the polymerization, Evaporated of the solvent and filtered the precipitate and washing by using ether then dried up in an oven at 50 °C.



Equation (2-15):synthesis of hetero-polymer (F15)

2.4.2.5 Synthesis of polymer (F16)

In a (50 mL) round bottom flask two neck, (0.2 gm, 0.00053 mmole) of monomer (F6) with 10mL of toluene and (0.038 g, 0.00053 mmole) of acrylic acid monomer ,was then sealed with a tight seal and placed in a water bath at 90 °C, and added two drops of methylethylketoneperoxide (MEKP), then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2hr. and at the end of the polymerization, Evaporated of the solvent and filtered the precipitate and washing by using ether then dried up in an oven at50 °C.



Equation (2-16):synthesis of hetero-polymer (F16)

2.5 Physical properties of the synthesis polymer

2.5.1 The characteristic of solubility

Very small amounts (0.0001g) were taken from the synthesis monomers and polymers (F1-F16) and were placed in small test tubes in (0.5 – 1 mL) from each solvent : (H_2O, Ethanol, Chloroform, Ether, Toluene, DMSO, Hexane, Petroleum ether and Acetone) were used and measured the solubility of prepared monomers and polymers.

2.5.2 Swelling ratio[113]

The swelling ratio was determined by immersing the xerogel (0.05 gm) from homo and hetero polymers, in 50 mL of different buffer solutions, pH (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 methods[114]:

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

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

2.6 Release of drug [115]

By using UV.-Visb. spectrophotometer, release the drug from the prepared polymer (homo and hetero) was determined in three different buffer solutions (2.2, 7.0 and 8.0) at constant temperature 37°C . (0.02 g) for each polymer of prepared polymers was used in the beaker (50 ml) and acidic, neutral and basal medium was used . Absorption (controlled drug release) was measured for 5 consecutive hours and measured for three days.

2.7 Biological activity [117,118].

2.7.1 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.

2.7.2 Cytotoxicity Assays

To determine the cytotoxic effect of (x- substances), the MTT cell viability assay was done using 96-well plates. Cell lines were seeded at

1×10^4cells/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:-

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

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

2.7.3 Antioxidant activity

DPPH radicals scavenging assay

Antioxidant activity of (x-substance) was measured using stable DPPH radicals with minor adjustments according to[116]. (X-substance) were used to investigate the scavenging activity. The samples were mixed with 450 µl of DPPH solution and then complete the volume of mixture to one ml using absolute ethanol. Ascorbic acid was uses as a positive control at concentration 10 µg/ml . The samples and control are left in dark at room temperature for 30 minute. The absorbance was measured at 517 nm. Scavenging activity measured according to the equation formula:

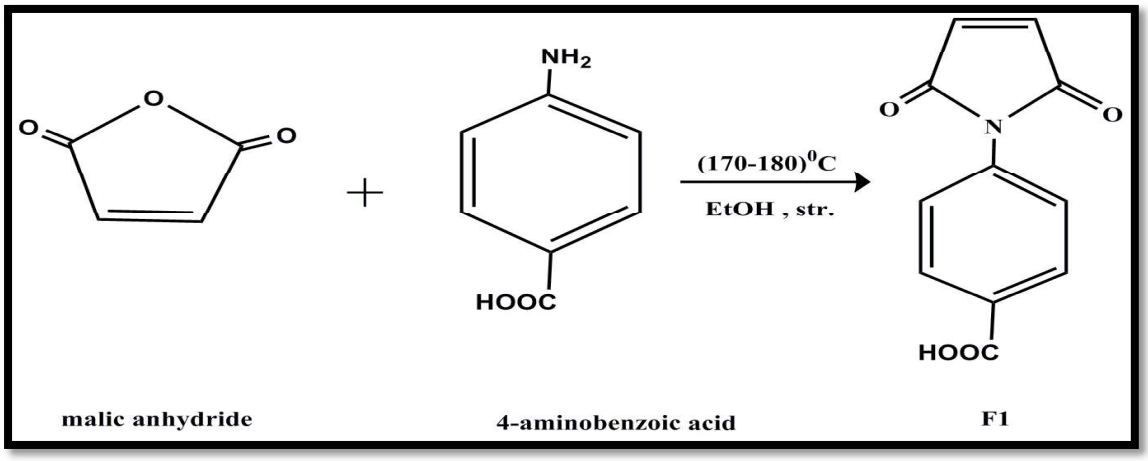
$$\textit{Scavenging}\ \% = \frac{\textit{Absorbance of control} - \textit{Abosrbance of sample}}{\textit{Absorbance of control}} \times \textbf{100\%}$$

Chapter three

Results and Discussion

3.1 Synthesis of the compound (F1)

4-aminobenzoic acid and malice anhydride, reacted in oil bath at (170-180) °C, for 10 min. , equation (3-1) represent synthesis the compound (F1).



Equation (2-1): synthesis the compound F1

Figure (3-1), showed the FT- I.R spectrum of compound [F1], shows appearance of absorption broad band approximately (3500-3200) cm^{-1} of O-H $_{carboxylic\ acid}$ and absorption bands for C=C-H_{amide} at (3100) and absorption band of C=O $_{carboxylic\ acid}$ at (1705) cm^{1}, and absorption band of C-N-C at (1380) cm^{-1} , and absorption band of C-O at (1175) cm^{-1}. [116] , Figure (3-2): Represent the ^{1}H-NMR spectrum for compound (F1) show appearance single-signal at 13.101 for $(OH)_{acid}$, and multiplet signal at (7.14-8.16) for (ph-H) single-signal at 3.430 for $(C=C-H)_{amide}$. Figure (3-3), represent the ^{13}C-NMR spectrum for compound (F1) show signal at 166.60 for $(C=O)_{carboxylic\ acid}$, and multiplet signal at (135.47-120.12) for $(C=C)_{ph}$, and single signal at 40.013 for $(C-O)_{carboxylic\ acid}$.

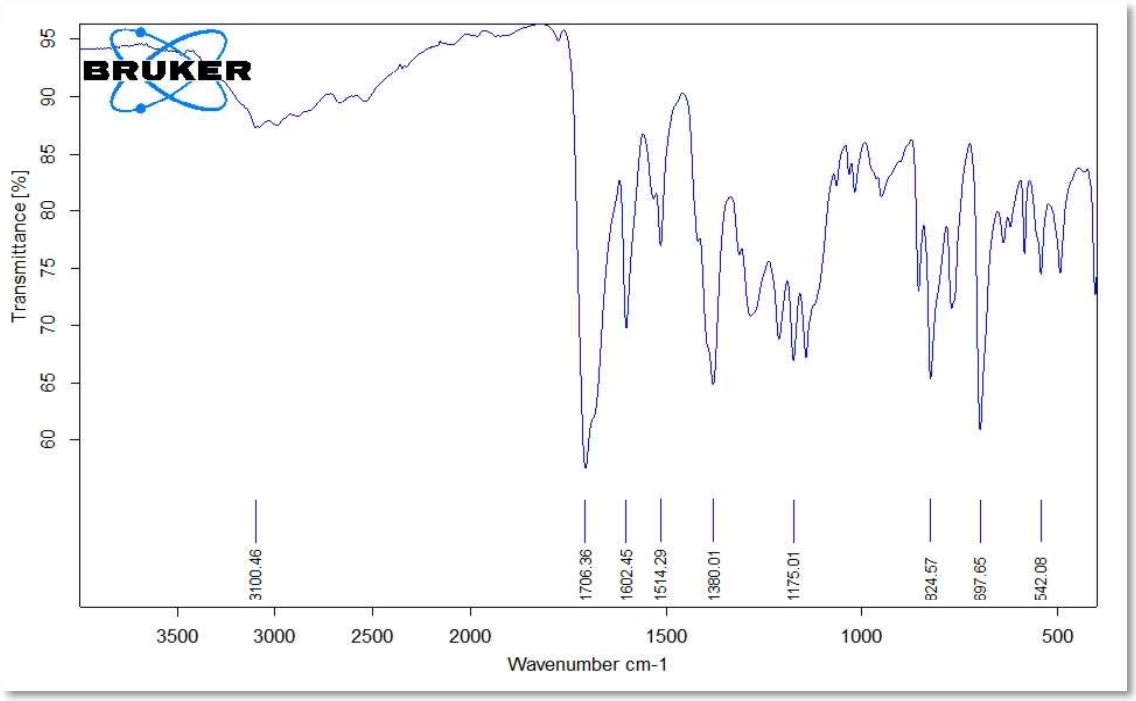


Figure (3-1): The FT- I.R spectrum of compound (F1)

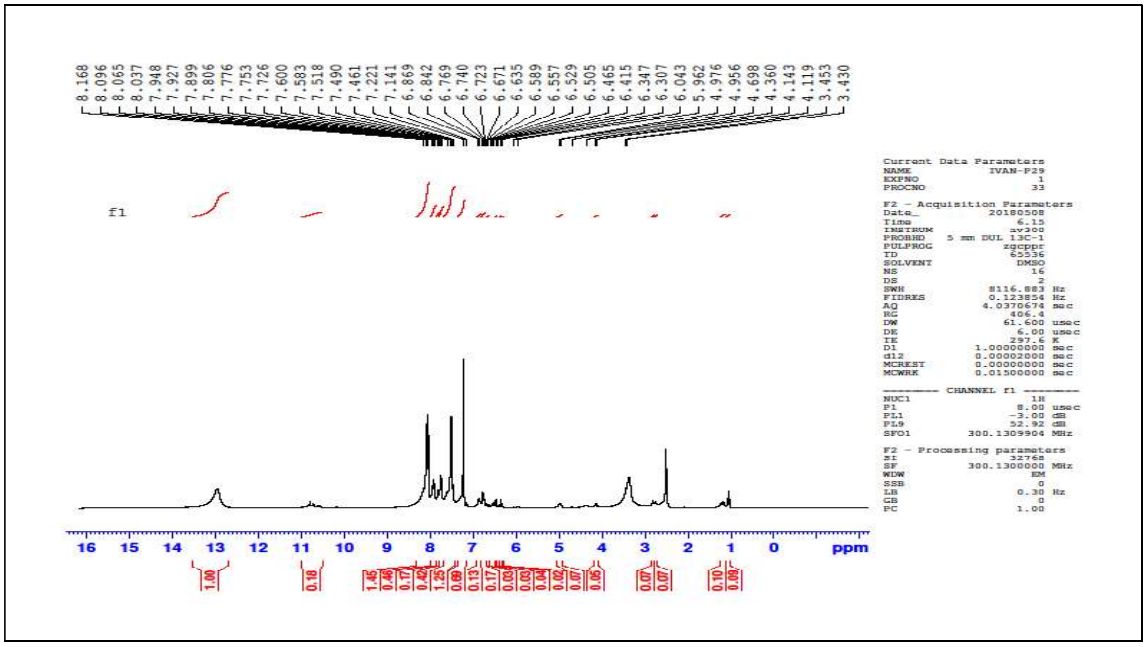


Figure (3-2): The ^{1}HNMR spectrum of compound (F1)

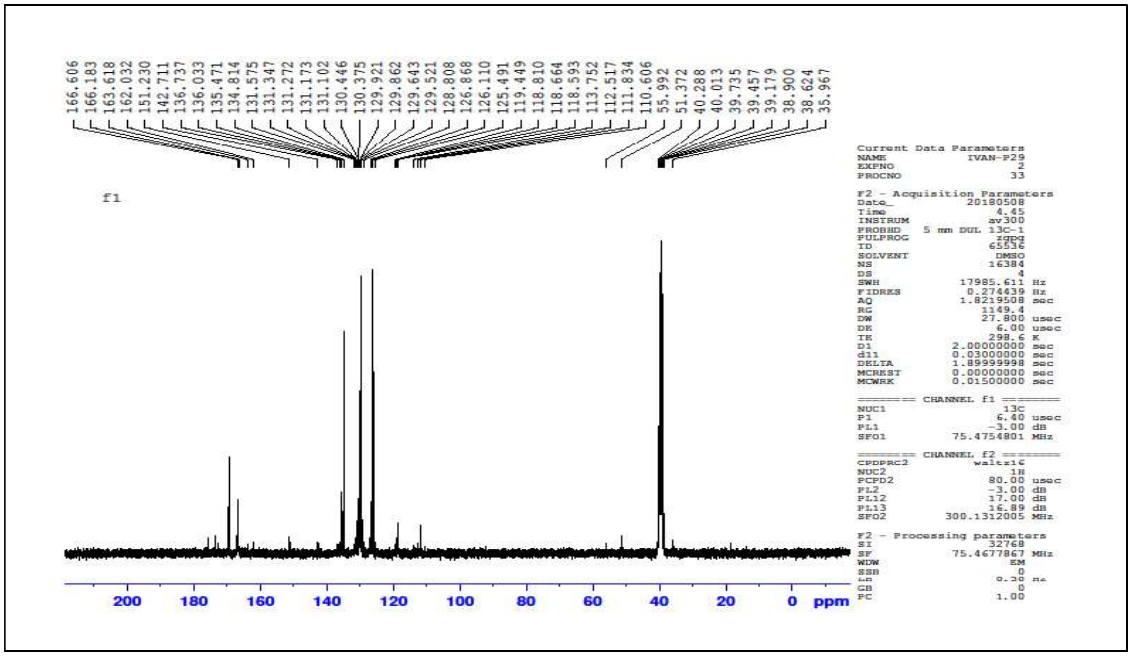
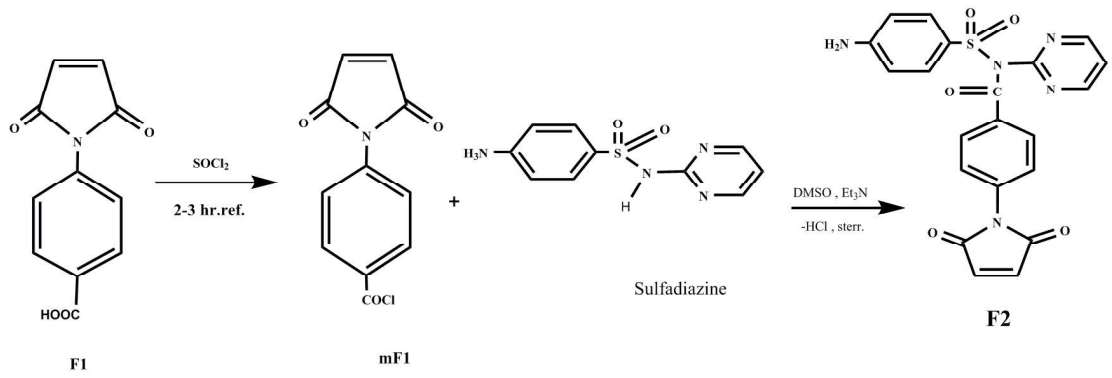


Figure (3-3): The ^{13}C-NMR spectrum for compound (F1)

3.2 Synthesis of the monomers

3.2.1 Synthesis of monomer (F2)

Amount of compound (F1) reacted with dimethylsulfoxide (DMSO) then add thionyl chloride($SOCl_2$), were mixed together and heating at (60-70) ºC, and then added triethylamine, after 2hr., add the drug of Sulfadiazine at 30ºC to 30 min., equation (3-2) represent synthesis the monomer (F2)



Equation (2-2): synthesis the monomer (F2)

Figure (3-4): showed the FT- I.R spectrum of compound (F2), shows disappearance absorption band of O-H and appearance of absorption band of NH_2 at (3306) cm^{-1} and absorption band of C=C-H $_{amide}$ at (3100) cm^{-1} and absorption band of C-N-C at (1381) cm^{-1}, and absorption band of S-N at (947) cm^{-1}, and absorption bands of C-S at (697) cm^{-1} .

The ^{1}H-NMR spectrum of compound (F2), Figure (3-5) shows disappearance signal for $(O-H)_{acid}$, and appearance multiplet signal at (7.89-7.22) for $(C=C-H)_{ph}$, and appearance a single signal at 6.3 for $(C=C-H)_{amid}$.

The ^{13}C-NMR spectrum for Compound (F2), Figure (3-6) showed, disappearance signal (C=O) acid, and appearance signal at(120.91-130.15) for $(C=C-H)_{ph}$.

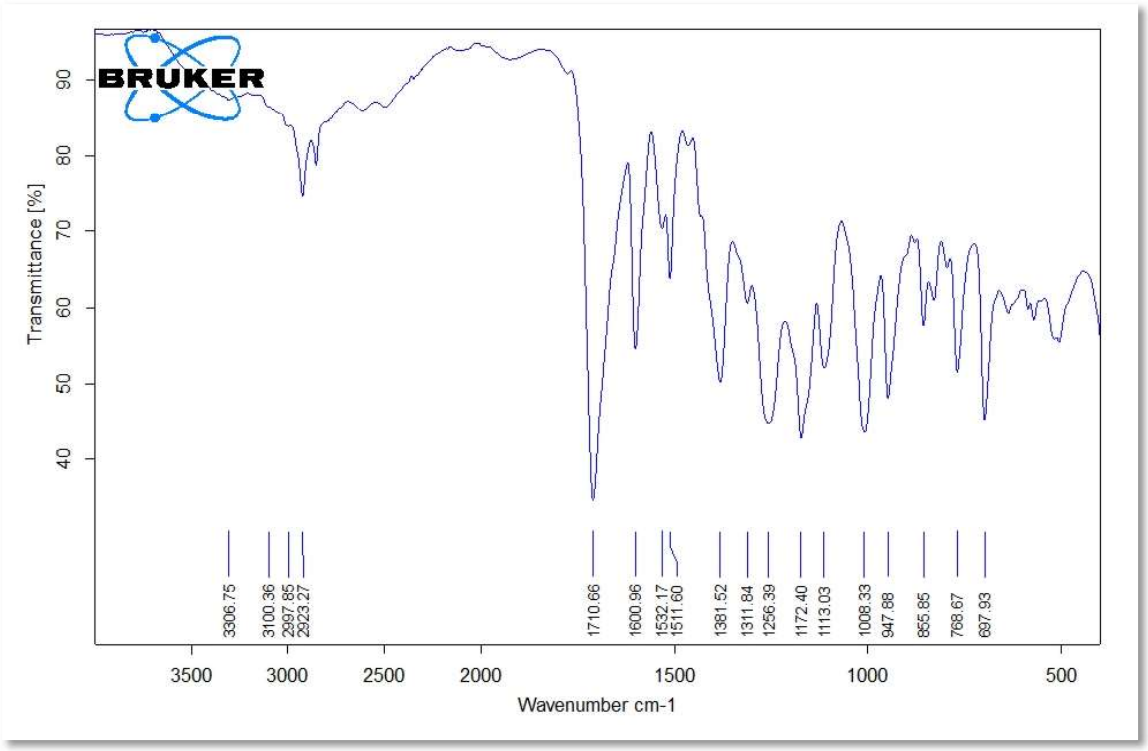


Figure (3-4): The FT-IR spectrum of monomer(F2)

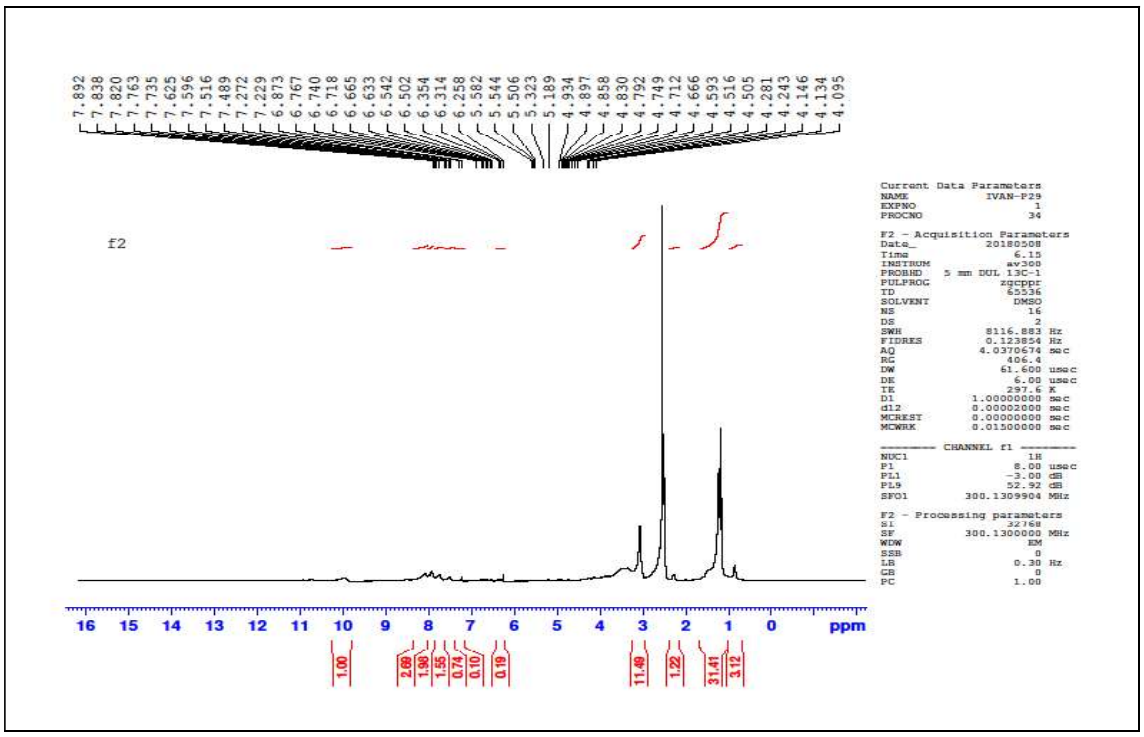


Figure (3-5): The [1]HNMR spectrum of monomer(F2)

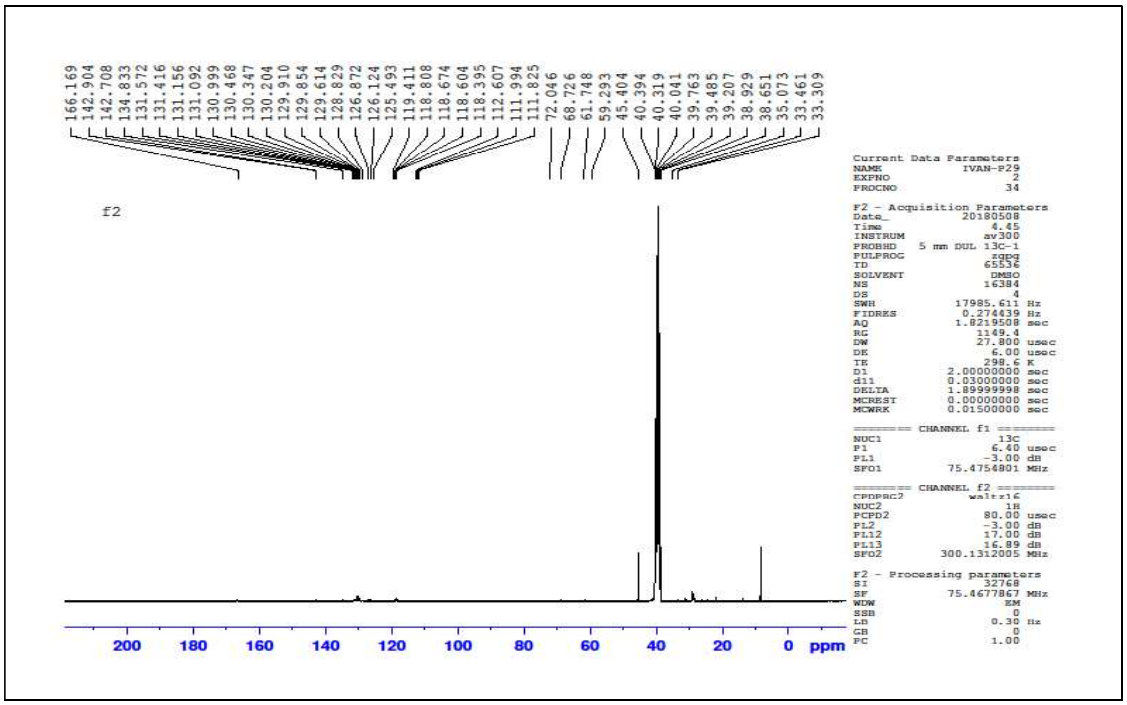
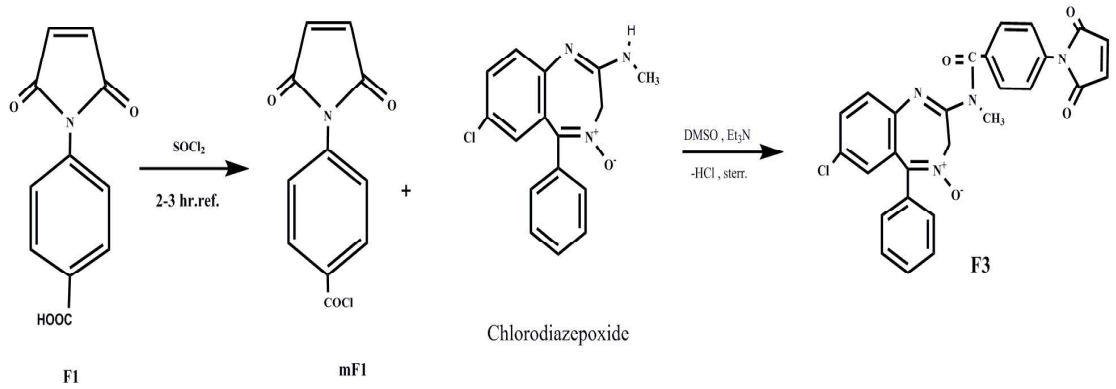


Figure (3-6): The [13]CNMR spectrum of monomer(F2)

3.2.2 Synthesis of monomer (F3)

Amount of compound (F1) and added dimethylsulfoxide (DMSO) then add thionylchloride ($SOCl_2$), were mixed together and heating at (60-70) ^oC, and then added triethylamine, after 2hr., add the drug of Chlorodiazepoxide at 30^oC to 30 min., equation (3-7) represent synthesis the monomer (F3)



Equation (3-3): synthesis the monomer (F3)

The FT-I.R spectrum of compound (F3), Figure (3-7), shows appearance of absorption band of C=C-H_{amide} at (3009) cm^{-1} and absorption band of C-C-H_{aliph} at (2926) cm^{-1} and absorption band at (1709) cm^{-1} of C=O $_{acid}$ and absorption band of at C-N-C (1380) cm^{-1} , , and absorption band of C-O at (1380) cm^{-1}, and appearance absorption band of C-Cl at (755) cm^{-1} . The ^{1}H-NMR spectrum for compound (F3), Figure (3-8), shows appearance a single signal for $(OH)_{drug}$ at 13.001 and appearance signal at (7.22-8.08) for $(C=C-H)_{ph}$, and appearance signal at 6.53 for $(C=C-H)_{amid}$, and appearance signal at 3.49 for (CH_3). The ^{13}C-NMR spectrum for compound (F3), Figure (3-9), showed, disappearance signal for $(C=O)_{acid}$, and show signal at (119.99-130.80) for $(C=C)_{ph}$, and show signal at 45.31 for (C-C).

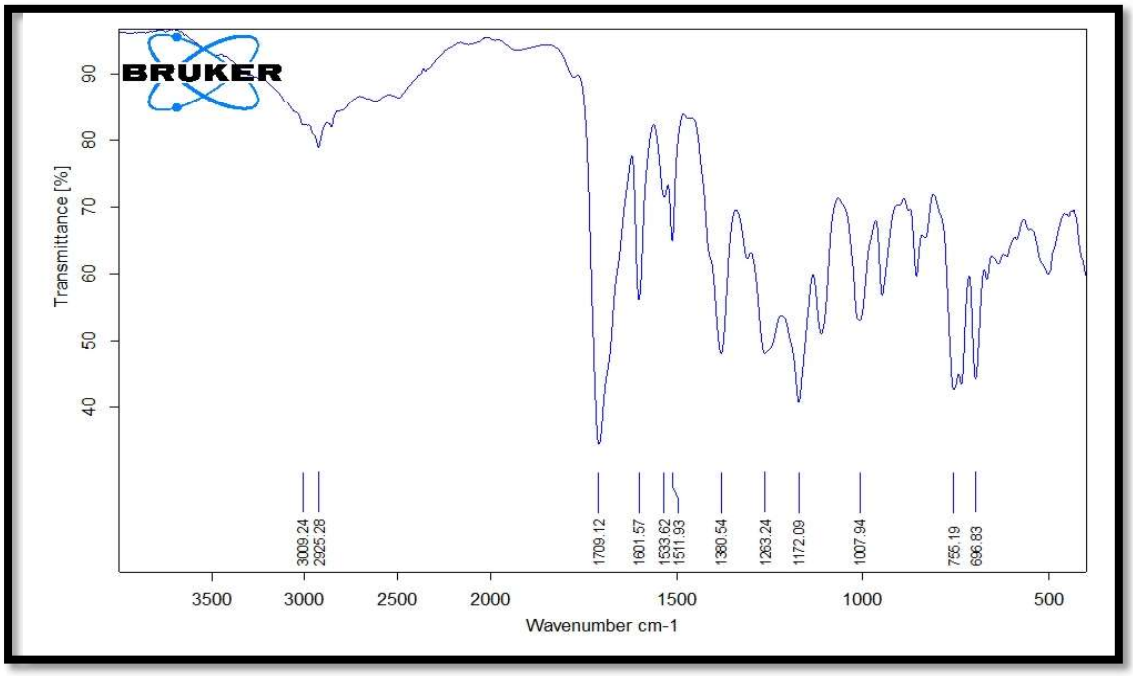


Figure (3-7): The FT-IR spectrum of monomer (F3)

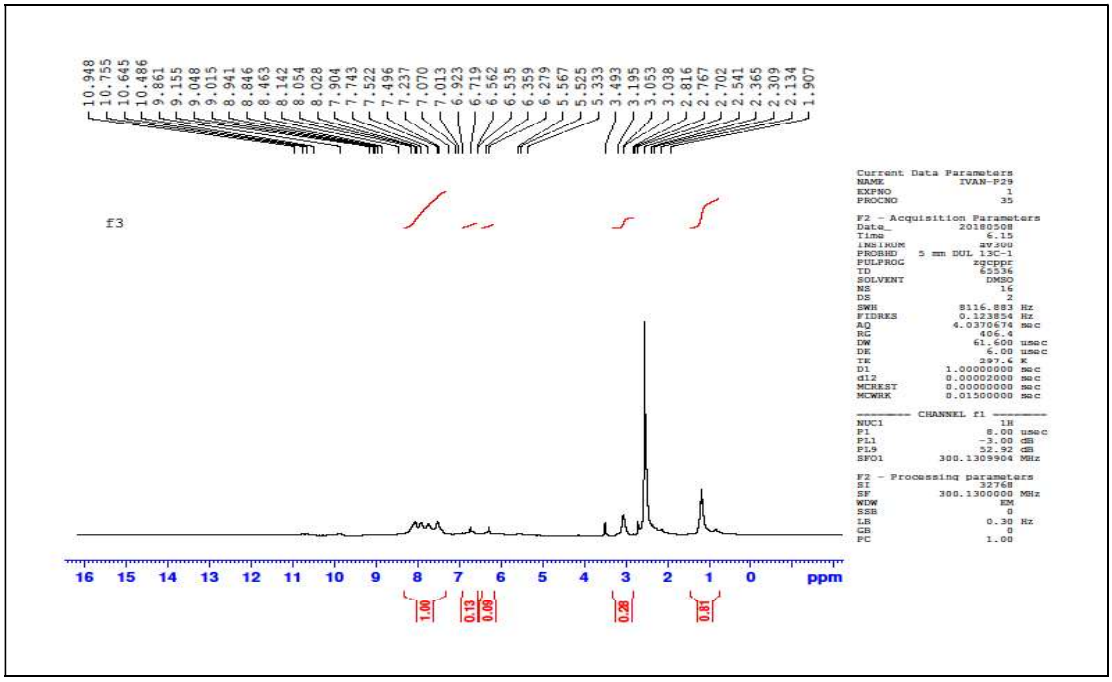


Figure (3-8): The ^{1}HNMR spectrum of monomer (F3)

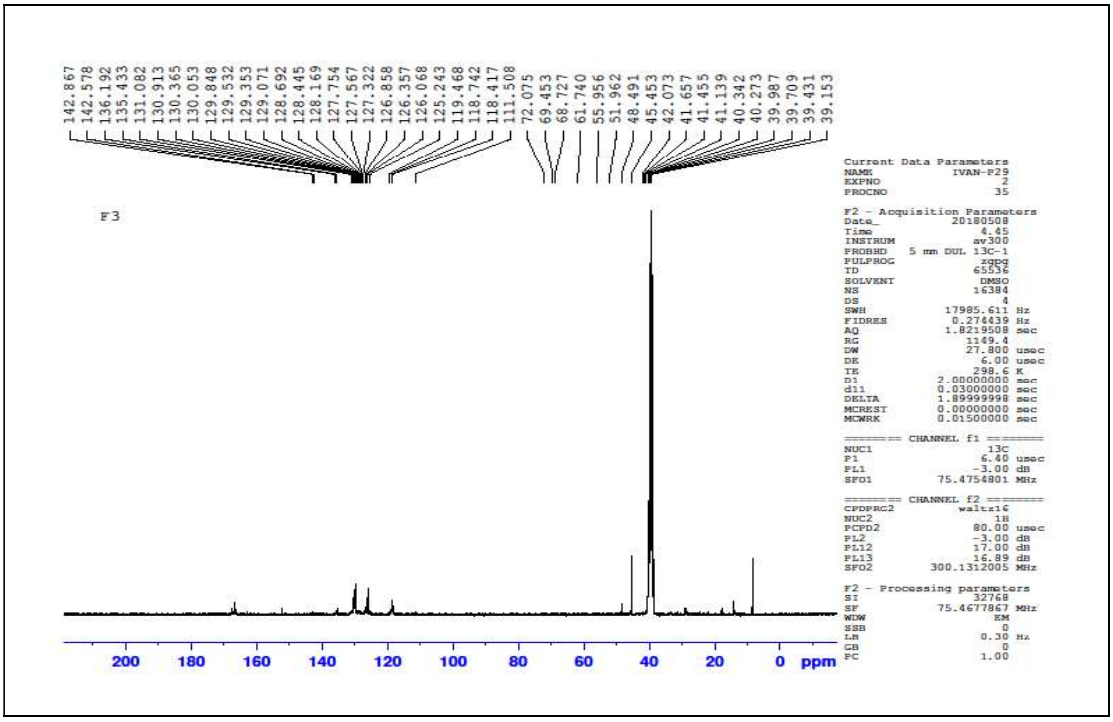
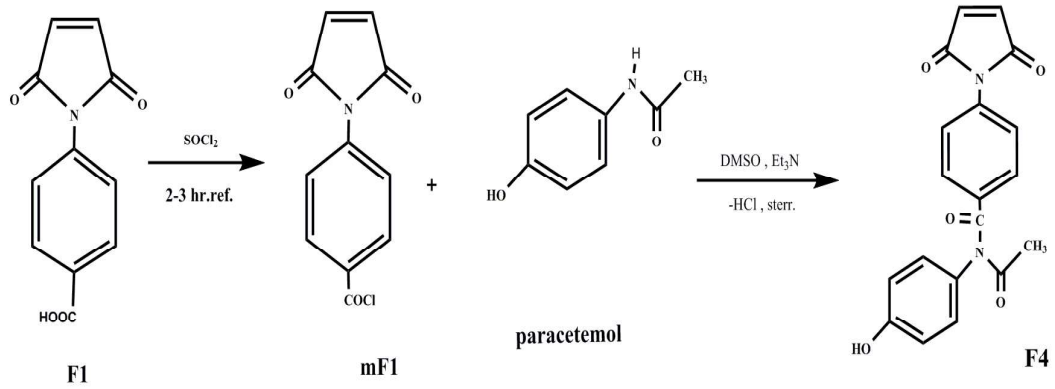


Figure (3-9): The ^{13}CNMR spectrum of monomer (F3)

3.2.3 Synthesis of monomer (F4)

Compound (F1)reacted with dimethylsulfoxide then add thionylchloride ($SOCl_2$), and heating at (60-70) ^oC, and then added triethylamine, after 2hr., add the drug of Paracetemol at 30 ^oC to 30 min., equation (3-4) represent synthesis the monomer (F4)



Equation (3-4): synthesis the monomer (F4)

Figure (3-10), showed the FT- I.R spectrum of compound (F4) shows absorption broad band of O-H at (3200-3476) cm^{-1} , and absorption band of C-H $_{amide}$ at (3300) cm^{-1}, and absorption band of C-C-H_{aliph} at (3088) $cm^{-1}$and absorption band of C=O $_{acid}$ at (1710) cm^{-1} , and absorption band of C-N at (1379) cm^{-1} . Figure (3-11) showed the ^{1}H-NMR spectrum for compound (F4) it disappearance of signals for (OH) $_{acid}$, and show signal at (7.22-8.08) for (C=C-H) $_{ph}$. , and appearance single signal at 6.8 for (C=C-H) $_{amide}$, and appearance signal at (3.35) for (CH_3). The ^{13}C-NMR spectrum for compound (F4), Figure (3-12), show signal at (120.85-134.82) for $(C=C)_{ph}$,and show signal at 110.15 for $(C=C)_{amide}$, and appearance signal at(45.46) for (CH_3).

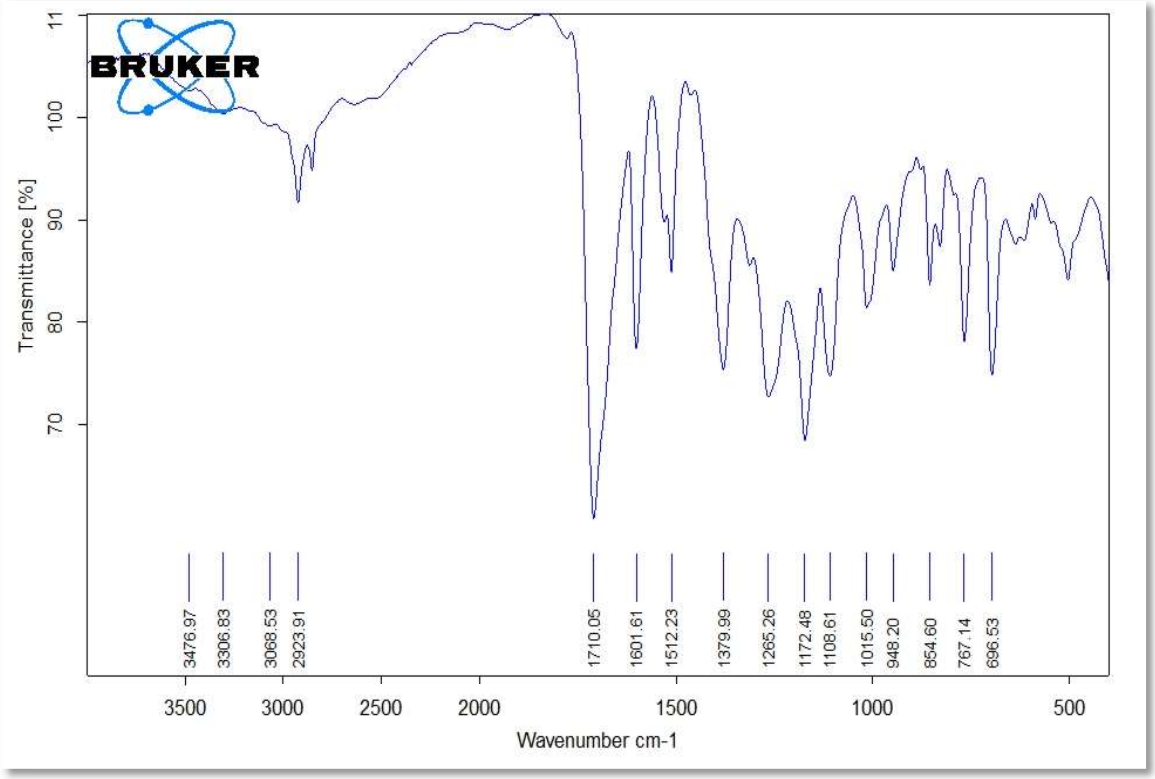


Figure (3-10): The FT-IR spectrum of monomer (F4)

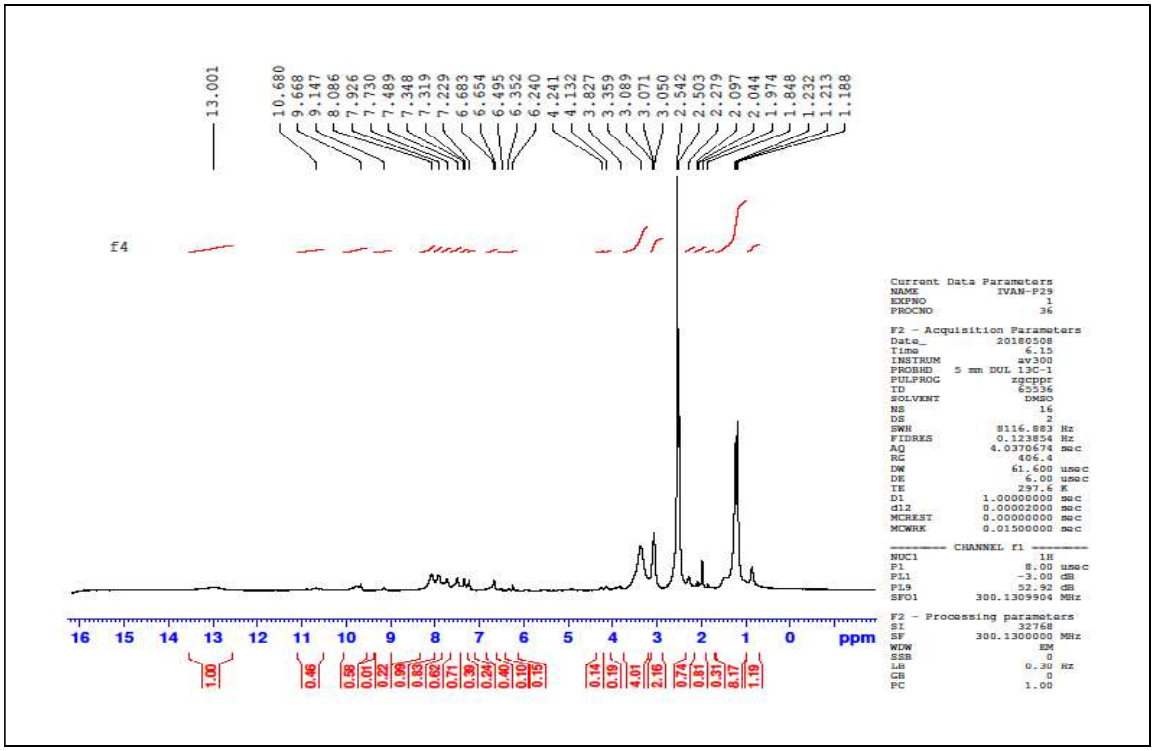


Figure (3-11): The[1]HNMR spectrum of monomer (F4)

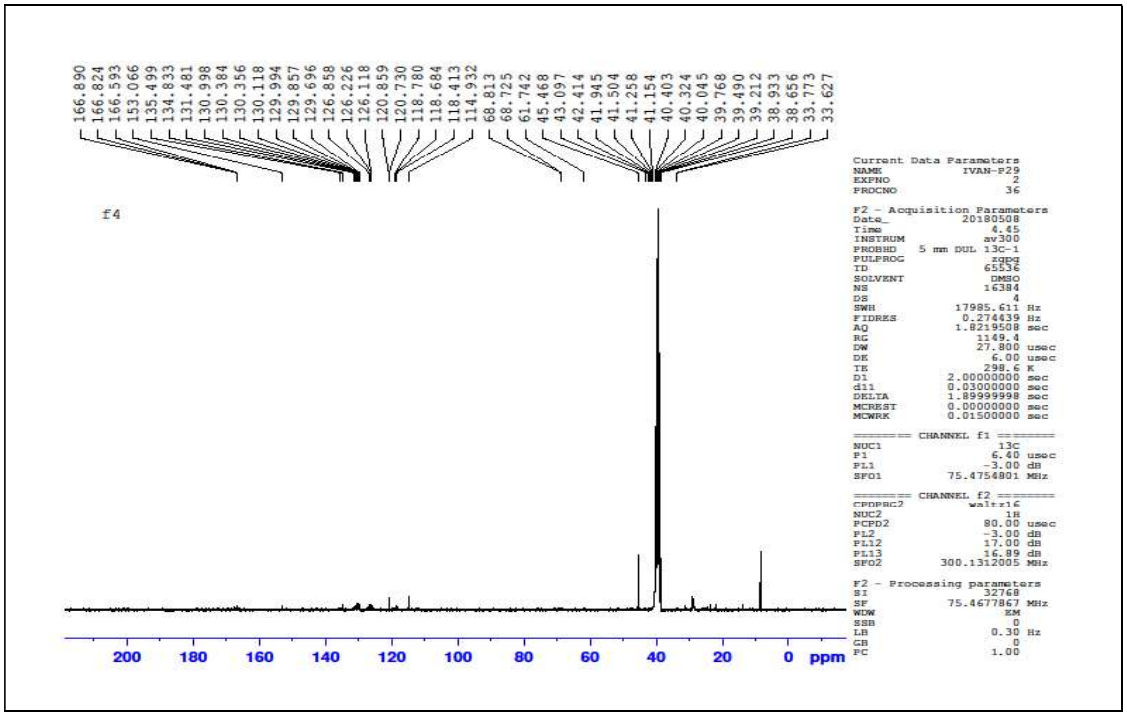
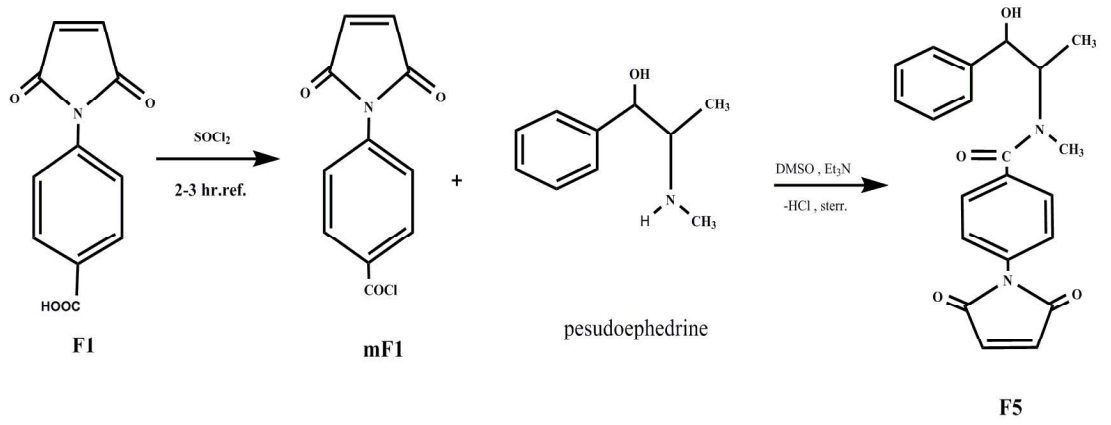


Figure (3-12): [13]CNMR spectrum of monomer (F4)

3.2.4 Synthesis of monomer (F5)

Compound (F1), dimethylsulfoxide with thionylchloride, were mixed together and heating at (60-70) °C, and then added triethylamine, after 2hr., add the drug of Pseudoephedrine at 30 °C to 30 min., equation (3-5) represent synthesis the monomer (F5)



Equation (3-5): synthesis the monomer (F5)

Figure (3-13), represent the FT-I.R spectrum of monomer (F5) shows absorption band of O-H at (3306-3476) cm^{-1}, and absorption band of C= C-H $_{amide}$ at (3068) cm^{-1} , and absorption band of C-C-H_{aliph} at (2923) cm^{-1} , and absorption band of C=O at (1710) cm^{-1} , and absorption band of C-N-C at (1379) cm^{-1}. The ^{1}H-NMR spectrum of monomer (F5), Figure (3-14), showed appearance single signal at (10.5-10.9) for (OH) ,and show multipelet signal at (7.15-8.08) for $(C=C-H)_{ph}$, and show signal (6.53) for $(C=C-H)_{amide}$, and show signal (3.09) for ($2CH_3$). Figure (3-15) represent the ^{13}C-NMR spectrum for monomer (F5) shows disappearance signal for (C, COOH). And show signal at (119.39-130.38) for $(C=C)_{ph}$, and appearance signal at(40.40) for (2C, CH_3).

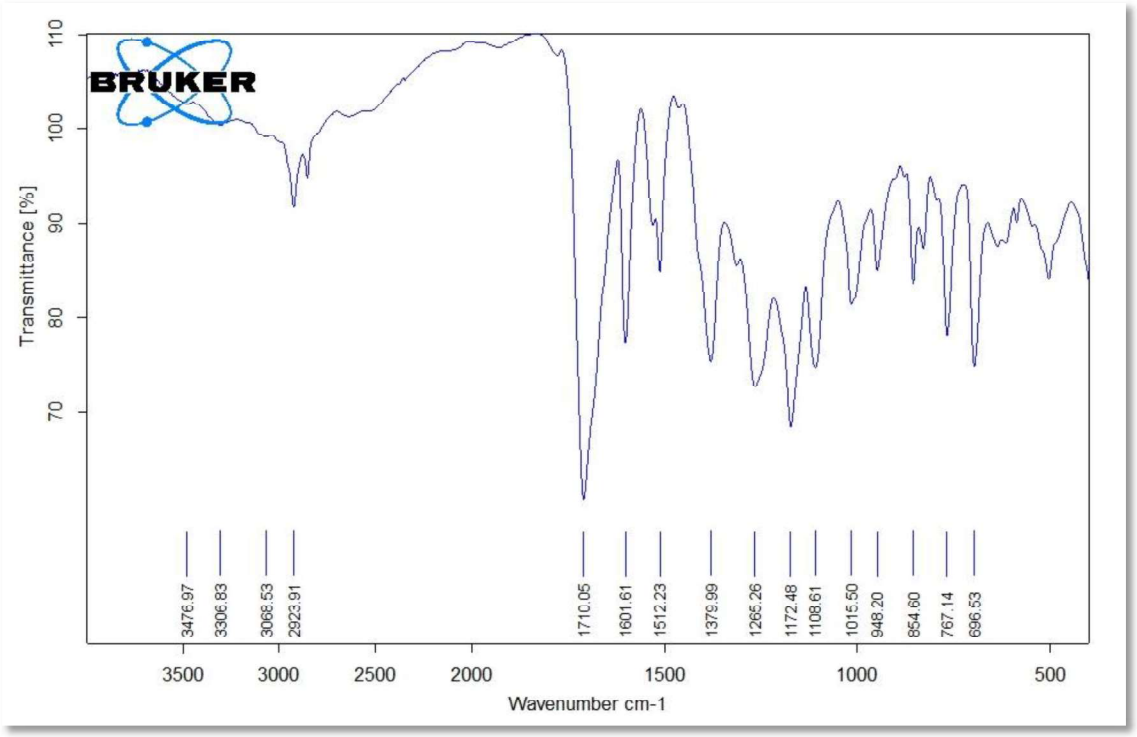


Figure (3-13): The FT-IR spectrum of monomer (F5)

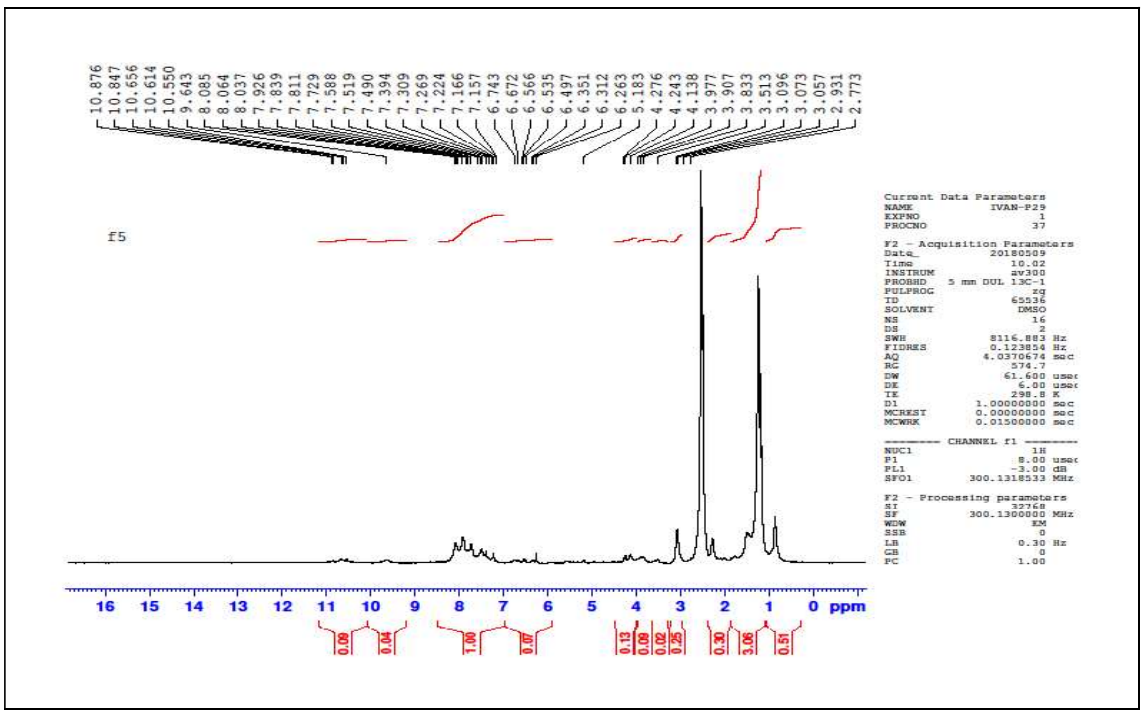


Figure (3-14): The[1]HNMR spectrum of monomer (F5)

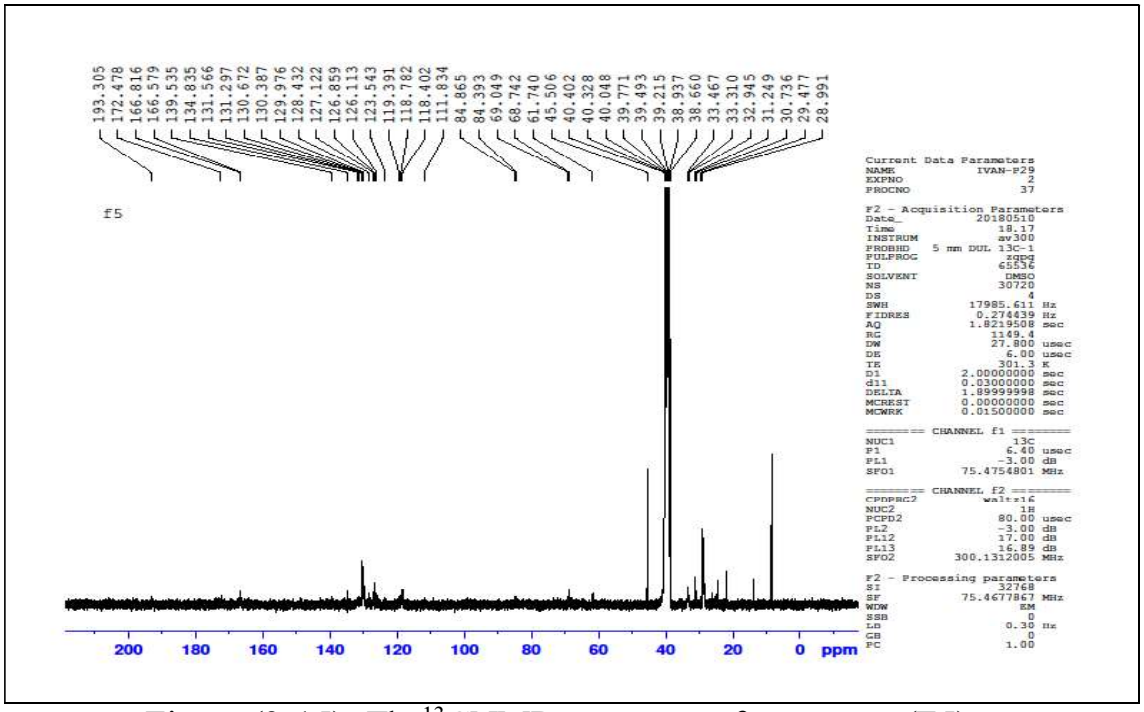
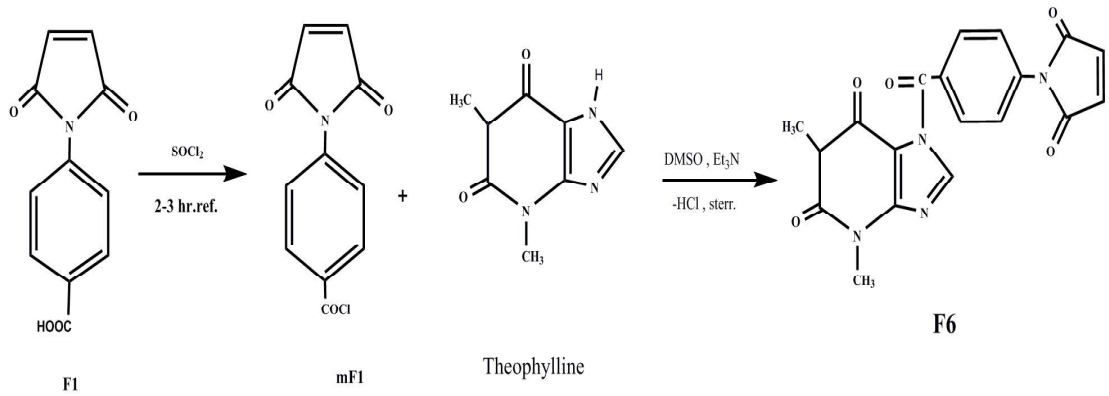


Figure (3-15): The^{13}CNMR spectrum of monomer (F5)

3.2.5 Synthesis of monomer (F6)

Amount of compound (F1) and dimethylsulfoxide then add thionylchloride, were mixed together and heating at (60-70) ºC, and then added triethylamine, after 2hr., add the drug of Theophylline and stirrer at 30 ºC to 30 min. Equation (3-6) represent this reaction.



Equation (2-6):synthesis of monomer (F6)

Figure (3-16), represent the FT-IR spectrum of monomer (F6) showed absorption band of C-H $_{amide}$ at (3051) cm^{-1}, and absorption band of C-H_{aliph} at (2998) cm^{-1} , and absorption band of C=O_{acid} at (1711) cm^{-1}, and absorption band of C-N-C at (1380) cm^{-1}.

Figure (3-17), showed the ^{1}H-NMR spectrum for monomer (F6) appearance multipliet signal at (7.24-8.09) for $(C=CH)_{ph}$, and appearance signal at 6.4 for $(C=CH)_{amide}$, and appearance signal at 3.151 for $(2CH_3)$, and Figure (3-18) showed the ^{13}C-NMR spectrum for monomer (F6) show appearance signal at (119.-130.78) for $(C=C)_{ph}$, and show appearance signal at(4.61) for $(2CH_3)$.

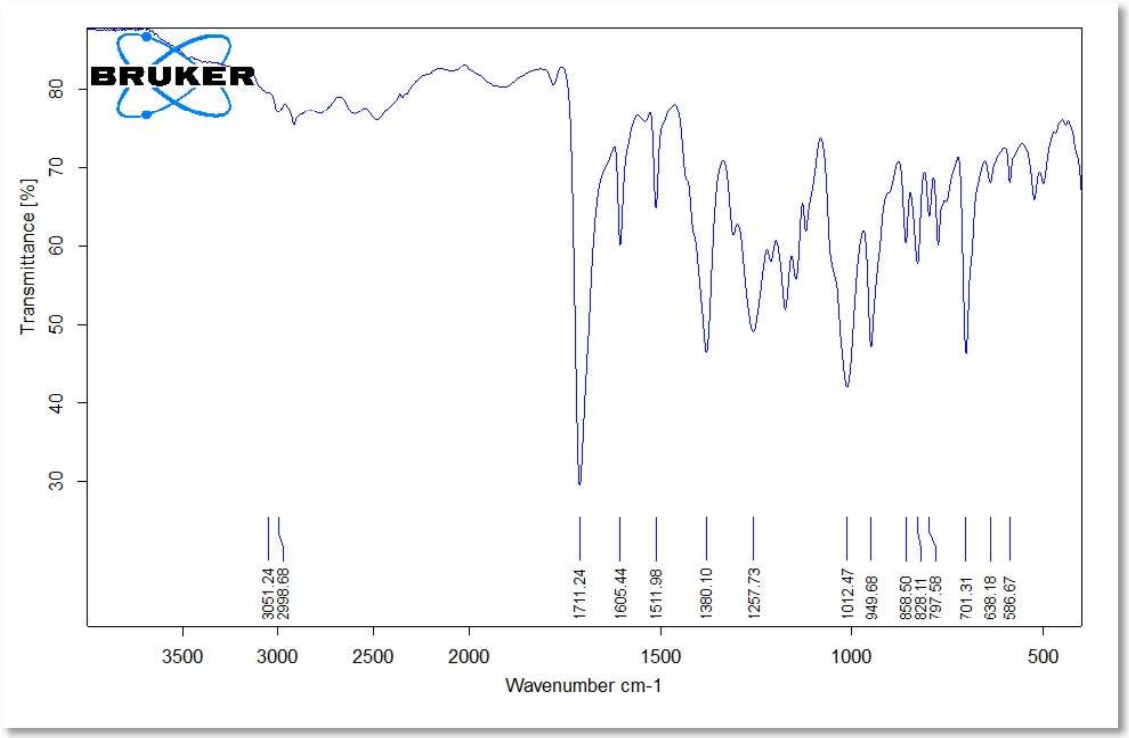


Figure (3-16): The FT-IR spectrum of monomer (F6)

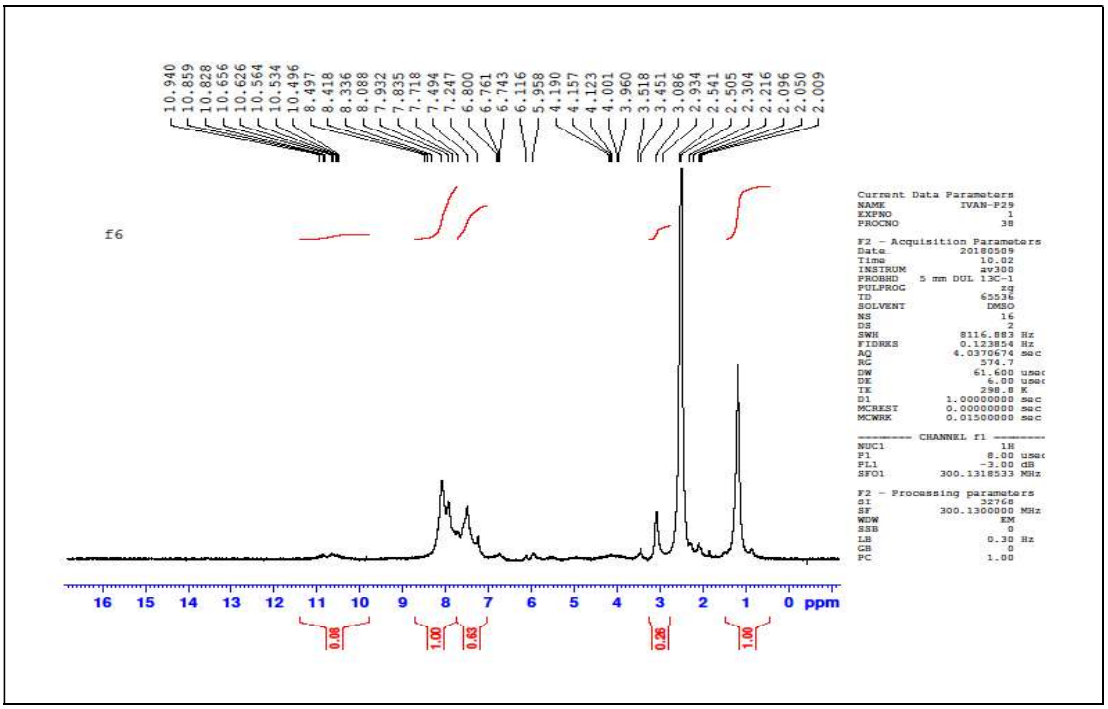


Figure (3-17): The [1]HNMR spectrum of monomer (F6)

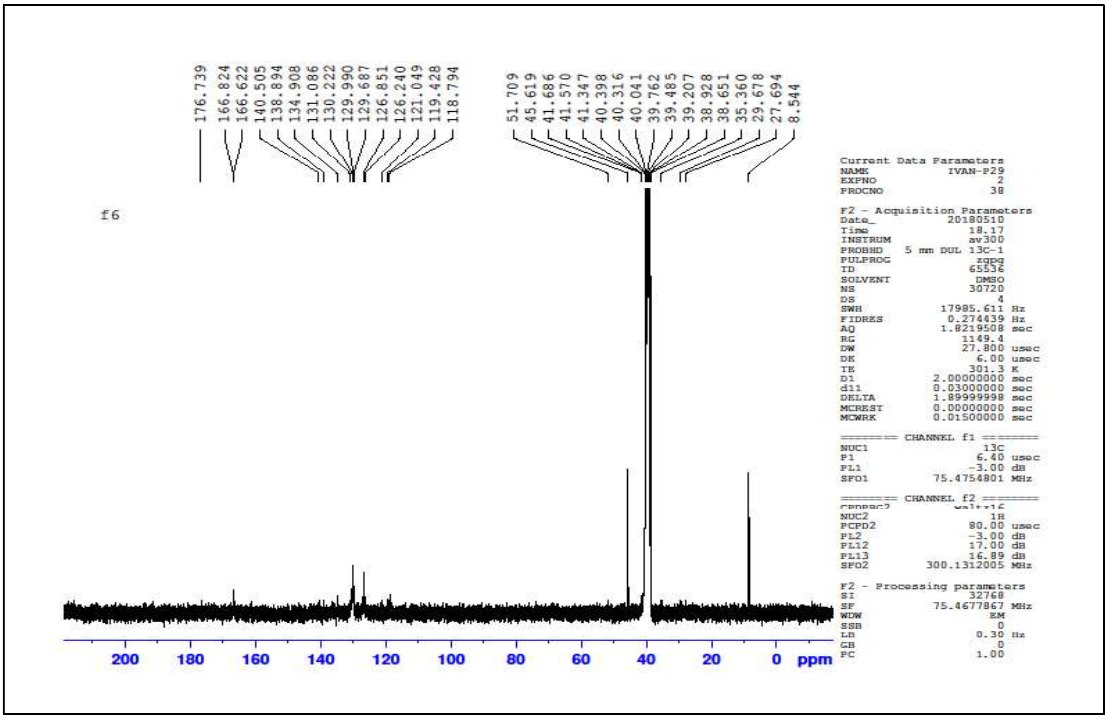


Figure (3-18): The[13]CNMR spectrum of monomer (F6)

Table (3-1): The physical properties synthesis of s monomers (F1-F6).

Comp. No.	m.p. (°C)	Yield %	color	M.Wt g/mol	M.F	TLC	
						Solvent	R_f
F1	242-245	82	Yellow	217	$C_{11}H_7O_4N$	Hexcan:aceton 2:3	0.79
F2	143 -145	68	yellow	449	$C_{21}H_{15}N_5O_5S$	Hexane: $CHCl_3$ 3:2	0.69
F3	135-138	65	Brown	498.5	$C_{27}H_{19}N_4O_4Cl$	Hexane:$CHCl_3$ 3:2	0.73
F4	196 -198	62	light yellow	350	$C_{19}H_{14}N_2O_5$	Hexane:$CHCl_3$ 3:2	0.66
F5	192 -195	82	light yellow	364	$C_{21}H_{20}N_2O_4$	Hexan:acetone 3:2	0.76
F6	252-255	68.8	Dark yellow	379	$C_{18}H_{13}N_5O_5$	Hexane:$CHCl_3$ 3:2	0.77

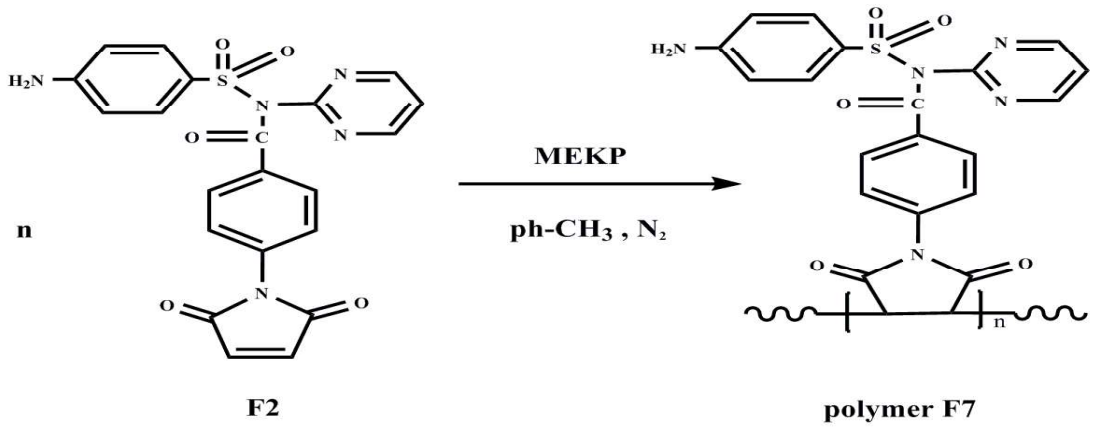
3.3 Synthesis of polymers

The polymerization process was done in both homogeneous and heterogeneous forms, as shown below:

3.3.1 Synthesis of homo-polymer

3.3.1.1 Synthesis of polymer (F7)

In round bottom flask, monomer (F2) with Toluene was then sealed with a tight seal and placed in a water bath at 90 °C , and added two drops of methylethylketone peroxide, then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2 hr. and at the end of the polymerization. Equation (3-7) represents this reaction.



Equation (3-7): synthesis of homo-polymer (F7)

The FT-IR spectrum of polymer (F7), Figure (3-19), shows disappearance absorption band of C=C-H $_{amide}$,and absorption band at (3078) cm^{-1} of NH_2 , appearance absorption band at (2885) cm^{-1} of C=C-H $_{ring\ of\ drug}$, and appearance of absorption band of C=O at (1712) cm^{-1}

Figure (3-20), shows the ^{1}H-NMR spectrum for polymer (F7) appearance single signal at 13.006 for (NH_2) , and show melti. Signal at (7.22-8.03) for $(C=C-H)_{ph}$, and show signal at (6.07) for $(C-C-H)_{amide}$.

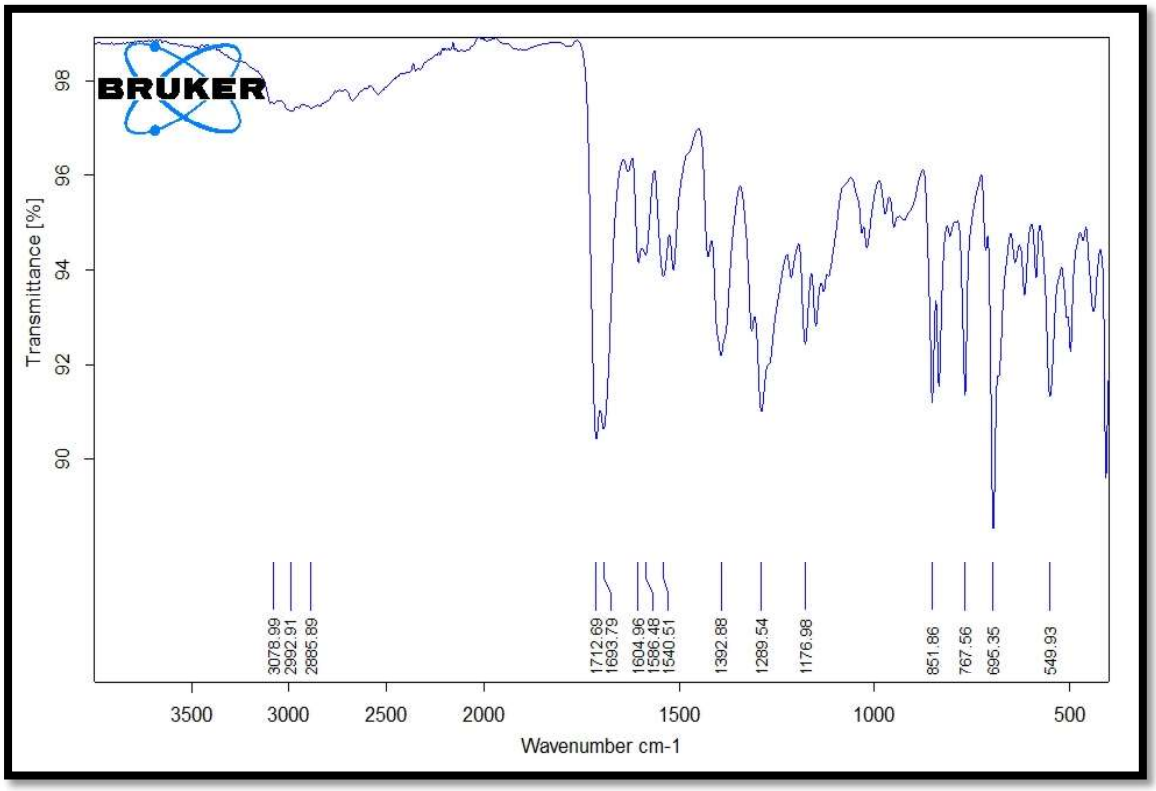


Figure (3-19): The FT-IR spectrum of homo-polymer (F7)

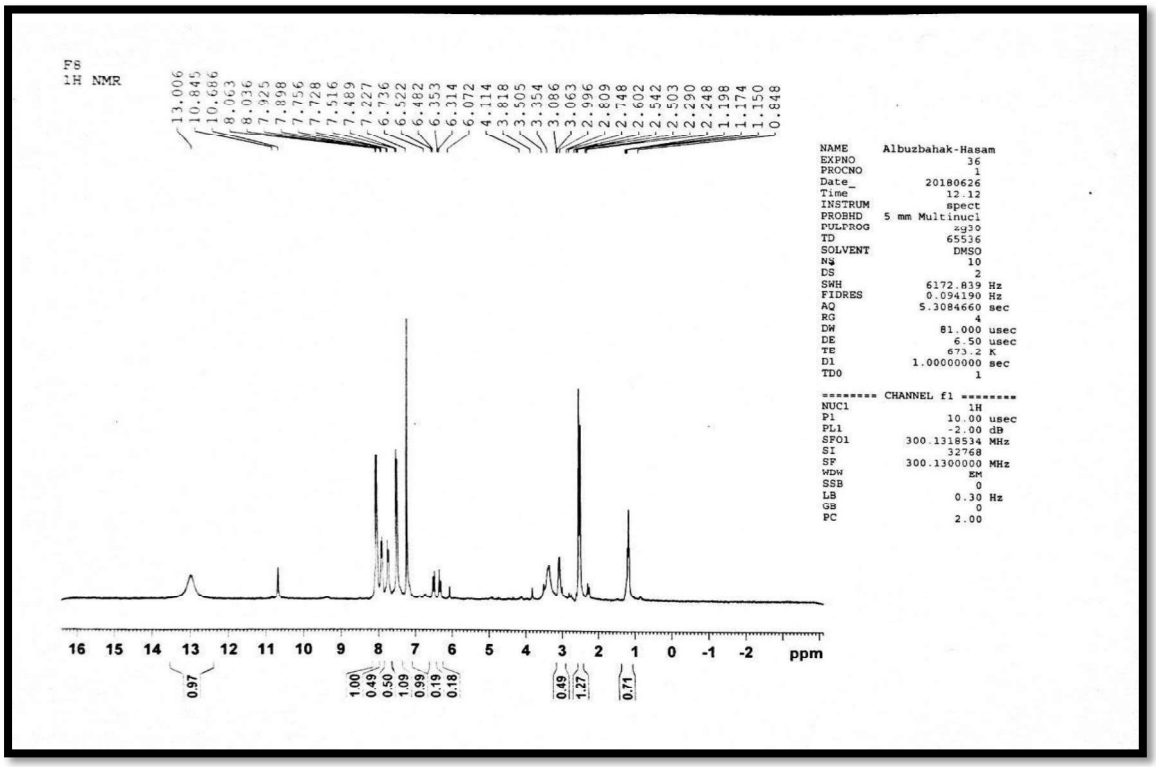
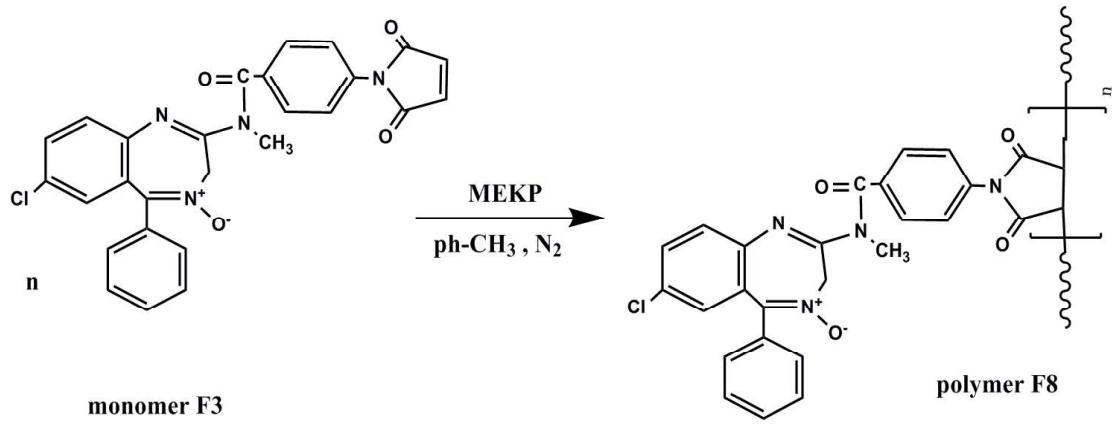


Figure (3-20): The [1]HNMR spectrum of homo-polymer (F7)

3.3.1.2 Synthesis of polymer (F8)

In round bottom flask, monomer (F3) with Toluene was then sealed with a tight seal and placed in a water bath at 90 °C , and added two drops of methylethylketone peroxide, then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2 hr. and at the end of the polymerization. Equation (3-8) represents this reaction.



Equation (3-8): synthesis of homo-polymer (F8)

The FT-IR spectrum of polymer (F8), Figure (3-21), shows disappearance absorption band of C=C-H $_{amide}$ and shows absorption band of C-C-H_{aliph} at (2885) cm^{-1} and absorption band at (1711) cm^{-1} of C=O. Figure (3-22), shows the ^{1}H-NMR spectrum for polymer (F8) shows appearance multi. Signal at (7.18-8.07) for $(C=C-H)_{ph}$, and show signal at (5.06) for $(C-C-H)_{amide}$, and show signal at (3.81) for $(C-H_3)$.

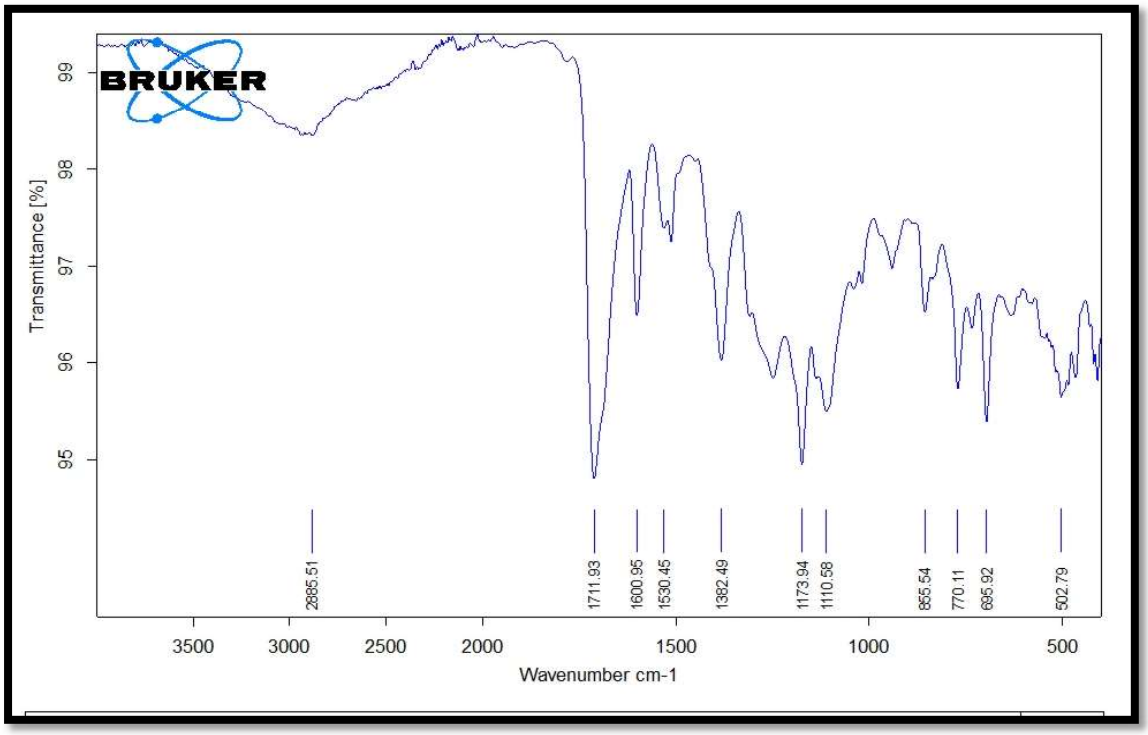


Figure (3-21): The FT-IR spectrum of homo-polymer (F8)

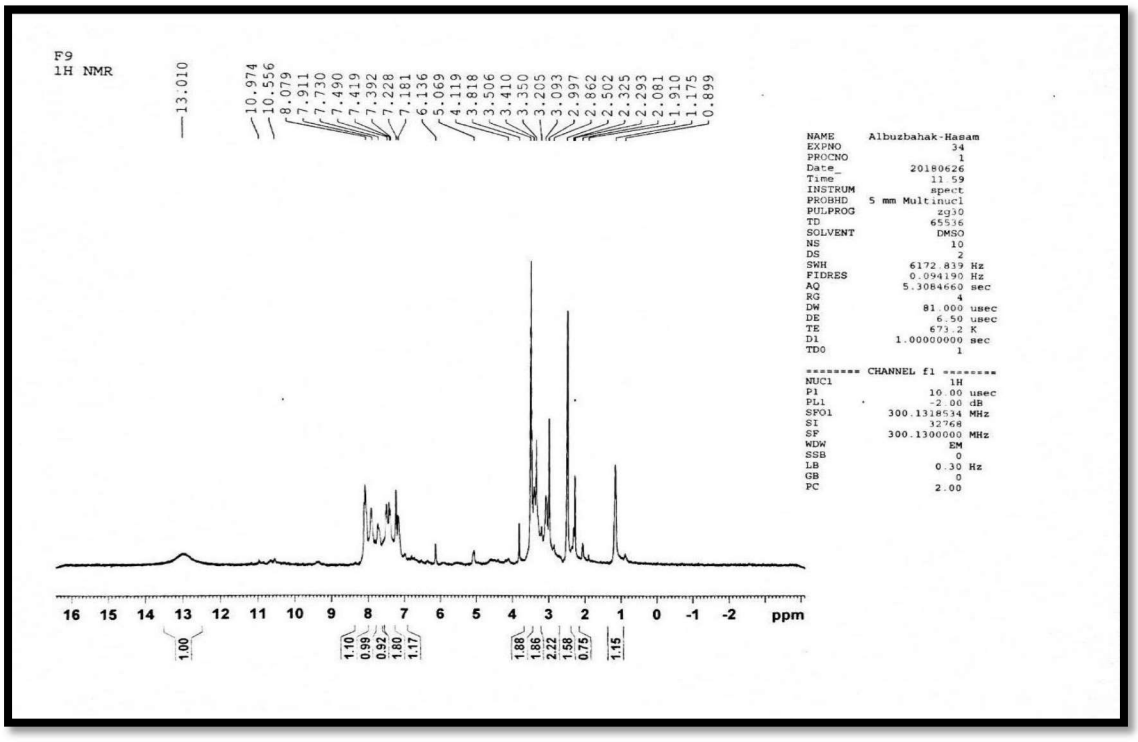
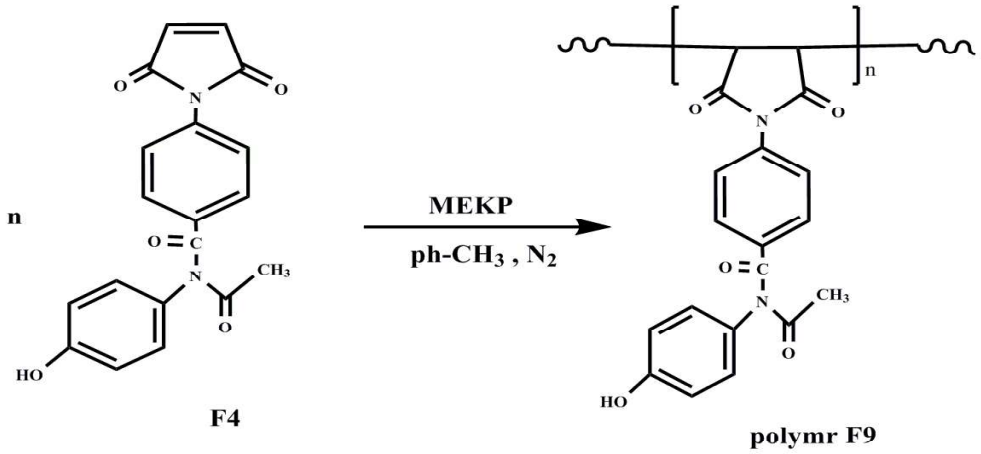


Figure (3-22): The ^{1}HNMR spectrum of homo-polymer (F8)

3.3.1.3 Synthesis of polymer (F9)

In round bottom flask, monomer (F4) with Toluene was then sealed with a tight seal and placed in a water bath at 90 °C , and added two drops of methylethylketone peroxide, then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2 hr. and at the end of the polymerization. Equation (3-9) represents this reaction.



Equation (3-9): synthesis of homo-polymer (F9)

The FT-IR spectrum of polymer (F9), Figure (3-23), shows absorption band of C=C-H_{ring} at (3101) cm^{-1}, and disappear absorption band of C-H_{amide}, and absorption band of C-C-H_{aliph} at (2911) cm^{-1}, and absorption band of C=O at (1706) cm^{-1}, and absorption band of C-N at (1380) cm^{-1} , and the last absorption band of substituted in position p- and m- . Figure (3-24), represent the ^{1}H-NMR spectrum for polymer (F9) appearance multiplet signal at (7.19-8.06) for $(C=C-H)_{ph}$, and show signal at (3.51) for (CH_3).

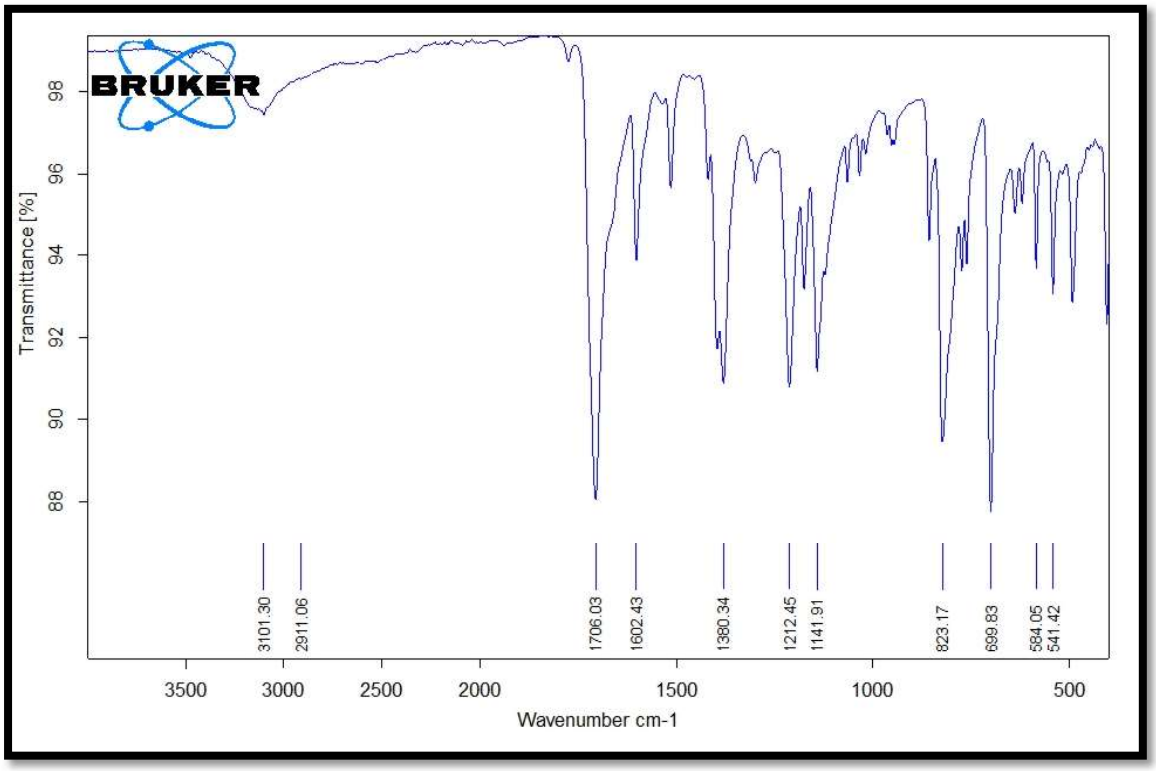


Figure (3-23): The FT-IR spectrum of homo-polymer (F9)

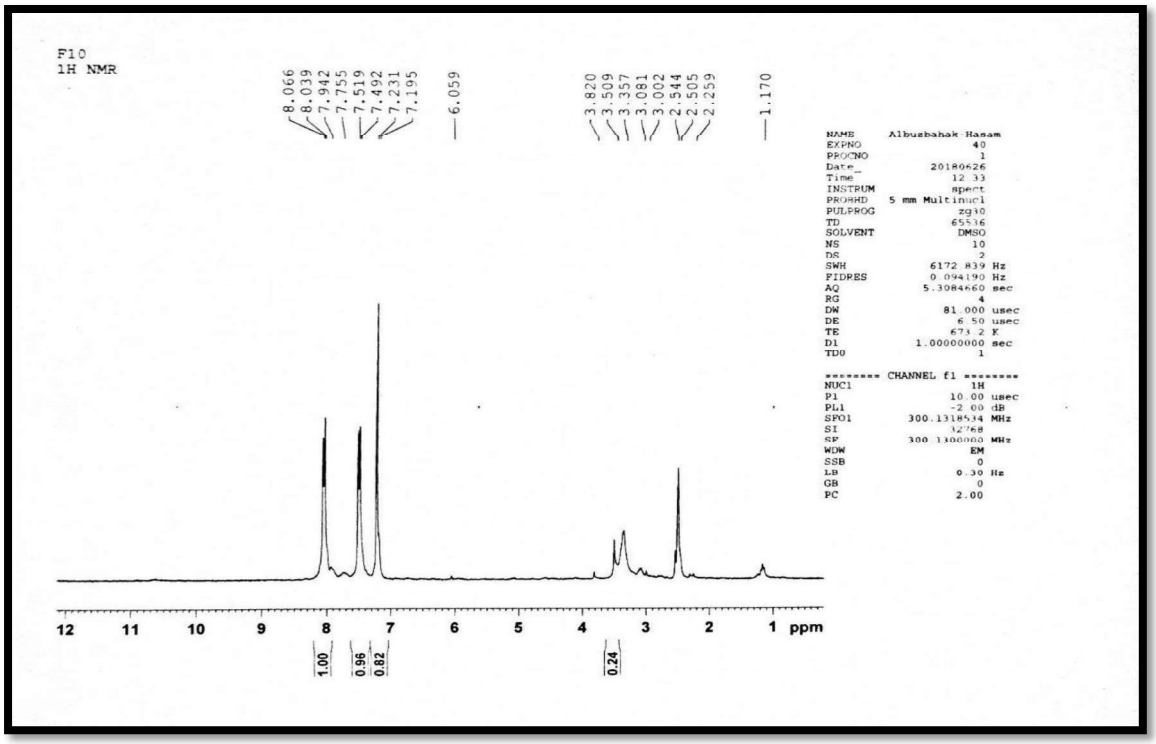
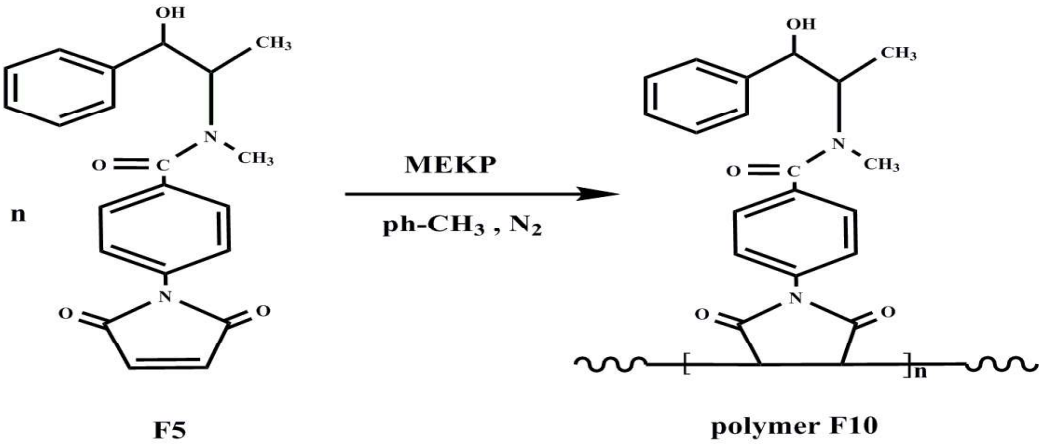


Figure (3-24): The [1]HNMR spectrum of homo-polymer (F9)

3.3.1.4 Synthesis of polymer (F10)

In round bottom flask, monomer (F5) with Toluene was then sealed with a tight seal and placed in a water bath at 90 °C , and added two drops of methylethylketone peroxide, then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2 hr. and at the end of the polymerization. Equation (3-10) represents this reaction.



Equation (3-10): synthesis of homo-polymer (F10)

The FT-IR spectrum of polymer (F10), Figure (3-25), shows absorption band at(3166) for (OH), and absorption band of $(C= C-H)_{ph}$ at (3101) cm^{-1}, and disappear absorption band of $C=C-H_{amid}$, and absorption band of $C-C-H_{aliph}$ at (2988) cm^{-1} , and absorption band of C=O at (1705) cm^{-1}, and absorption band of C-N-C at (1380) cm^{-1}. Figure (3-26), represent the ^{1}H-NMR spectrum for Compound (F10) appearance multipelet at (7.22-8.05) for $(C=C-H)_{ph}$, and show signal at (3.49) for (CH_3).

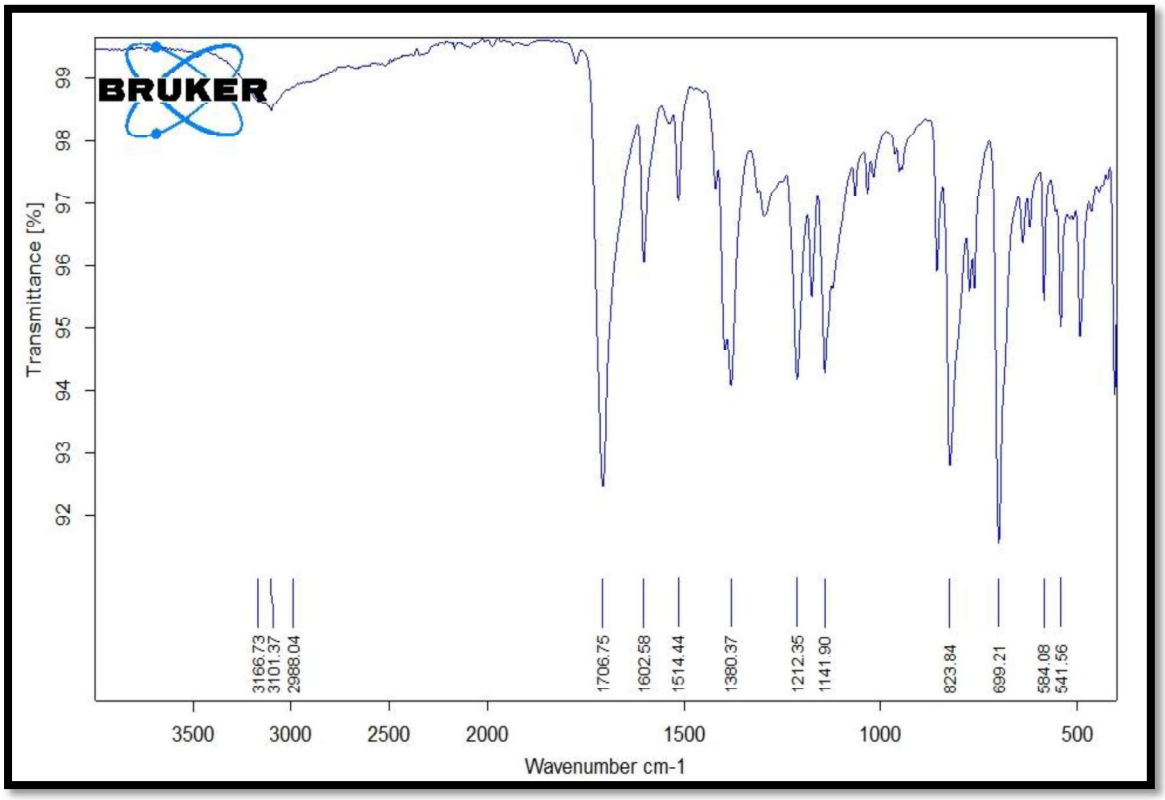


Figure (3-25): The FT-IR spectrum of homo-polymer (F10)

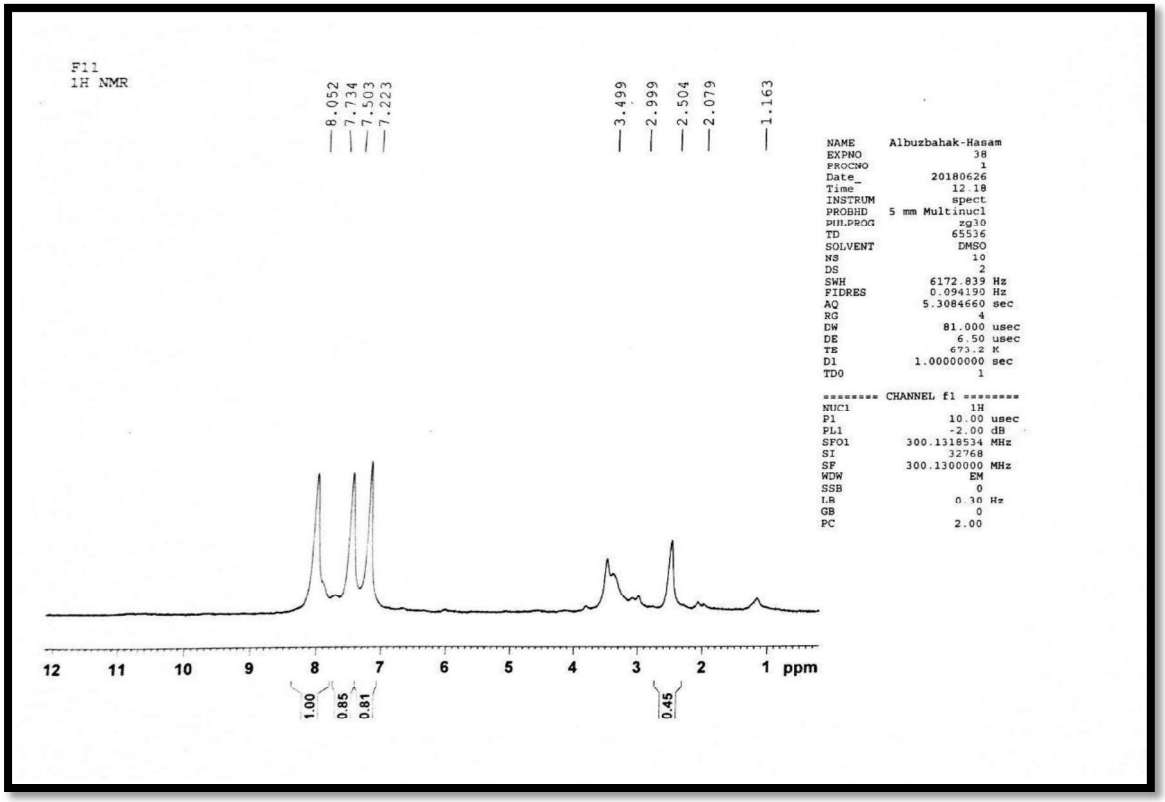
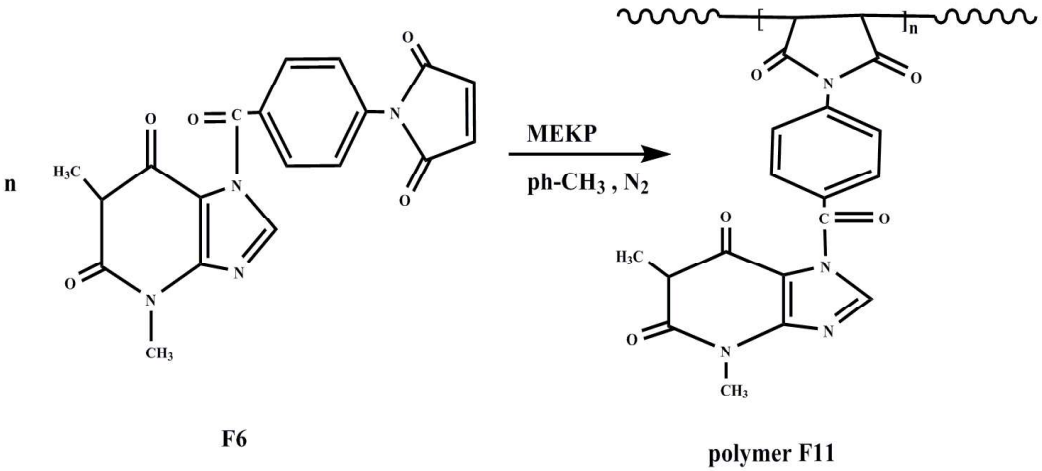


Figure (3-26): The ^{1}HNMR spectrum of homo-polymer (F10)

3.3.1.5 Synthesis of polymer (F11)

In round bottom flask, monomer (F6) with Toluene was then sealed with a tight seal and placed in a water bath at 90 °C , and added two drops of methylethylketone peroxide, then pass the nitrogen gas from one of the flask nozzle. The reaction continued for 2 hr. and at the end of the polymerization. Equation (3-11) represents this reaction.



Equation (3-11): synthesis of homo-polymer (F11)

The FT-IR spectrum of polymer (F11), Figure (3-27), shows absorption band of $(C=C-H)_{ph}$ at (3118) cm^{-1}, and disappear absorption band of $(C-H)_{amide}$, and absorption band of $C-H_{aliph}$ at (2928) cm^{-1} , and absorption band of C=O at (1704) cm^{-1} , and absorption band of C-N-C at (1380) cm^{-1}**.** Figure (3-28), represent the ^{1}H-NMR spectrum for Compound (F11) appearance at multi signal at (7.22-8.05) for $(C=C-H)_{ph}$, and show signal at (5.44) for $(C-C-H)_{amide}$,and show signal at (4.78) for $(C-H_3)$.

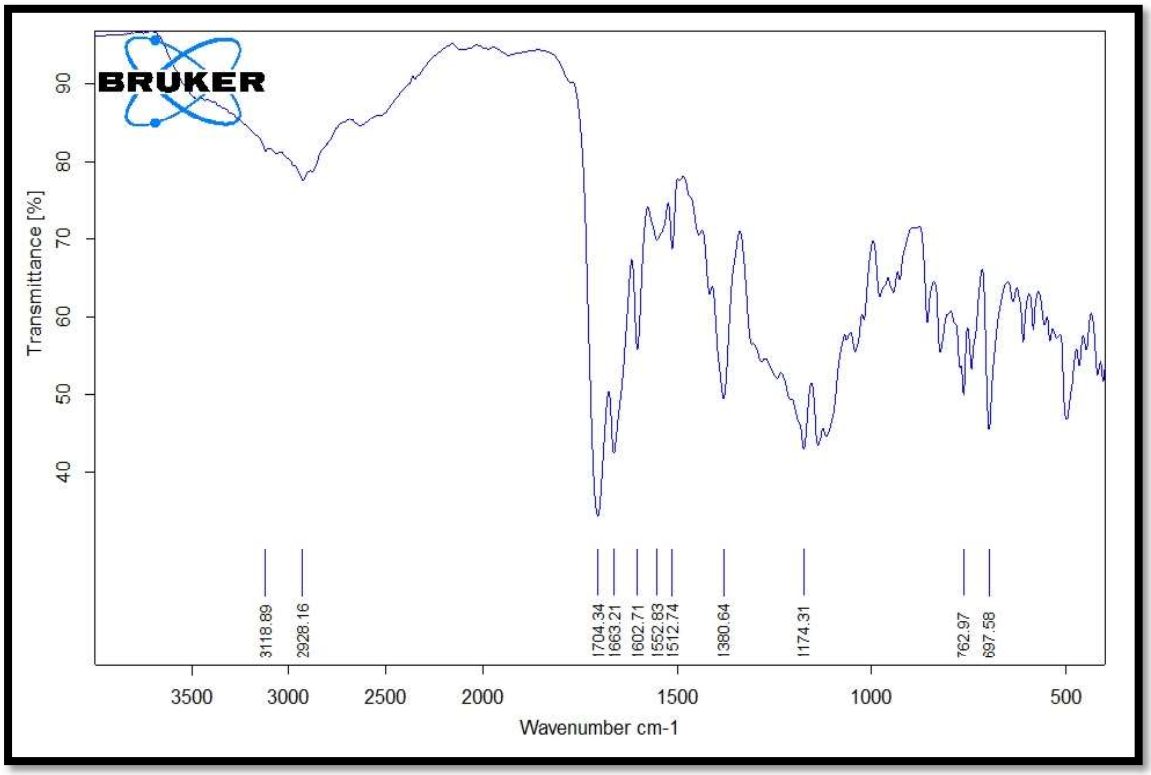


Figure (3-27): The FT-IR spectrum of homo-polymer (F11)

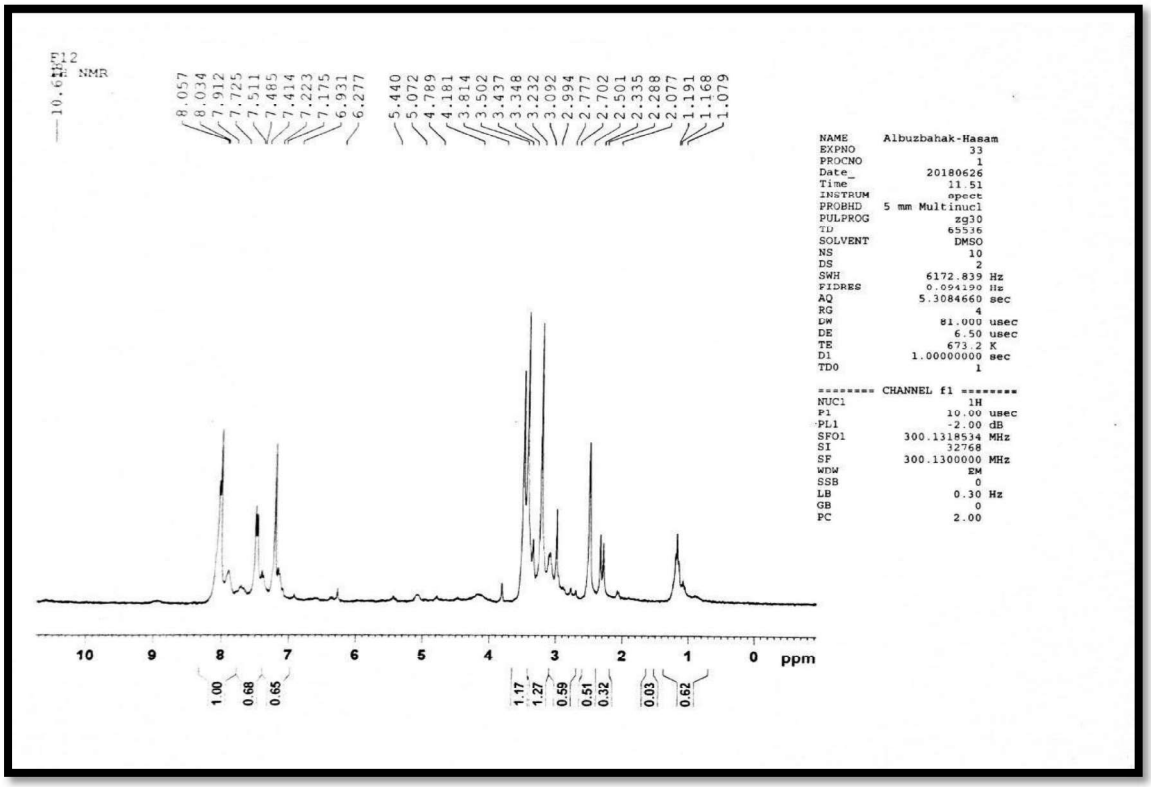
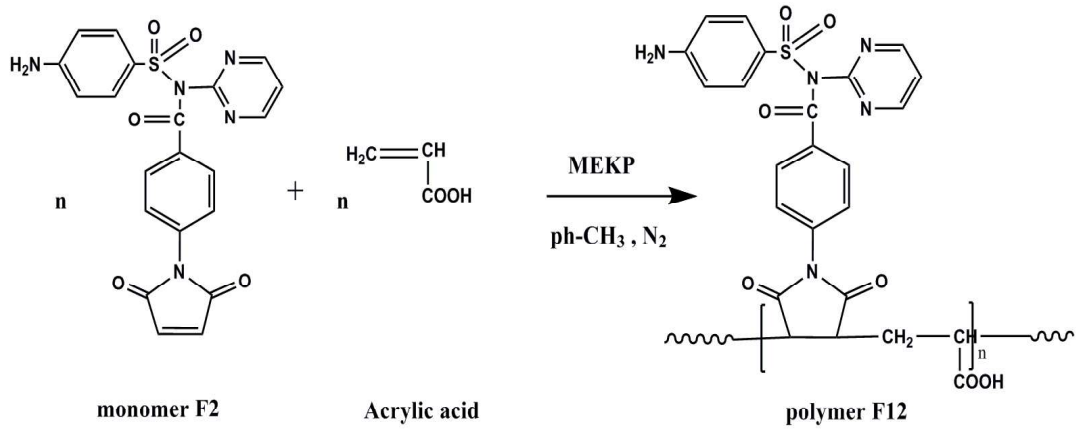


Figure (3-28): The ^{1}HNMR spectrum of homo-polymer (F11)

3.3.2 Synthesis of hetero-polymer

3.3.2.1 Synthesis of polymer (F12)

In a round bottom flask, monomer (F2) with toluene and acrylic acid monomer, was then sealed with a tight seal and placed in a water bath at 90 °C , and added two drops of methylethylketone peroxide, then pass the nitrogen gas from one of the flask nozzle. Equation (3-12) represents this reaction.



Equation (3-12):synthesis of hetero-polymer (F12)

The FT-IR spectrum of polymer (F12),Figure (3-29), shows disappearance absorption band of O-H and appearance of absorption band of C=C-H $_{benzamide}$ at (3105) cm^{-1}, and disappearance absorption band of C=C-H $_{amide}$ and appearance absorption band at (3075) cm^{-1} of C=CH $_{acrylic\ acid}$, appearance absorption band at (2981) cm^{-1} of C-C-$H_{aliph.}$, and appearance of absorption band of C=O at (1714) cm^{-1} and absorption band of C-N-C at (1383) cm^{-1}. Figure (3-30), represent the ^{1}H-NMR spectrum for Compound (F12) appearance multi signal at (7.18-8.52) for $(C=C-H)_{ph}$, and show signal at(5.95) for $(C-C-H)_{amide}$, and show signal at(4.21) for $(C-H)_{aliph}$.

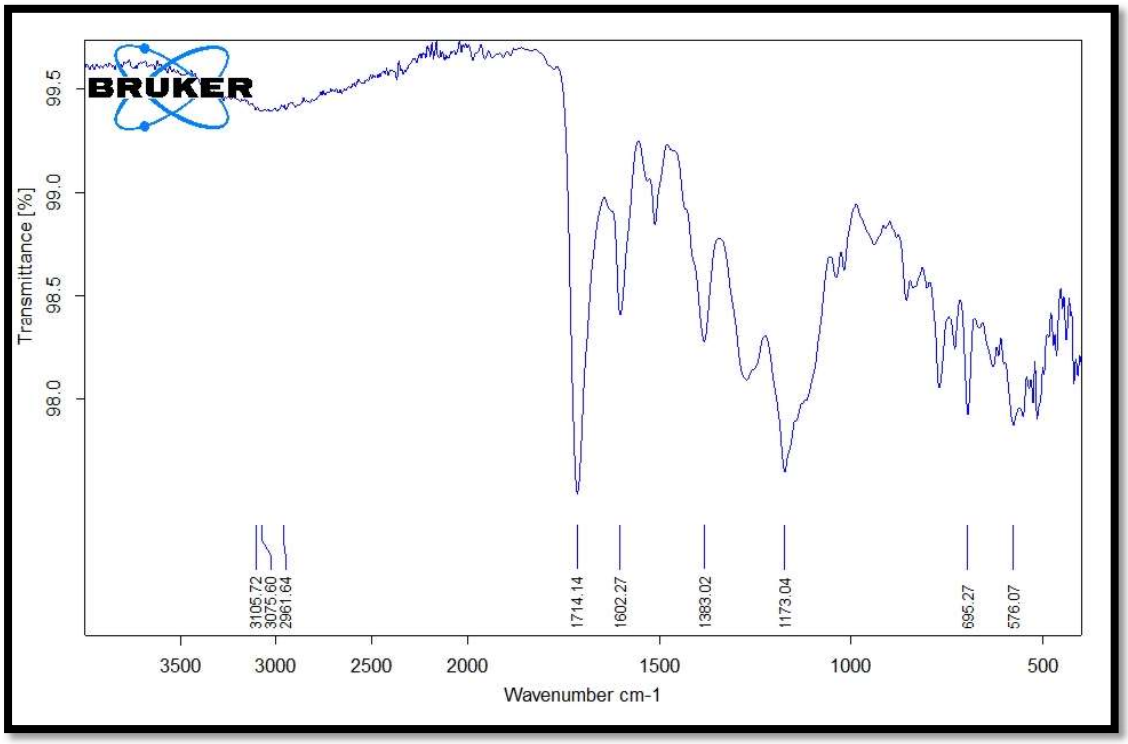


Figure (3-29): The FT-IR spectrum of hetero-polymer (F12)

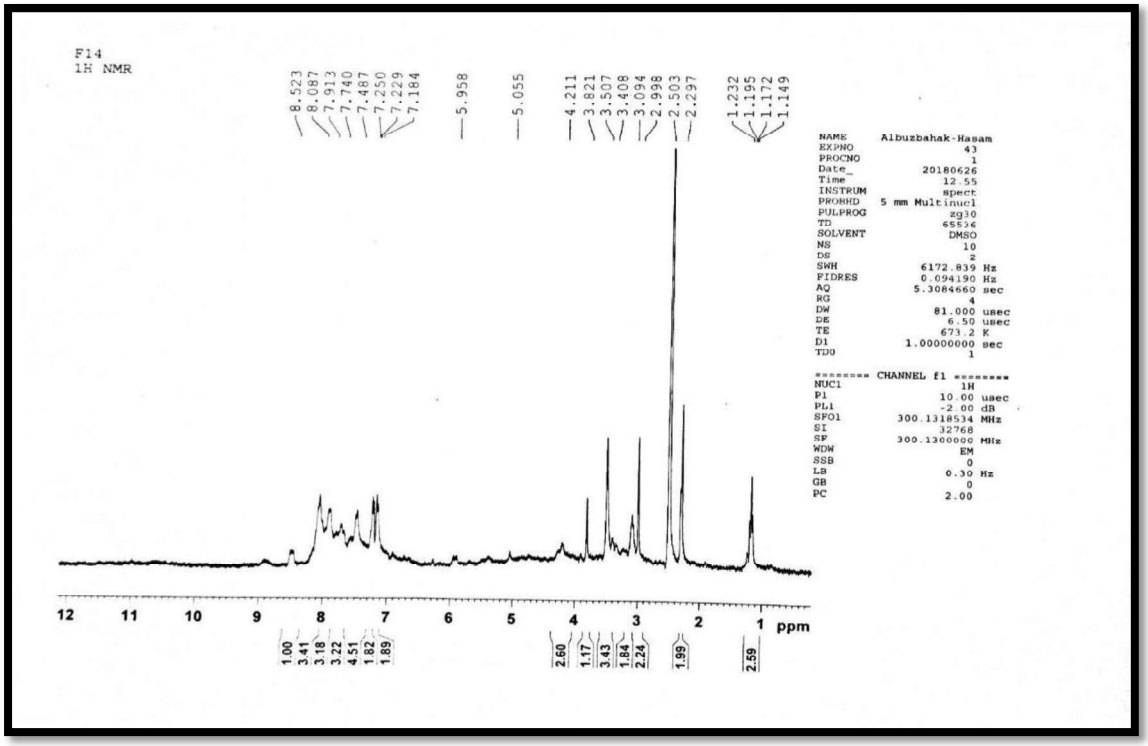
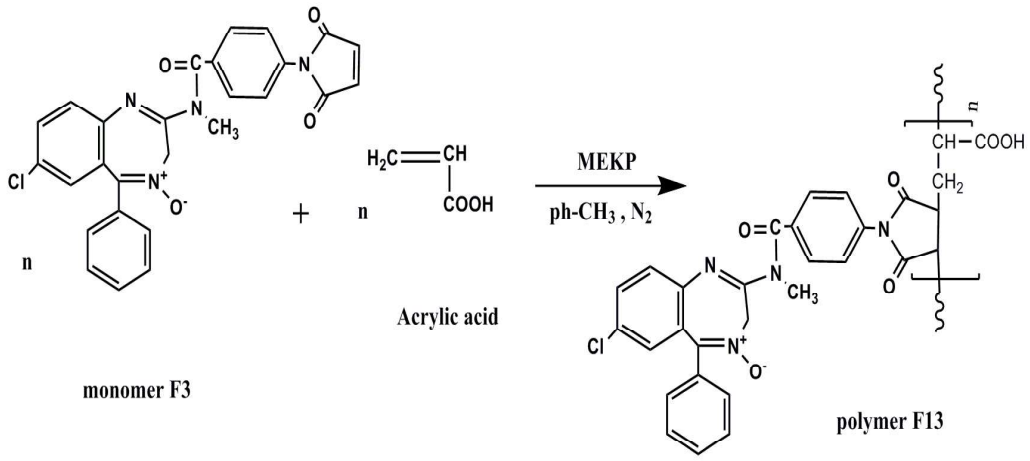


Figure (3-30): The ^{1}HNMR spectrum of hetero-polymer (F12)

3.3.2.2 Synthesis of polymer (F13)

In a round bottom flask, monomer (F3) with toluene and acrylic acid monomer, was then sealed with a tight seal and placed in a water bath at 90 °C , and added two drops of methylethylketone peroxide, then pass the nitrogen gas from one of the flask nozzle. Equation (3-13) represents this reaction.



Equation (3-13):synthesis of hetero-polymer (F13)

The FT-IR spectrum of polymer(F13), Figure (3-31), shows appearance of absorption band of $C\text{-}H_{aliph}$ at (2929) cm^{-1} and appearance absorption band at (3010)cm^{-1} for $(C=C)_{acrylic\ acid}$ and disappearance absorption band of $C=C\text{-}H_{amide}$, and appearance absorption band of $C=O_{amide}$ at (1711) cm^{-1} , and appearance absorption band of C-N-C at(1381)cm^{-1} ,and appearance absorption band of C-Cl at (695)cm^{-1} .Figure (3-32),represent the ^{1}H-NMR spectrum for Compound (F13) appearance multiplet signal at (7.49-8.06) for $(C=C\text{-}H)_{ph}$, and show signal at (4.21) for $(C\text{-}H)_{aliph}$.

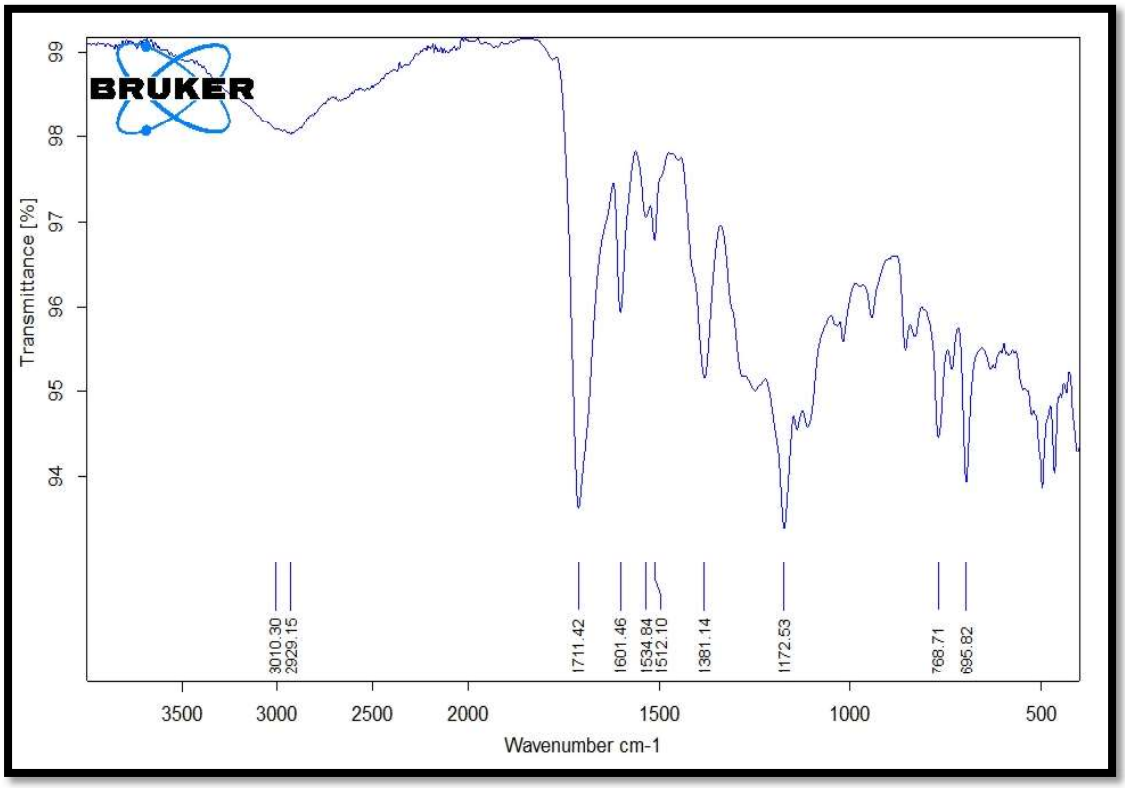


Figure (3-31): The FT-IR spectrum of hetero-polymer (F13)

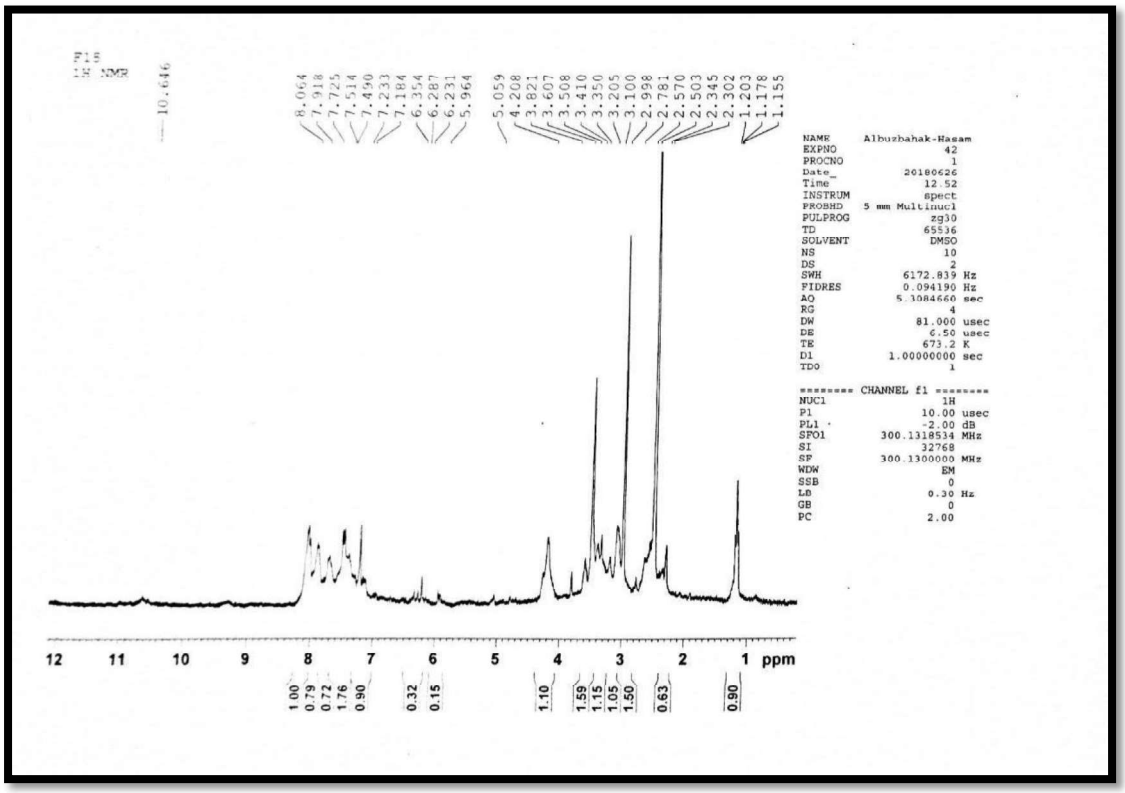
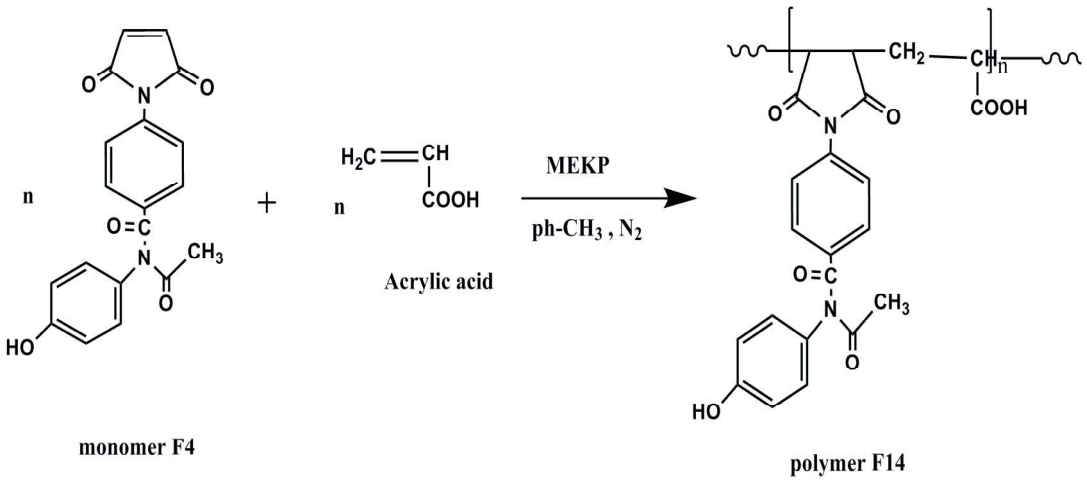


Figure (3-32): The ^{1}HNMR spectrum of hetero-polymer (F13)

3.3.2.3 Synthesis of polymer (F14)

In a round bottom flask, monomer (F4) with toluene and acrylic acid monomer, was then sealed with a tight seal and placed in a water bath at 90 °C , and added two drops of methylethylketone peroxide, then pass the nitrogen gas from one of the flask nozzle. Equation (3-14) represents this reaction.



Equation (3-14):synthesis of hetero-polymer (F14)

The FT-IR spectrum of polymer (F14), Figure (3-33), shows appearance absorption band at (3268)cm^{-1} of $O\text{-}H_{drug}$, and appearance of absorption band of $(C{=}C\text{-}H)_{ph.}$ at (3065) cm^{-1} , and appearance of absorption band of $C\text{-}C\text{-}H_{aliph}$. at (2929) cm^{-1} , and disappearance absorption band of $C{=}C\text{-}H_{amide}$, and appearance of absorption band of C=O at (1710) cm^{-1} , appearance of absorption band of C-N-C at (1380) cm^{-1} . Figure (3-34), represent the ^{1}H-NMR spectrum for Compound (F14) show signal at (10.66) for $(OH)_{drug}$, and appearance multi. signal at (7.23-8.08) for $(C{=}C\text{-}H)_{ph}$, and show signal at (4.21) for $(C\text{-}H)_{aliph}$.

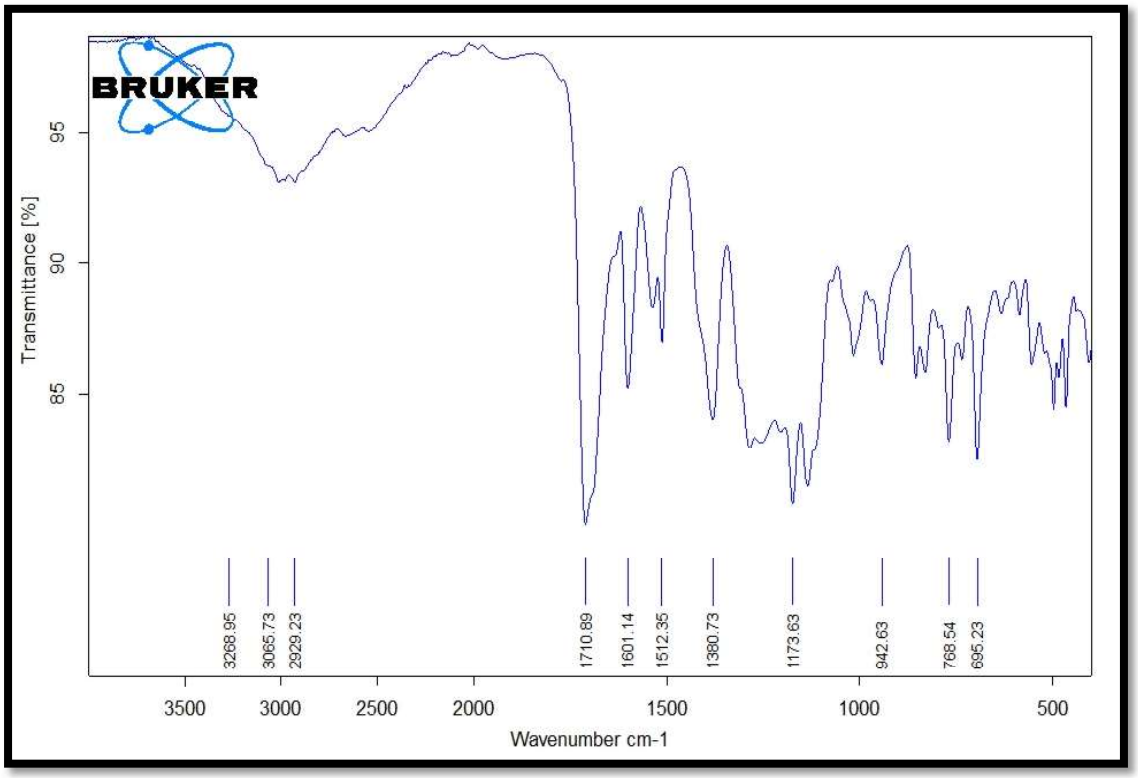


Figure (3-33): The FT-IR spectrum of hetero-polymer (F14)

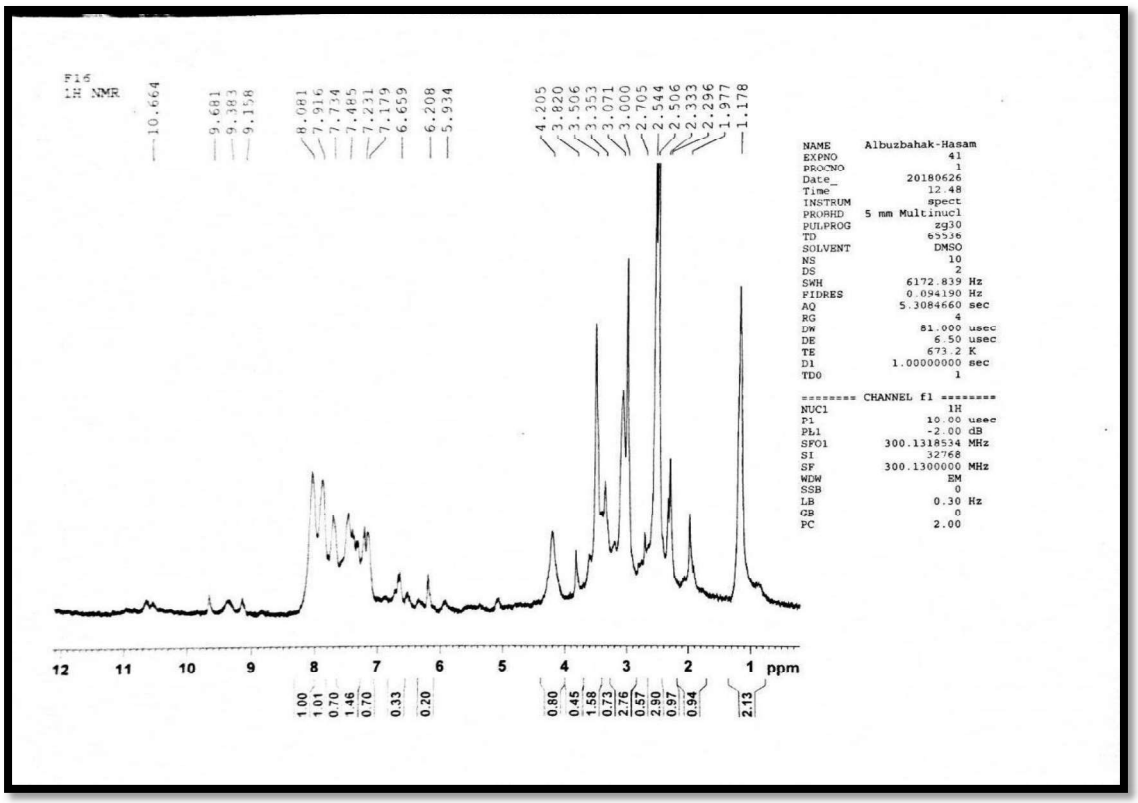
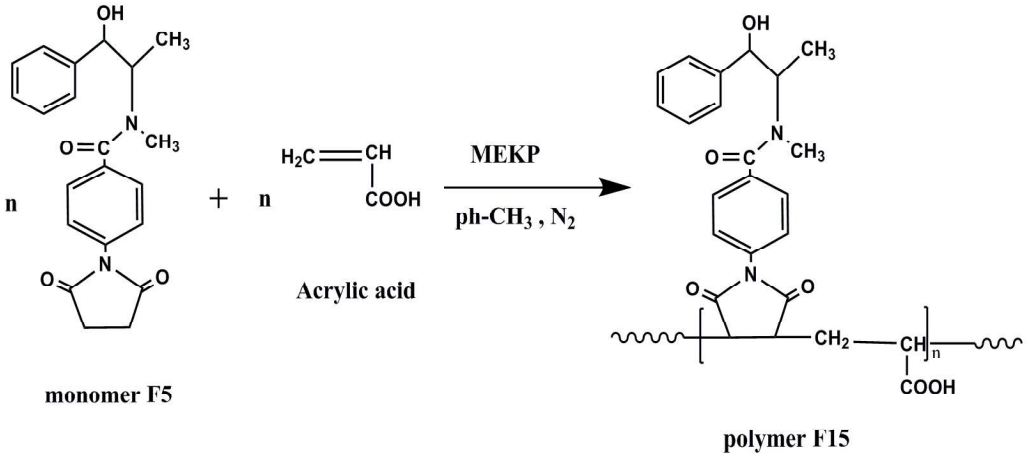


Figure (3-34): The [1]HNMR spectrum of hetero-polymer (F14)

3.3.2.4 Synthesis of polymer (F15)

In a round bottom flask, monomer (F5) with toluene and acrylic acid monomer, was then sealed with a tight seal and placed in a water bath at 90 °C , and added two drops of methylethylketone peroxide, then pass the nitrogen gas from one of the flask nozzle. Equation (3-15) represents this reaction.



Equation (3-15):synthesis of hetero-polymer (F15)

The FT-IR spectrum of polymer(F15),Figure (3-35) ,shows appearance of absorption band of C=C-H_{drug} at (2965) cm^{-1} ,absorption band of C-C-H_{aliph} at (2933) cm^{-1} , and disappearance absorption band of C=C-H_{amide}, and appearance absorption band of C=O at (1710) cm^{-1} , and appearance absorption band of C-N-C at (1387) cm^{-1} . Figure (3-36), represent the ^{1}H-NMR spectrum for polymer (F15) appearance multi. signal at (7.22-8.08) for $(C=C-H)_{ph}$, and show signal at (4.21) for $(C-H)_{aliph.}$.

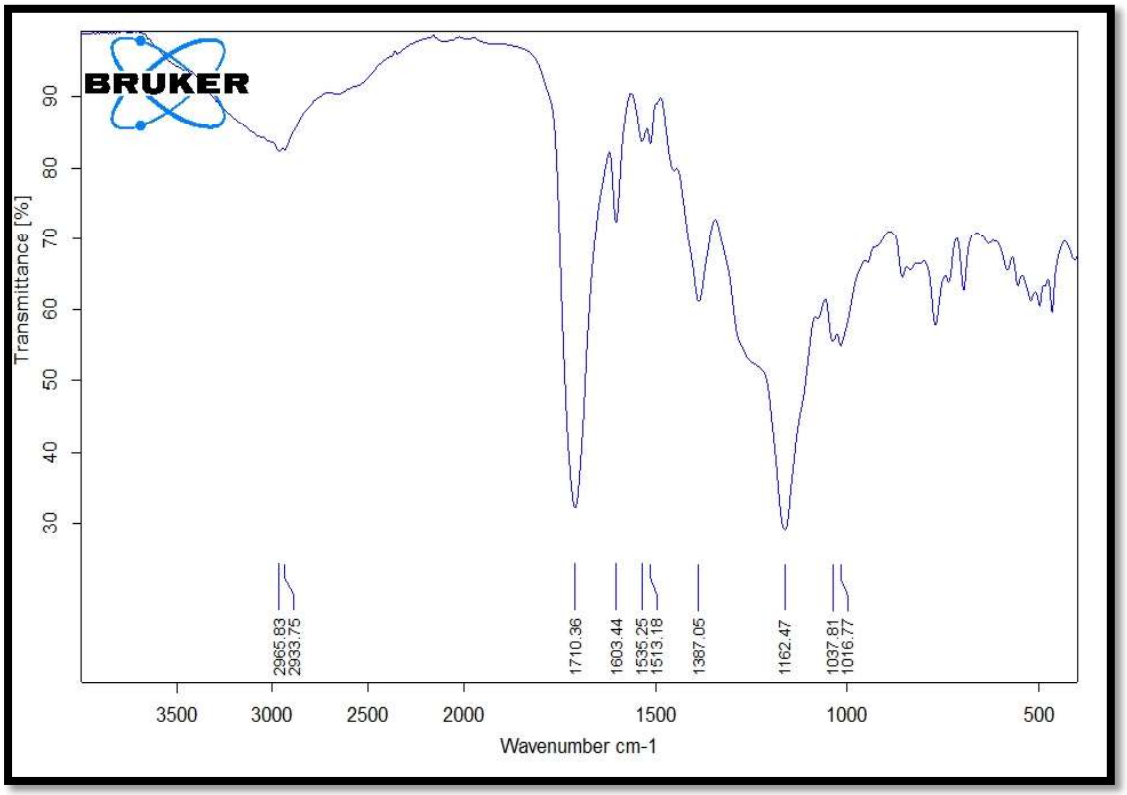


Figure (3-35): The FT-IR spectrum of hetero-polymer (F15)

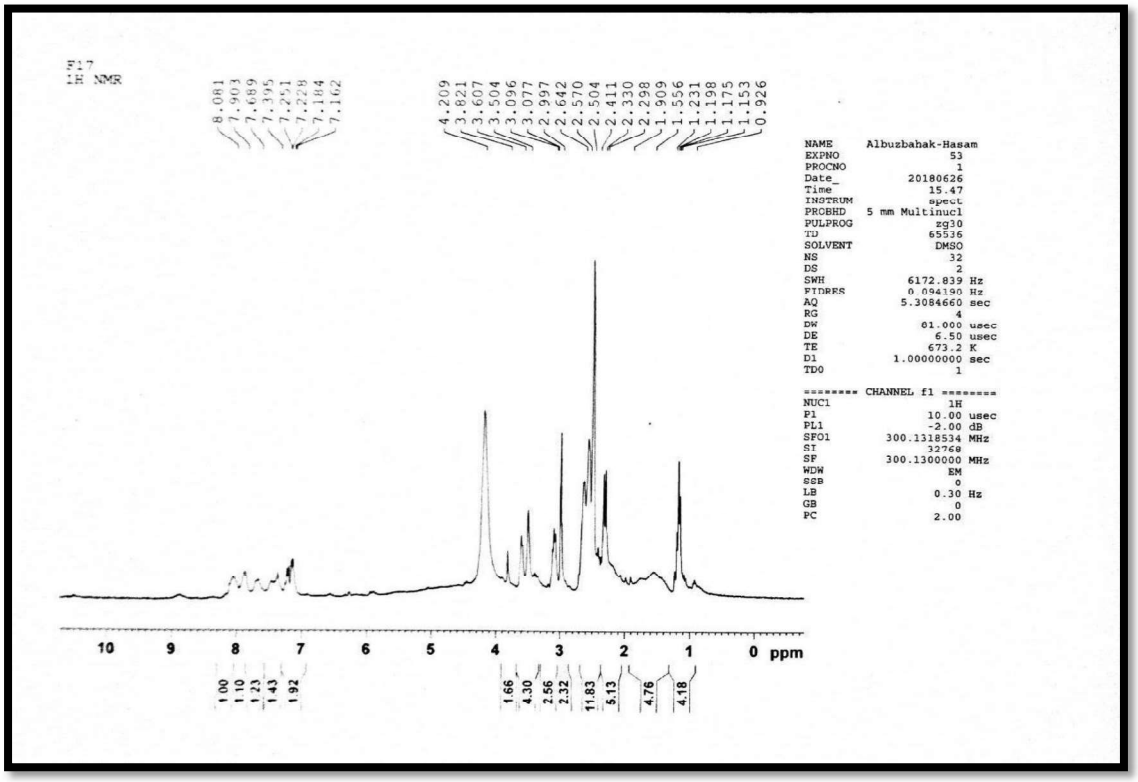
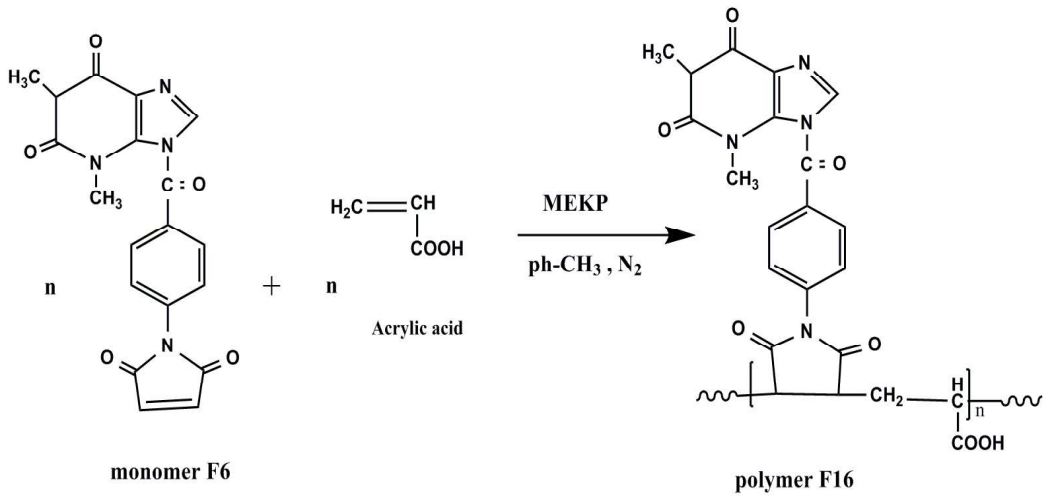


Figure (3-36): The ^{1}HNMR spectrum of hetero-polymer (F15)

3.3.2.5 Synthesis of polymer (F16)

In a round bottom flask, monomer (F6) with toluene and acrylic acid monomer, was then sealed with a tight seal and placed in a water bath at 90 °C , and added two drops of methylethylketone peroxide, then pass the nitrogen gas from one of the flask nozzle. Equation (3-16) represents this reaction.



Equation (3-16):synthesis of hetero-polymer (F16)

The FT-IR spectrum of polymer (F16), Figure (3-37), shows appearance absorption band of $(C=C-H)_{ph}$ at (3080) cm^{-1}, and appearance of absorption band of $(C-C-H)_{aliph.}$ at (2948) cm^{-1}, and disappearance absorption band of $(C=C-H)_{amide}$, and appearance of absorption band of C=O at (1711) cm^{-1} , and appearance of absorption band of C-N-C at (1383) cm^{-1}. Figure (3-38), represent the ^{1}H-NMR spectrum for polymer (F16) appearance melti. signal at (7.22-8.06) for $(C=C-H)_{ph}$, and show signal at(4.20) for $(C-H)_{aliph.}$.

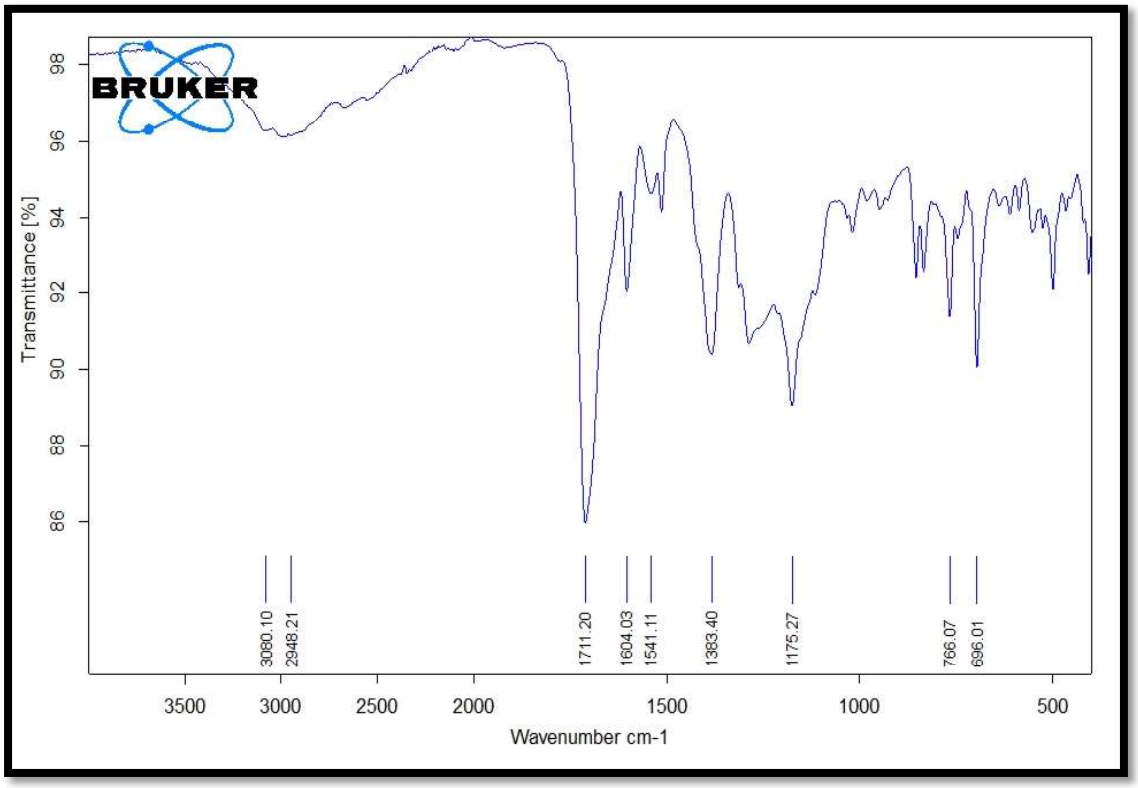


Figure (3-37): The FT-IR spectrum of hetero-polymer (F16)

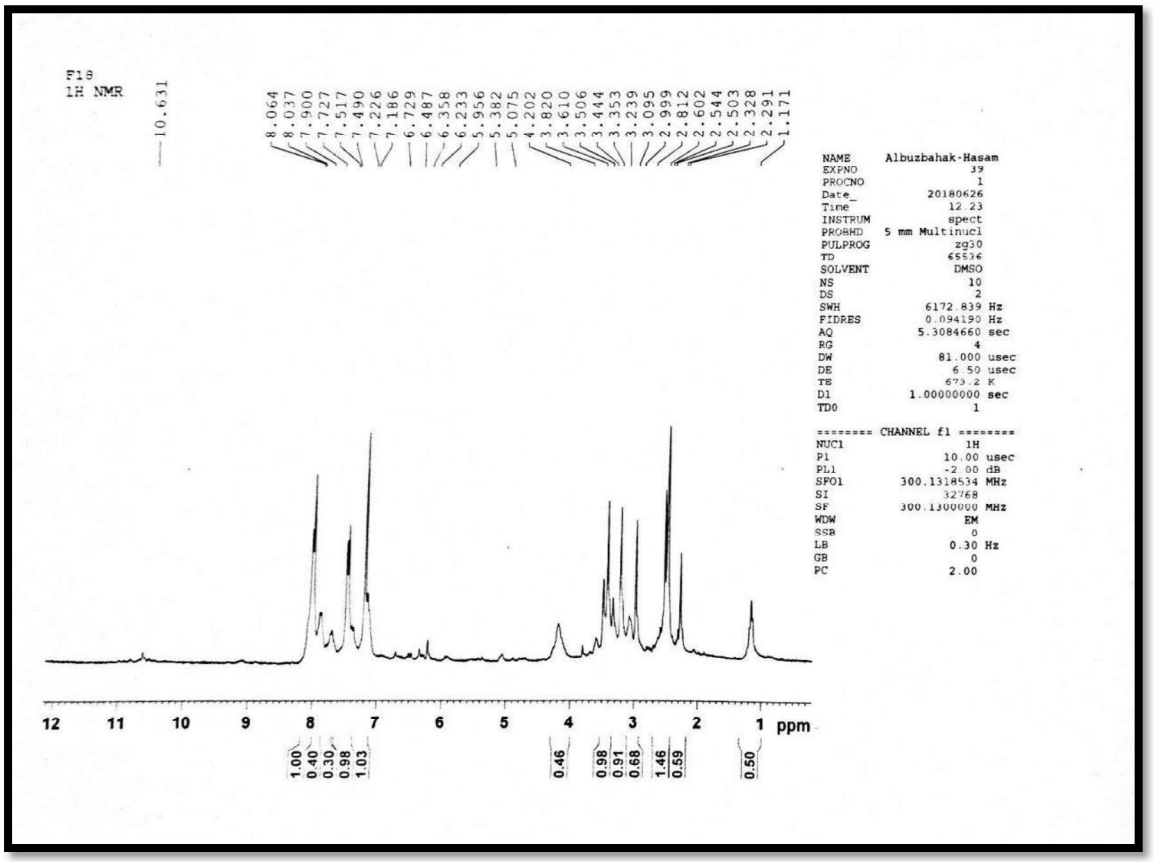


Figure (3-38): The ^{1}HNMR spectrum of hetero-polymer (F16)

Table (3-2): Some of the physical properties of prepared polymers

polymer	color	T °C	$t_{D.W}$ (s)	$T_{pol.}$ (s)	$d_{pol.}$ (g/cm^3)	$d_{D.W}$ (g/cm^3)	$\eta_{D.w}$ (g/cm.s)	$\eta_{pol.}$ (g/cm.s)
F7	Yellow	25	62	54	0.786	0.99	0.904	0.62
F8	Brown			58	0.782			0.67
F9	light yellow			61	0.788			0.71
F10	Yellow			52	0.785			0.59
F11	yellow			59	0.783			0.66
F12	light yellow			54	0.783			0.61
F13	Brownlight			53	0.786			0.60
F14	light yellow			52	0.782			0.58
F15	light yellow			51	0.785			0.57
F16	yellow			50	0.783			0.56

Where d:density , ŋ:viscosity , t: time for polymer and distil water.

3.4 Physical properties of the synthesis polymer

3.4.1 The characteristic of solubility

The solubility properties of monomers and polymers prepared, in different solvents (H_2O, Ethanol, $CHCl_3$, Ether, Toluene, DMSO, Hexane, Petroleum ether and Acetone) were studied. The solubility of the polymers was observed, some of which were completely dissolved (+) and some solids were partially dissolved (partially),and another has not

been dissolved (-), as shown in Tables (3-3) and (3-4), for monomers and homo and hetero polymers respectively.

Table (3-3): The solubility of synthesis monomers

Monomer	H_2O	EtOH	$CHCl_3$	Ether	Toluene	DMSO	Hexane	Petroleum ether	Acetone
F1	+	partial	+	-	partial	+	partial	-	+
F2	partial	-	+	-	partial	+	+	-	+
F3	partial	-	+	-	partial	+	+	-	+
F4	partial	-	+	-	partial	+	+	-	+
F5	partial	-	+	-	partial	+	+	-	+
F6	partial	-	+	-	partial	+	+	-	+

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

Types of Polymers	H_2O	EtOH	Ether	Toluene	DMSO	Hexane	Ptrolum ether	Acetone
Homo-polymer								
F7	partial	partial	-	partial	+	-	-	+
F8	partial	+	-	partial	+	-	-	+
F9	partial	+	-	partial	+	-	-	+
F10	partial	+	-	partial	+	-	-	+
F11	partial	+	-	partial	+	-	-	+
Hetero- polymer								
F12	partial	partial	-	partial	+	-	-	+
F13	partial	+	-	partial	+	-	-	+
F14	partial	+	-	partial	+	-	-	+
F15	partial	+	-	partial	+	-	-	+
F16	partial	+	-	partial	+	-	-	+

3.4.2 Swelling ratio

The swelling ratio was determined by immersing the xerogel (0.05 gm) from homo and hetero polymers, in 50 ml of different buffer solutions, pH (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.

Tables (3-5) to (3-10), represent the swelling ratio of homo and hetero polymers. Figures (2-39) to (2-50), represent the behavior curve of swelling in different time (hour and day).

Table (3-5): Swelling ratio % of homo-polymer at pH=2.2 and 37°C.

Time	Swelling Ratio %				
	Types of polymers				
Hour	F7	F8	F9	F10	F11
1	1.1857	0.1996	0.5964	0.99	0.7936
2	1.3806	0.3948	0.841	1.1693	0.99
3	1.96	0.4961	1.2841	1.7861	1.5748
4	2.1526	0.7936	1.582	1.9607	1.7862
5	2.1526	0.7936	1.582	1.9607	1.7862
Day					
1	2.5341	1.1857	2.3437	1.9607	2.1526
2	2.7237	1.3807	2.5341	2.231	2.3461
3	3.1007	1.5748	2.9126	2.521	2.658
4	3.4749	1.751	3.2542	2.874	3.1007
5	3.6608	1.9607	3.4781	3.01	3.2882
6	3.8461	2.0216	3.7632	3.2 35	3.637
7	3.9943	2.1251	3.8746	3.435	3.647
8	4.1263	2.1341	3.9003	3.435	3.6607
9	4.1263	2.1341	3.9003	3.435	3.6607

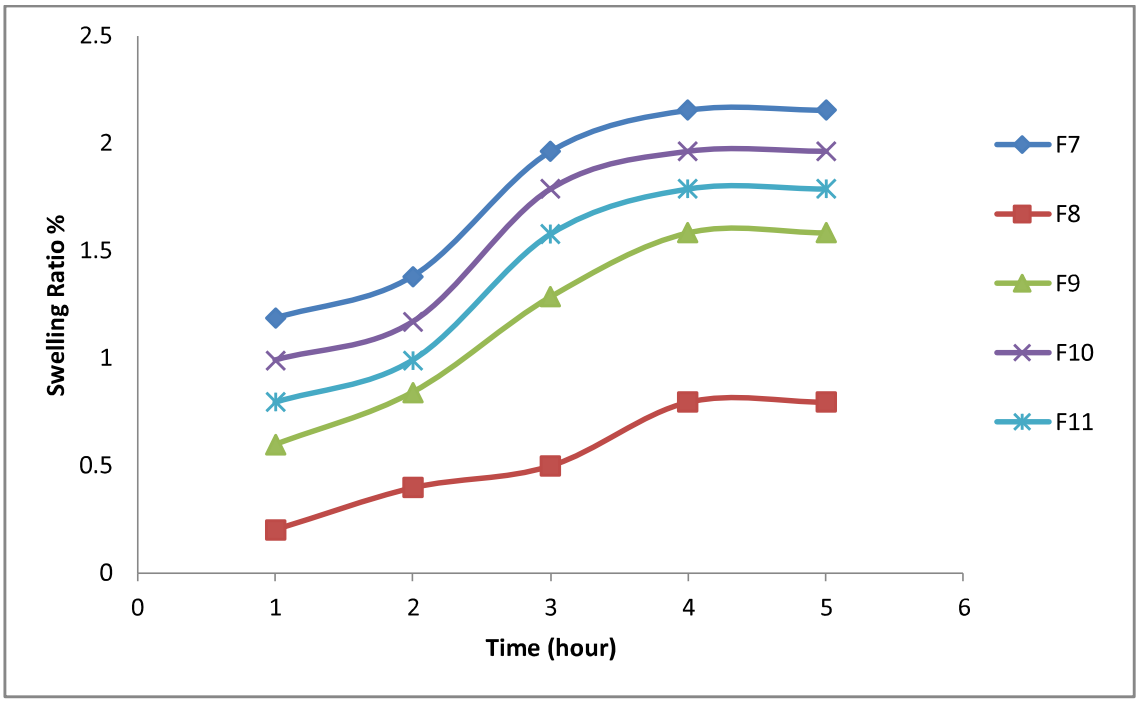


Figure (3-39): The swelling ratio of homo polymer in different hour in pH=2.2 at 37°C.

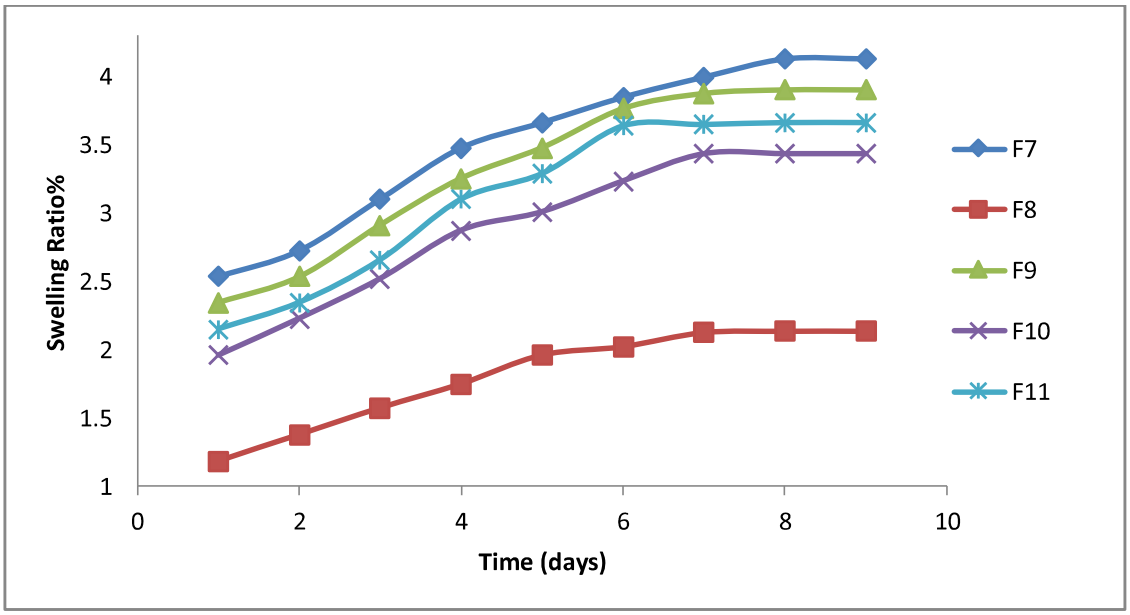


Figure (3-40): The swelling ratio of homo polymer in different days in pH=2.2 at 37°C.

Table (3-6): Swelling ratio % of homo-polymer in pH=7.0 at 37ºC.

Time	Swelling Ratio %				
	Types of polymers				
Hour	F7	F8	F9	F10	F11
1	1.3806	0.3984	0.99	0.7936	1.1857
2	1.574	0.5964	1.112	0.875	1.235
3	1.9607	0.7946	1.342	1.1832	1.5748
4	2.5341	0.894	2.1521	1.9607	2.3437
5	2.5341	0.894	2.1521	1.9607	2.3437
Day					
1	2.5356	1.3806	2.435	1.998	2.1837
2	2.9126	1.5748	2.7237	2.1923	2.4628
3	3.2882	1.7861	3.1007	2.6101	2.9126
4	3.6608	1.9541	3.4749	2.9126	3.1173
5	3.865	2.1526	3.6608	3.1007	3.3145
6	3.9112	2.3437	3.6875	3.213	3.4749
7	3.9313	2.5341	3.6975	3.213	3.5132
8	3.9313	2.7412	3. 715	3.213	3.5132
9	3.9313	2.7412	3. 715	3.213	3.5132

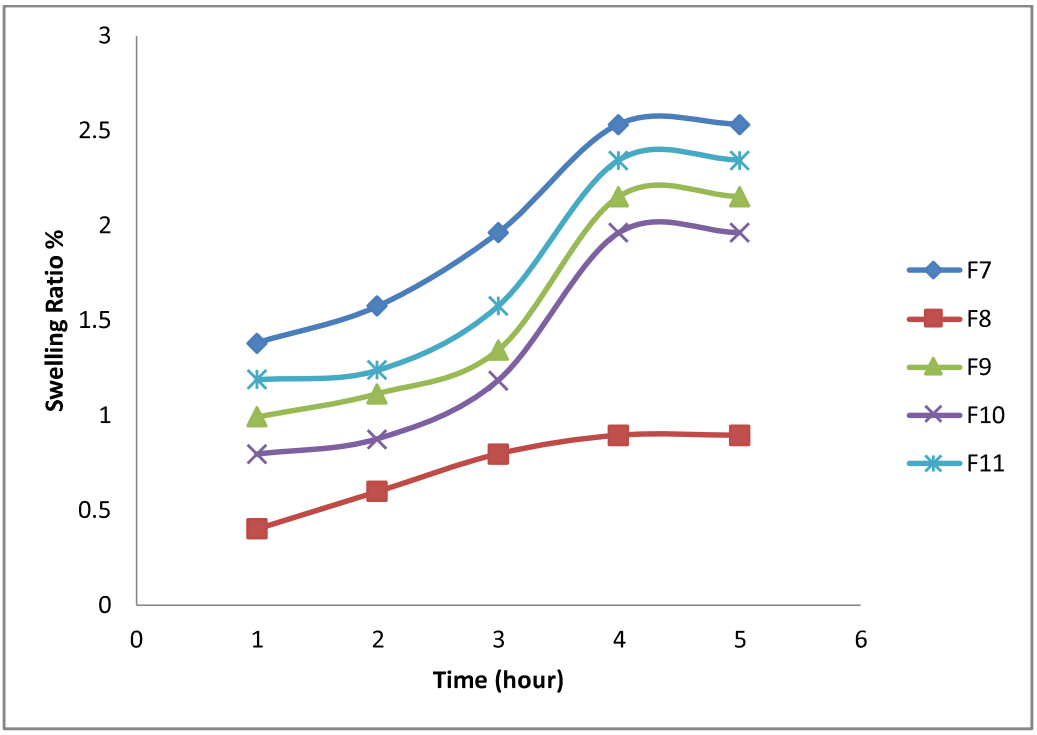


Figure (3-41): The swelling ratio of homo polymer in different hour in pH=7.0 at 37°C.

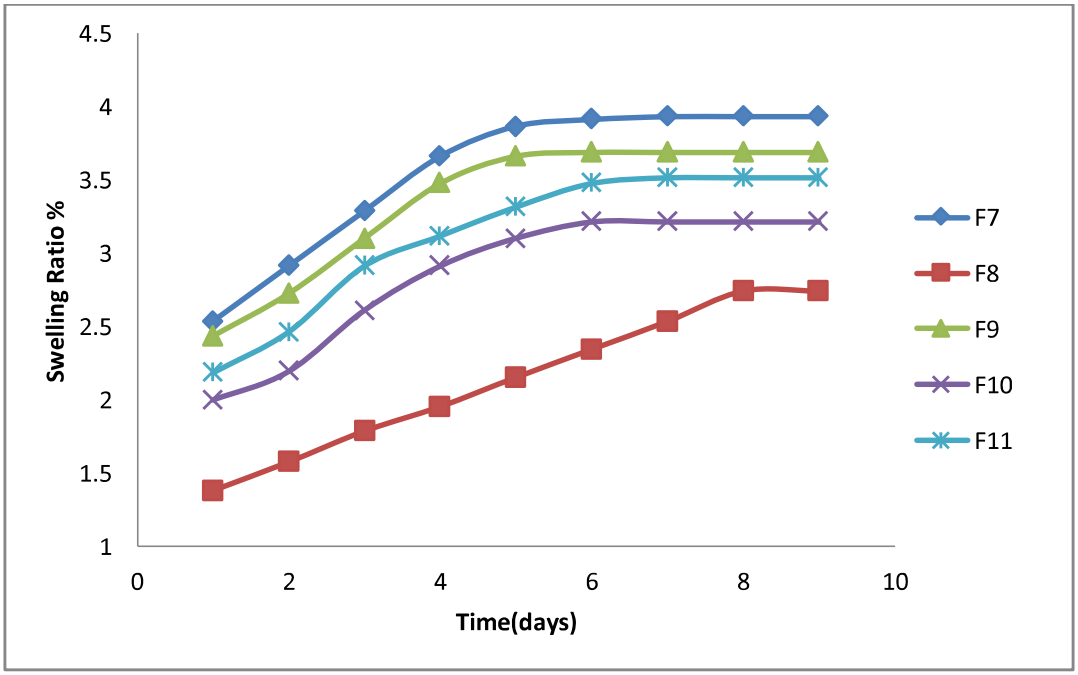


Figure (3-42): The swelling ratio of homo polymer in different days in pH=7.0 at 37°C.

Table (3-7): Swelling ratio % of homo-polymer at pH=8.0 and 37°C.

Time	Swelling ratio %				
	Types of polymers				
Hour	F7	F8	F9	F10	F11
1	1.56	0.5964	0.9945	1.325	1.1857
2	1.9607	0.896	1.3805	1.7683	1.574
3	2.3437	1.035	1.5631	2.001	1.7607
4	2.7237	1.323	1.9607	2.3041	2.1527
5	2.7237	1.323	1.9607	2.3041	2.1527
Day					
1	3.109	1.5748	2.886	2.345	2.597
2	3.196	1.7716	2.998	2.507	2.726
3	3.342	1.8607	3.093	2.606	2.832
4	3.452	2	3.105	2.686	2.923
5	3.463	2.121	3.179	2.726	3
6	3.467	2.21	3.249	2.766	3.104
7	3.474	2.452	3.353	2.826	3.154
8	3.474	2. 493	3.356	2.916	3.164
9	3.474	2. 493	3.356	2.916	3.164

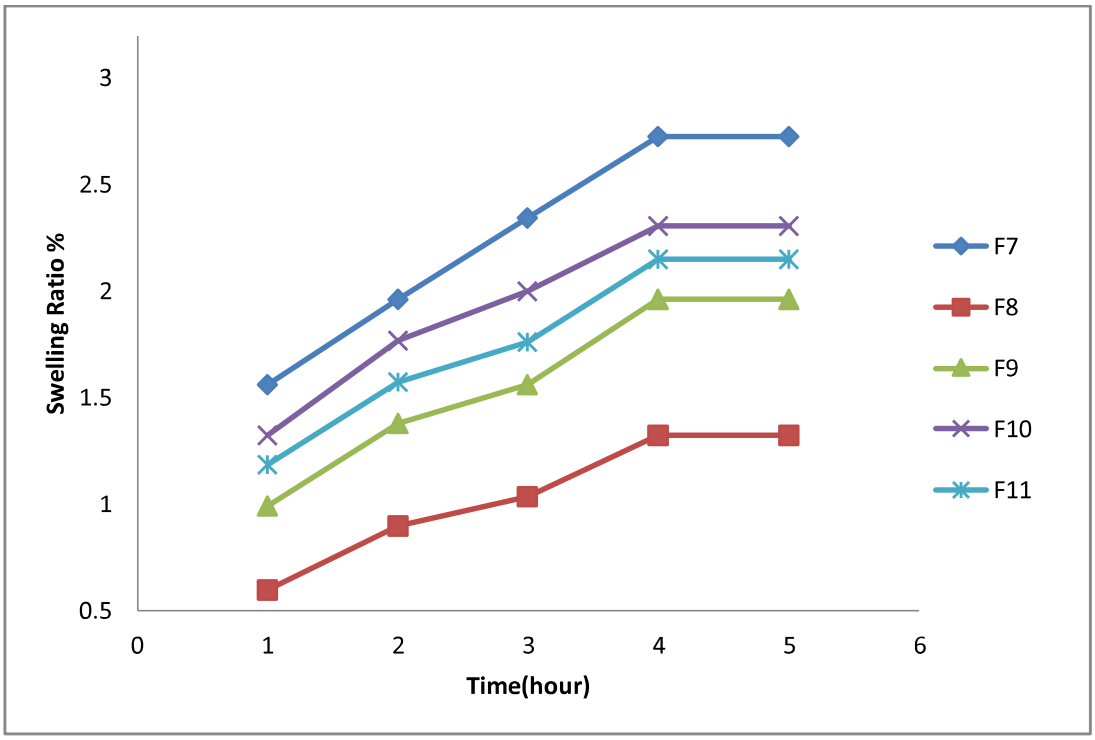


Figure (3-43): The swelling ratio of homo polymer in different hour in pH=8.0 at 37°C.

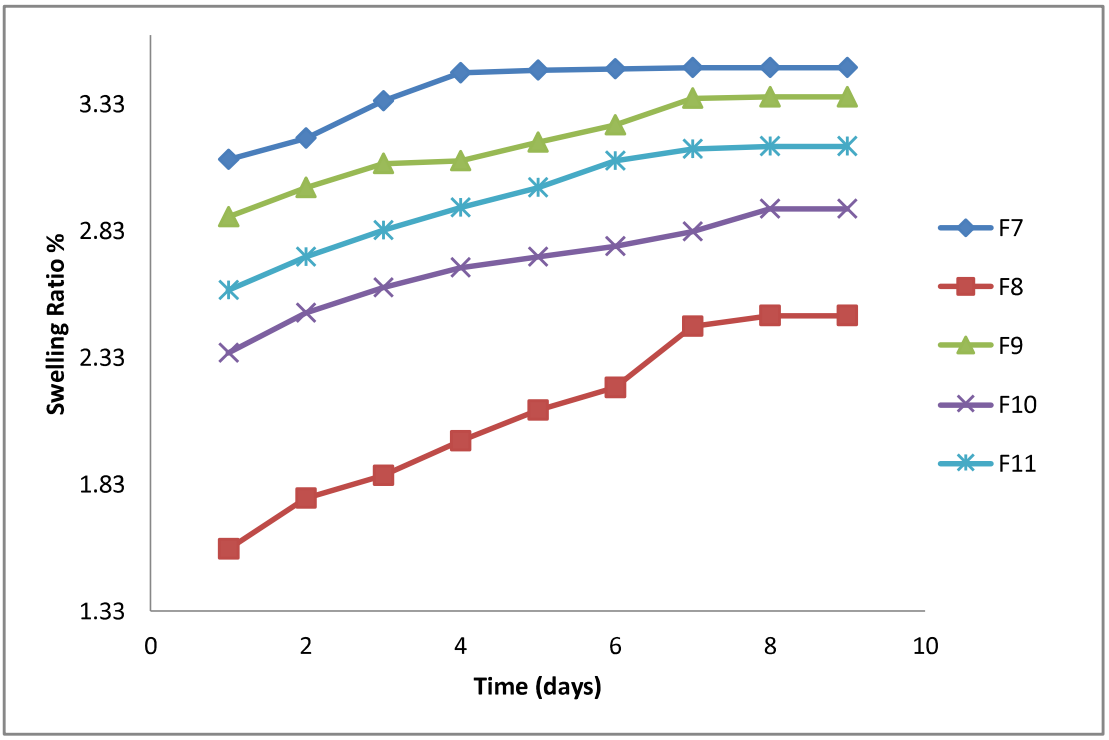


Figure (3-44): The swelling ratio of homo polymer in different days in pH=8.0 at 37°C.

Table (3-8): Swelling ratio % of hetero polymer at pH=2.2 and 37ºC.

Time	Swelling ratio %				
	Types of polymers				
Hour	F12	F13	F14	F15	F16
1	1.1857	0.1996	0.3984	0.5964	0.7936
2	1.498	0.3984	0.5964	0.7936	0.99
3	1.7681	0.4964	0.7936	1	1.257
4	2.024	0.696	0.99	1.218	1.469
5	2.5341	0.851	1.208	1.407	1.764
6	2.5341	1.00	1.298	1.767	2.00
7	2.5341	1.00	1.298	1.767	2.00
Day					
1	2.7237	1.7681	1.9607	2.1526	2.3437
2	2.9126	1.9607	2.1526	2.3437	2.5341
3	3.1007	2.1526	2.3437	2.5341	2.7347
4	3.2882	2.3437	2.5341	2.7237	2.9126
5	3.4749	2.5341	2.7237	2.9726	3.1007
6	3.8461	2.7237	3.00	3.1007	3.4749
7	4.0307	2.7237	3.00	3.2882	3.6608
8	4.0307	2.7237	3.00	3.2882	3.6608

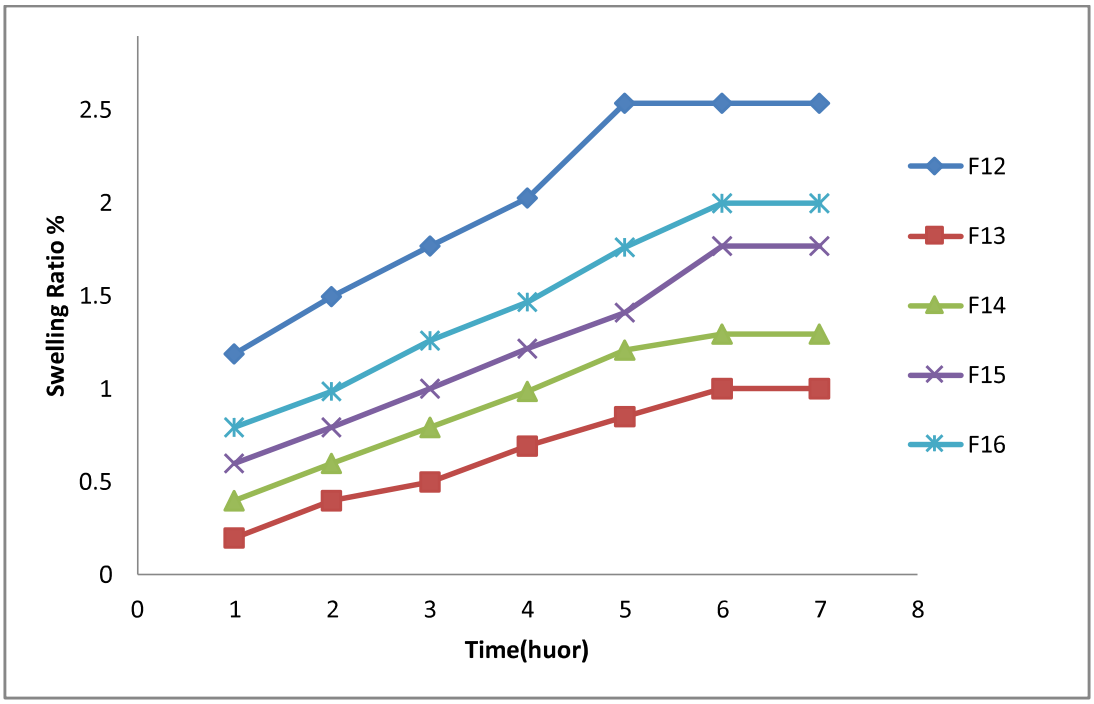


Figure (3-45): The swelling ratio of hetero polymer in different hours in pH=2.2 at 37°C.

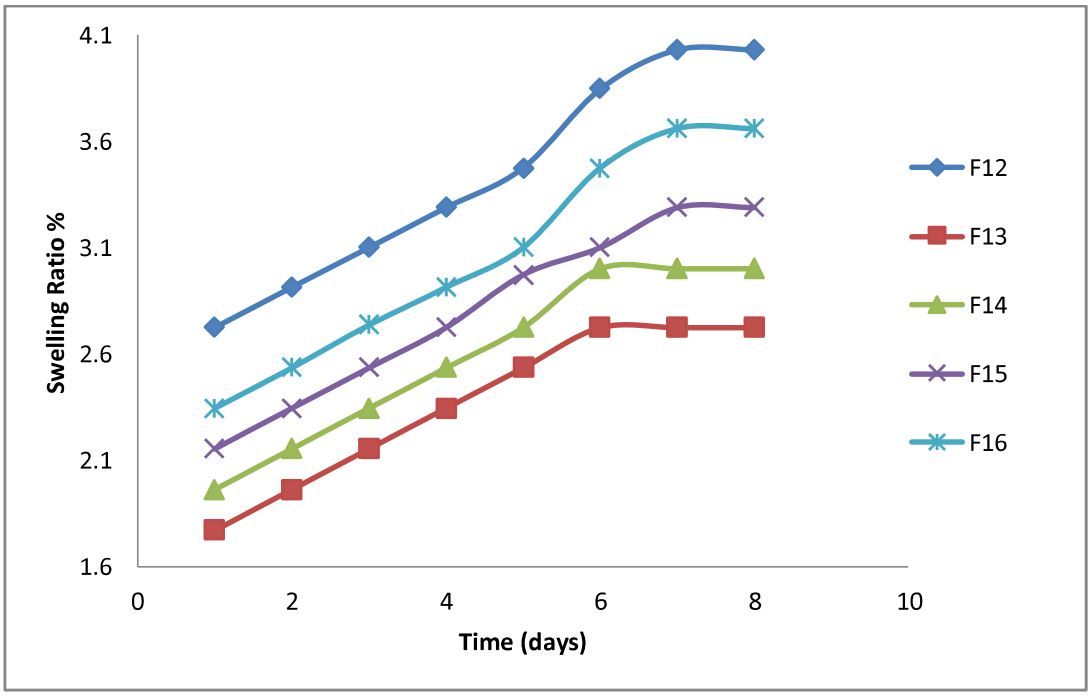


Figure (3-46): The swelling ratio of hetero polymer in different days in pH=2.2 at 37°C.

Table (3-9): Swelling ratio % of hetero polymer at pH=7.0 and 37°C.

Time	Swelling ratio %				
	Types of polymers				
Hour	F12	F13	F14	F15	F16
1	1.3806	0.3984	0.5964	0.7936	0.99
2	1.7681	0.5064	0.7936	0.99	1.2311
3	1.9607	0.7936	0.9908	1.121	1.3806
4	2.1526	0.9932	1.1876	1.3806	1.673
5	2.6341	1.542	1.7681	1.921	2.218
6	2.9126	1.542	1.781	2	2.4018
7	2.9126	1.542	1.781	2	2.4018
Day					
1	2.9126	1.9607	2.1526	2.5341	2.7237
2	3.1007	2.1526	2.3437	2.7237	2.9126
3	3.3608	2.2261	2.5461	2.9835	3.101
4	3.7461	2.4783	2.806	3.107	3.2882
5	4.0307	2.4983	2.806	3.6608	3.8007
6	4.2145	2.523	2.806	3.8461	3.957
7	4.3417	2.567	2.806	3.8461	4.037
8	4.3417	2.567	2.806	3.8462	4.037

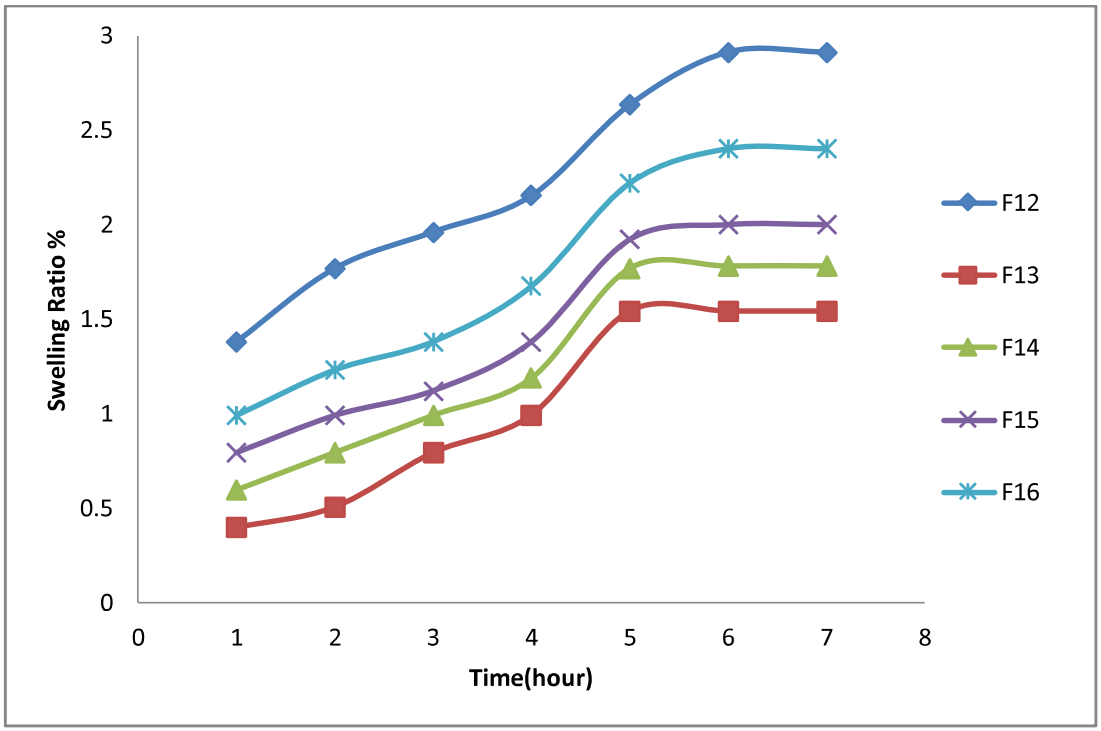


Figure (3-47): The swelling ratio of hetero polymer in different hours in pH=7.0 at 37°C.

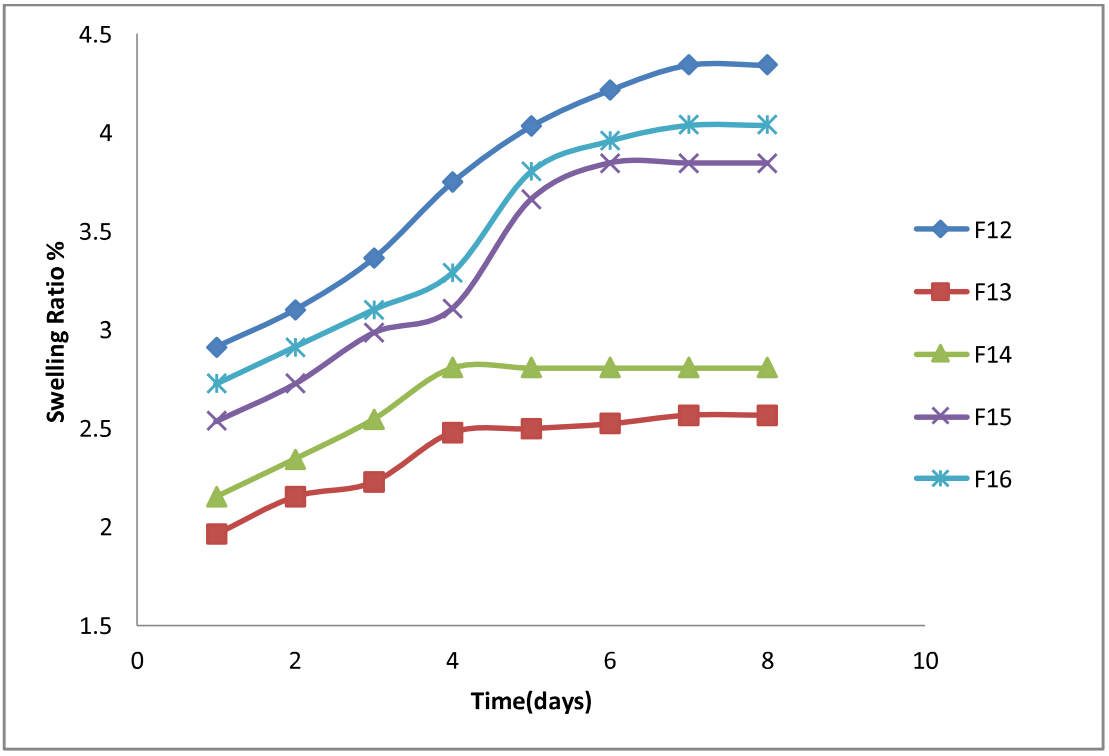


Figure (3-48): The swelling ratio of hetero polymer in different days in pH=7.0 at 37°C.

Table (3-10): Swelling ratio % of hetero polymer at pH=8.0 and 37°C.

Time	Swelling ratio %				
	Types of polymers				
Hour	F12	F13	F14	F15	F16
1	1.7681	1.1857	0.7936	0.99	1.3806
2	1.9607	1.3806	0.99	1.1857	1.5748
3	2.1526	1.7081	1.3806	1.543	1.8748
4	2.5341	1.9607	1.565	1.7431	2.1521
5	3	2.283	1.604	1.9177	2.4941
6	3.1007	2.3437	1.654	1.998	2.5341
7	3.1007	2.3437	1.654	1.998	2.5341
Day					
1	3.1007	2.1526	2.3437	2.7237	2.5341
2	3.2882	2.3437	2.5341	2.9126	2.7237
3	3.5261	2.537	2.7632	3.1034	2.9224
4	3.895	2.7235	2.9126	3.2783	3.1005
5	4.2145	3	3.1865	3.6452	3.4325
6	4.2145	3.2658	3.6034	3.8452	3.7045
7	4.2145	3.4748	3.6034	3.8452	3.7345
8	4.2145	3.4748	3.6034	3.8452	3.7345

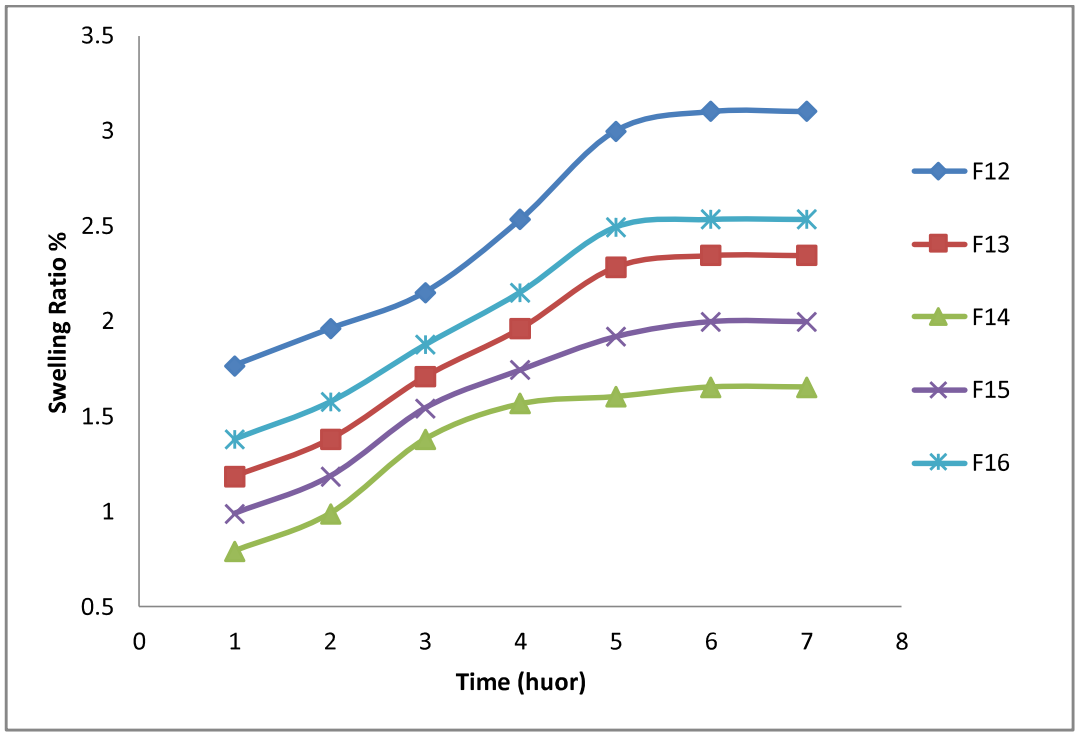


Figure (3-49): The swelling ratio of hetero polymer in different hours in pH=8.0 at 37°C.

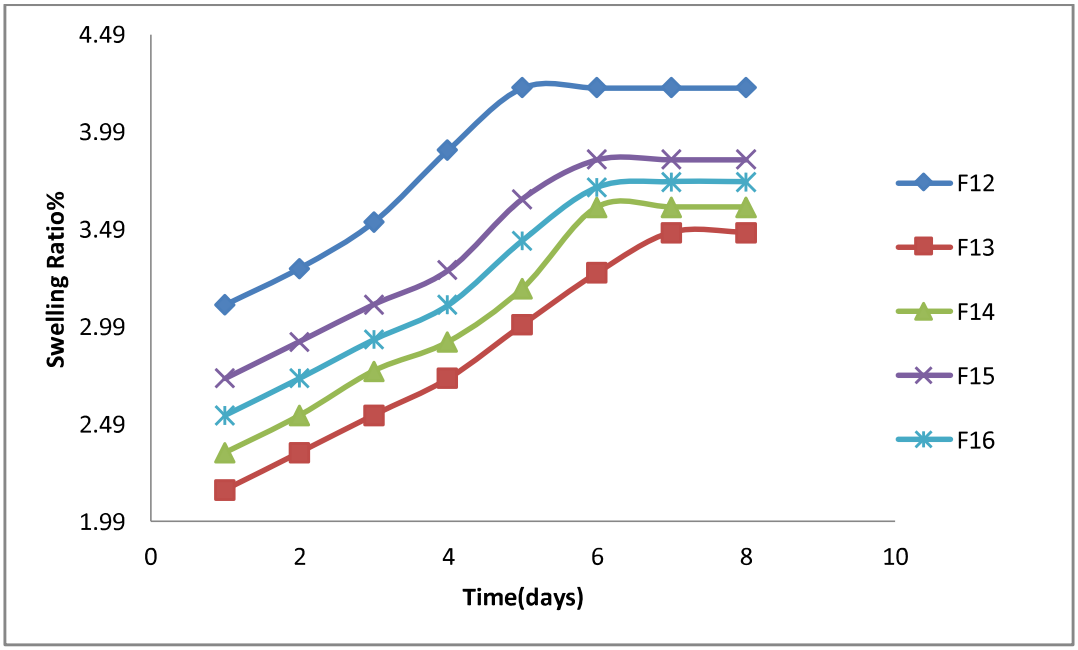
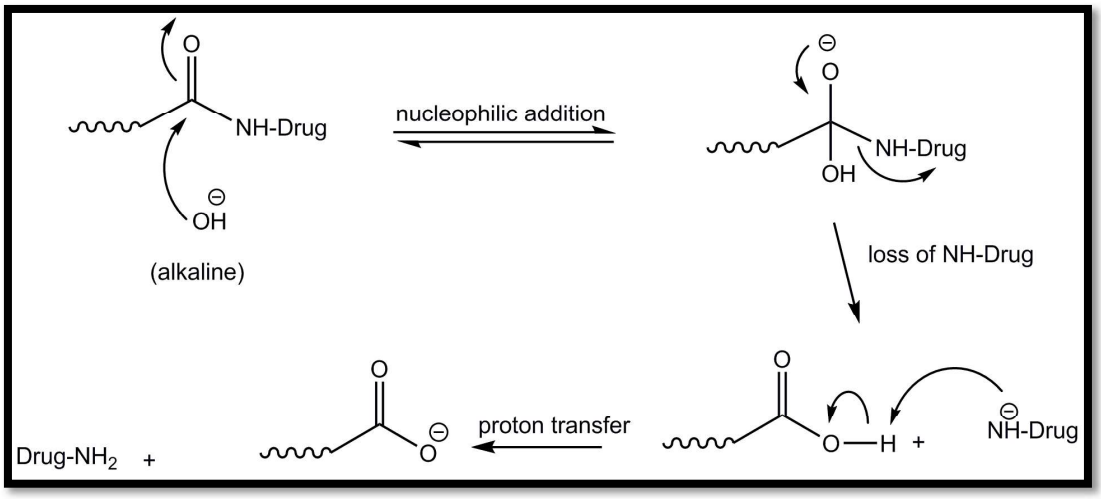


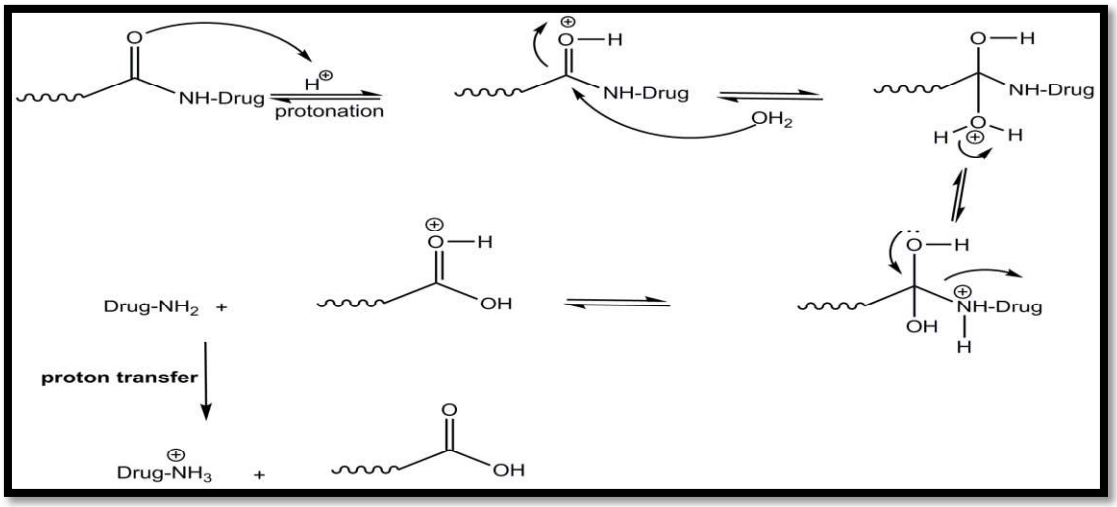
Figure (3-50): The swelling ratio of hetero polymer in different days in pH=8.0 at 37°C.

3.5 Release of drug

By using UV.-Visb. Spectrophotometer, release the drug from the prepared polymer (homo and hetero) was determined in three different buffer solutions (2.2, 7.0 and 8.0) at constant temperature 310 K , as in Mechanisms[119].



Mechanism for Release of drug in acid medium



Mechanism for Release of drug in base medium.

Tables (3-11) to (3-16), represent the drug release from the prepared polymer and Figures (3-51) to (3-62), showed the behavior curves of the drug release.

Table (3-11): Release of drug of the homo-polymers at pH=2.2 and 37ºC.

Time	Release of drug (Absorbance)				
	Types of polymers				
Hour	F7	F8	F9	F10	F11
1	0.300	0.109	0.199	0.245	0.236
2	0.311	0.111	0.211	0.266	0.257
3	0.319	0.122	0.232	0.287	0.275
4	0.349	0.133	0.255	0.310	0.300
5	0.349	0.133	0.255	0.310	0.300
Day					
1	1.235	0.15	0.769	0.407	0.593
2	1.563	0.16	0.989	0.604	0.796
3	2.032	0.17	1.231	0.756	0.878
4	2.308	0.209	1.352	0.978	1.110
5	2.606	0.243	1.532	1.047	1.210
6	2.921	0.322	1.732	1.100	1.324
7	2.999	0.421	1.987	1.159	1.421
8	3.460	0.442	2.223	1.159	1.541
9	3.460	0.442	2.223	1.159	1.541

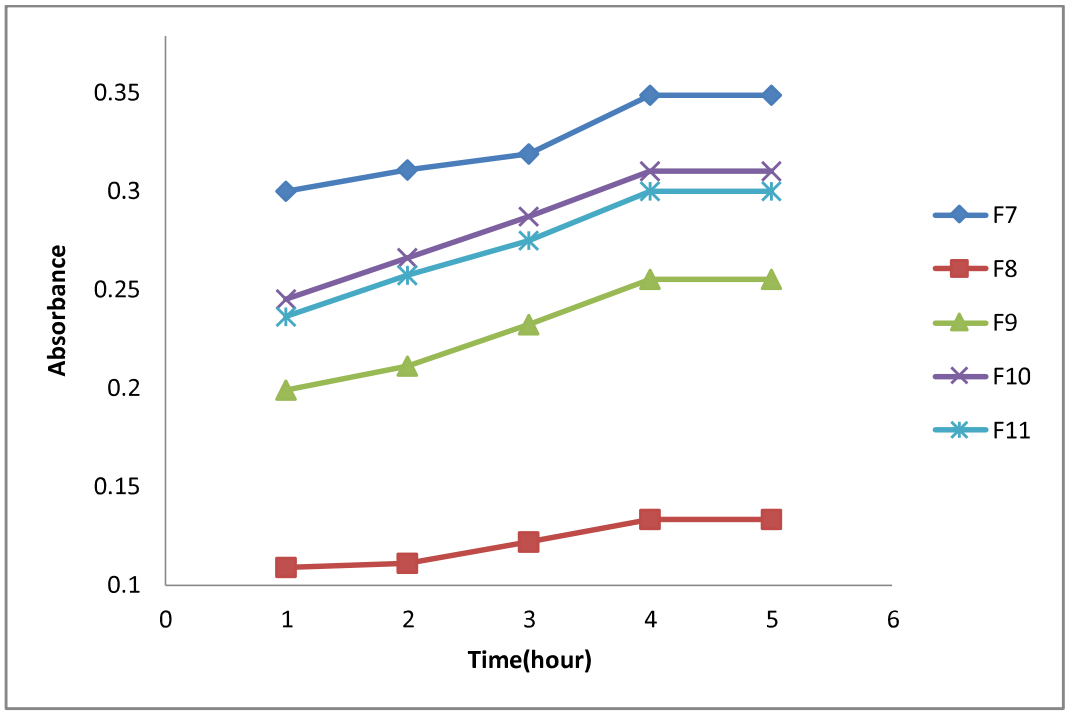


Figure (3-51): The drug release of homo polymer in different hour in pH=2.2 at 37°C.

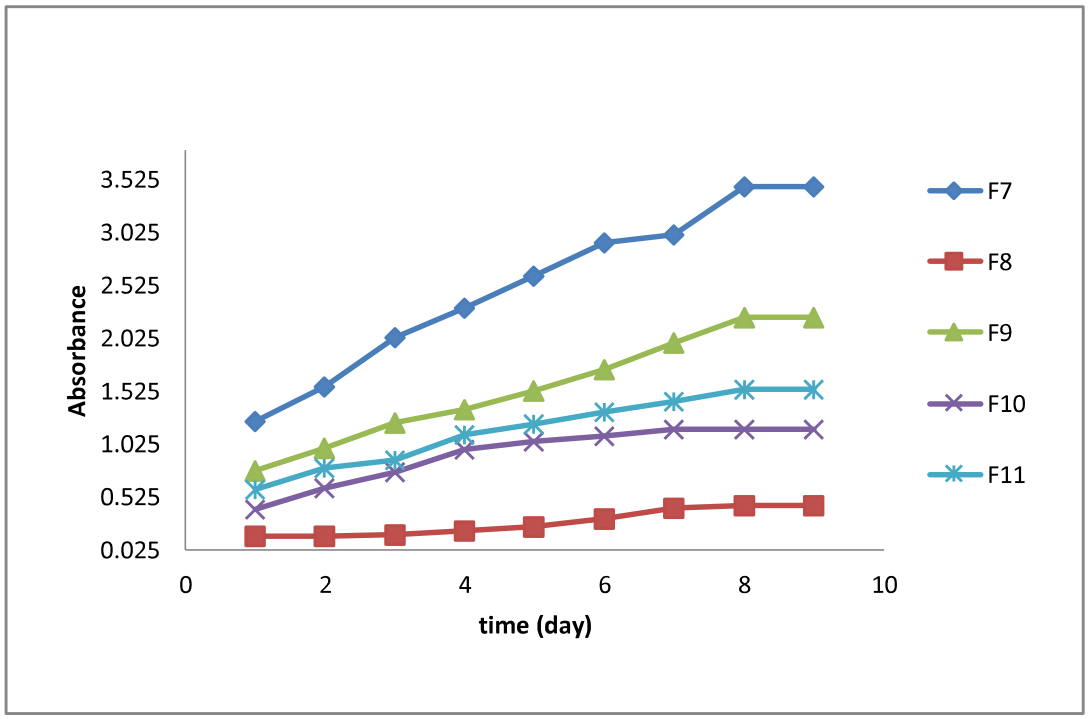


Figure (3-52): The drug release of homo polymer in different days in pH=2.2 at 37°C.

Table (3-12): Release of drug of homo-polymer at pH=7.0 and 37ºC.

Time	Release of drug (Absorbance)				
	Types of drug				
Hour	F8	F9	F10	F11	F12
1	0.357	0.26	0.293	0.274	0.311
2	0.366	0.266	0.300	0.289	0.322
3	0.376	0.271	0.313	0.300	0.332
4	0.390	0.28	0.330	0.318	0.350
5	0.390	0.28	0.330	0.318	0.350
Day					
1	2.213	0.144	1.211	0.709	0.884
2	2.517	0.148	1.431	0.742	1.001
3	2.697	0.159	1.629	0.931	1.18
4	3.000	0.194	1.929	1.061	1.374
5	3.187	0.228	2.235	1.245	1.571
6	3.699	0.276	2.621	1.632	1.843
7	4.000	0.367	3.000	1.632	2.215
8	4.000	0.474	3.478	1.632	2.215
9	4.000	0.474	3.478	1.632	2.215

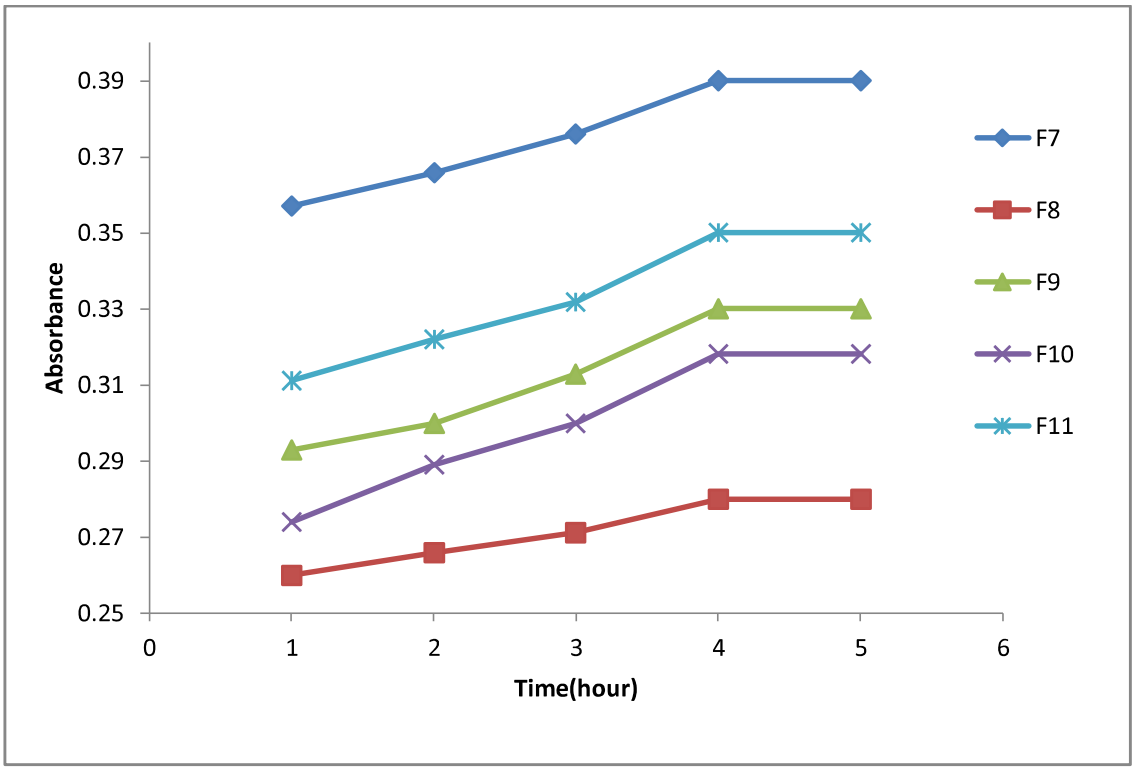


Figure (3-53): The drug release of homo polymer in different hour in pH=7.0 at 37°C.

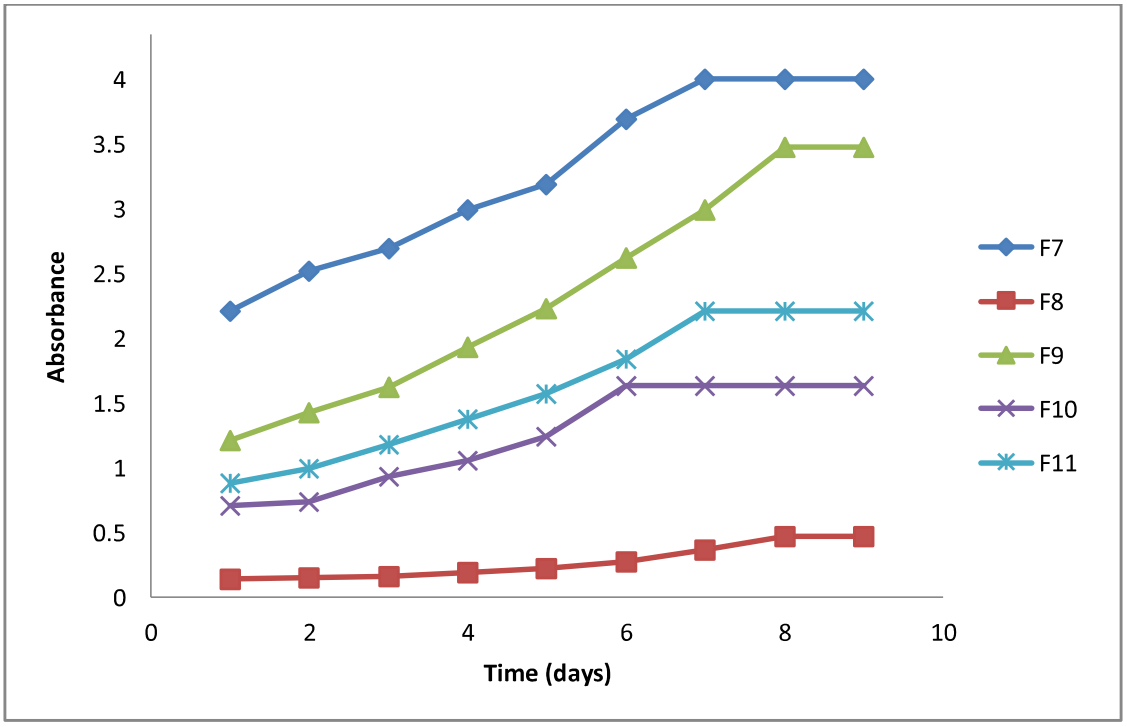


Figure (3-54): The drug release of homo polymer in different days in pH=7.0 at 37°C.

Table (3-13): Release of drug for homo-polymer at pH=8.0 and 37°C.

Time	Release of drug (Absorbance)				
	Types of polymers				
Hour	F7	F8	F9	F10	F11
1	0.344	0.261	0.271	0.308	0.279
2	0.364	0.271	0.288	0.329	0.299
3	0.382	0.282	0.306	0.349	0.318
4	0.391	0.291	0.329	0.358	0.336
5	0.391	0.291	0.329	0.358	0.336
Day					
1	1.356	0.310	1.223	0.621	0.867
2	1.541	0.352	1.362	0.876	1.006
3	1.981	0.368	1.562	0.996	1.324
4	2.54	0.397	1.885	1.230	1.561
5	3.15	0.530	2.31	1.673	1.945
6	3.681	0.590	2.760	2.000	2.310
7	4.000	0.621	3.42	2.653	3.000
8	4.000	0.834	3.873	3.210	3.542
9	4.000	0.834	3.873	3.210	3.542

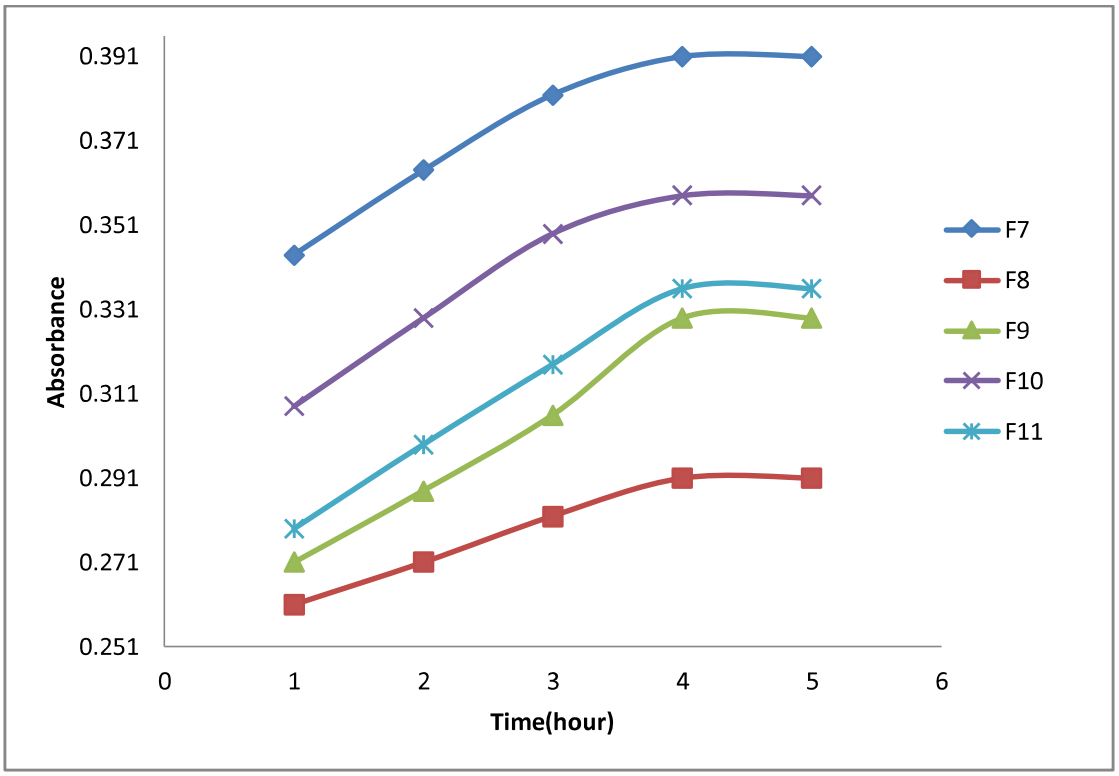


Figure (3-55): The drug release of homo polymer in different hour in pH=8.0 at 37°C.

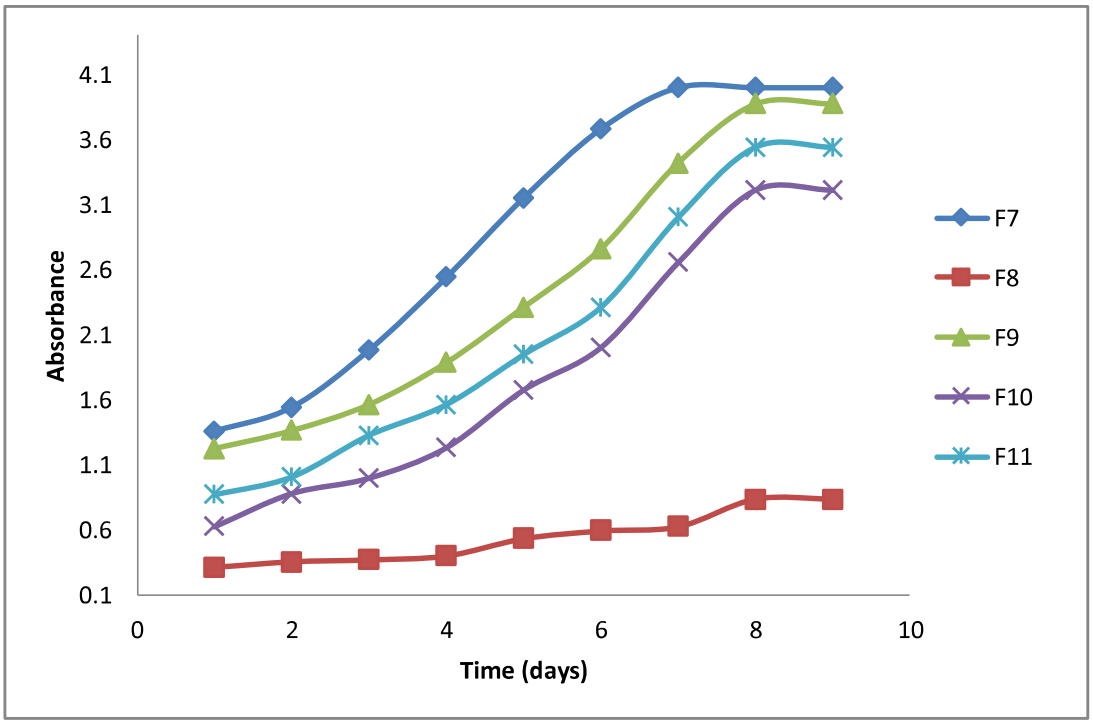


Figure (3-56): The drug release of homo polymer in different days in pH=8.0 at 37°C.

Table (3-14): Release of drug for hetero polymer at pH=2.2 and 37ºC.

Time	Release of drug (Absorbance)				
	Types of polymers				
Hour	F12	F13	F14	F15	F16
1	0.853	0.065	0.128	0.182	0.225
2	0.962	0.071	0.130	0.217	0.240
3	1.000	0.079	0.149	0.251	0.276
4	1.0321	0.087	0.155	0.276	0.300
5	1.121	0.093	0.162	0.301	0.352
6	1.223	0.100	0.189	0.310	0.385
7	1.223	0.100	0.189	0.310	0.385
Day					
1	1.220	0.121	0.244	0.405	0.549
2	1.349	0.125	0.274	0.569	0.696
3	1.367	0.132	0.352	0.747	0.850
4	1.496	0.153	0.449	0.868	0.957
5	1.852	0.159	0.532	1.030	1.116
6	2.116	0.165	0.535	1.091	1.245
7	2.421	0.165	0.535	1.332	1.502
8	2.421	0.165	0.535	1.332	1.502

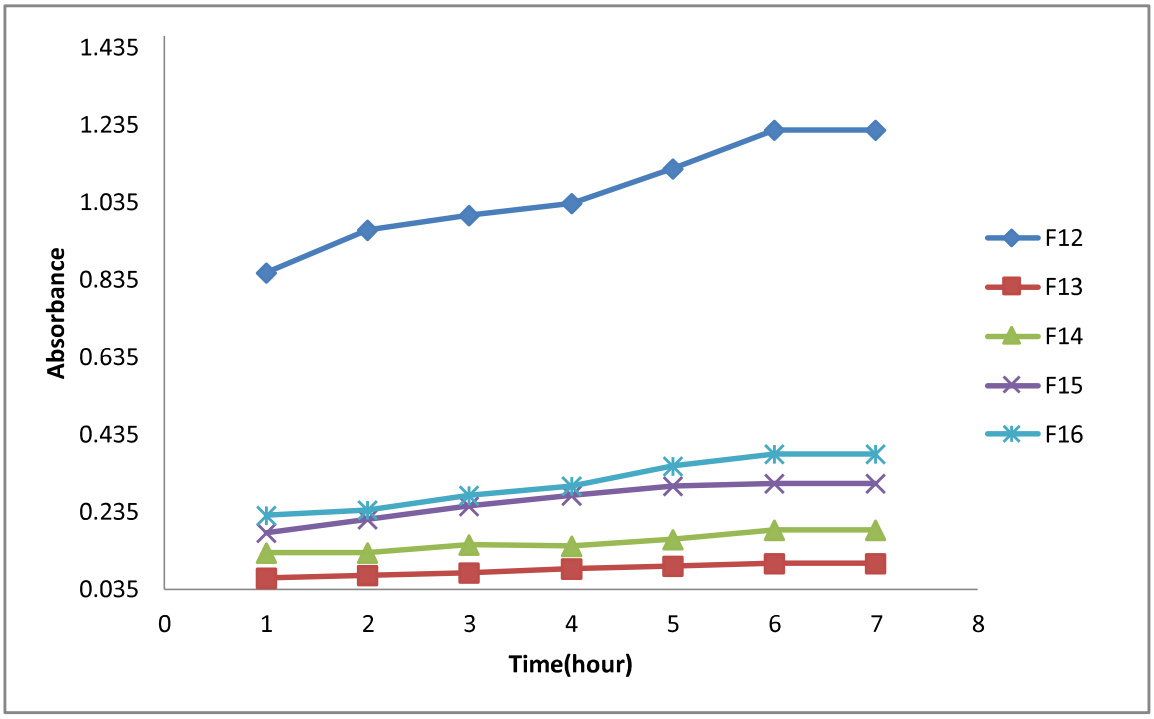


Figure (3-57): The drug release of hetero polymer in different hour in pH=2.2 at 37°C.

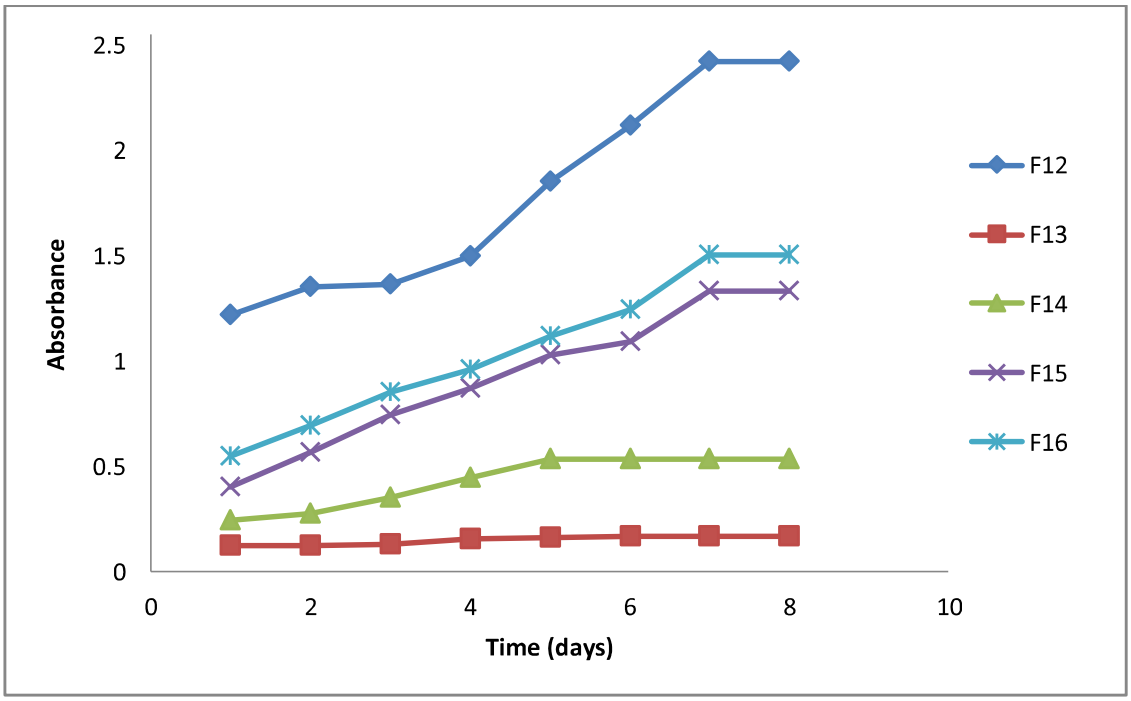


Figure (3-58): The drug release of hetero polymer in different days in pH=2.2 at 37°C.

Table (3-15): Release of drug for hetero polymer at pH=7.0 and 37ºC.

Time	Release of drug (Absorbance)				
	Types of polymers				
Hour	F12	F13	F14	F15	F16
1	0.985	0.09	0.245	0.166	0.419
2	1.054	0.096	0.263	0.199	0.485
3	1.121	0.097	0.3	0.232	0.563
4	1.209	0.099	0.332	0.244	0.662
5	1.308	0.121	0.383	0.315	0.714
6	1.404	0.121	0.411	0.342	0.768
7	1.404	0.121	0.411	0.342	0.768
Day					
1	2.000	0.138	0.472	1.000	1.321
2	2.311	0.140	0.568	1.085	1.525
3	2.529	0.151	0.677	1.291	1.739
4	2.787	0.176	0.940	1.481	1.984
5	3.079	0.205	0.940	1.64	2.241
6	3.328	0.234	0.940	2.100	2.457
7	3.622	0.234	0.940	2.100	2.797
8	3.622	0.234	0.940	2.100	2.797

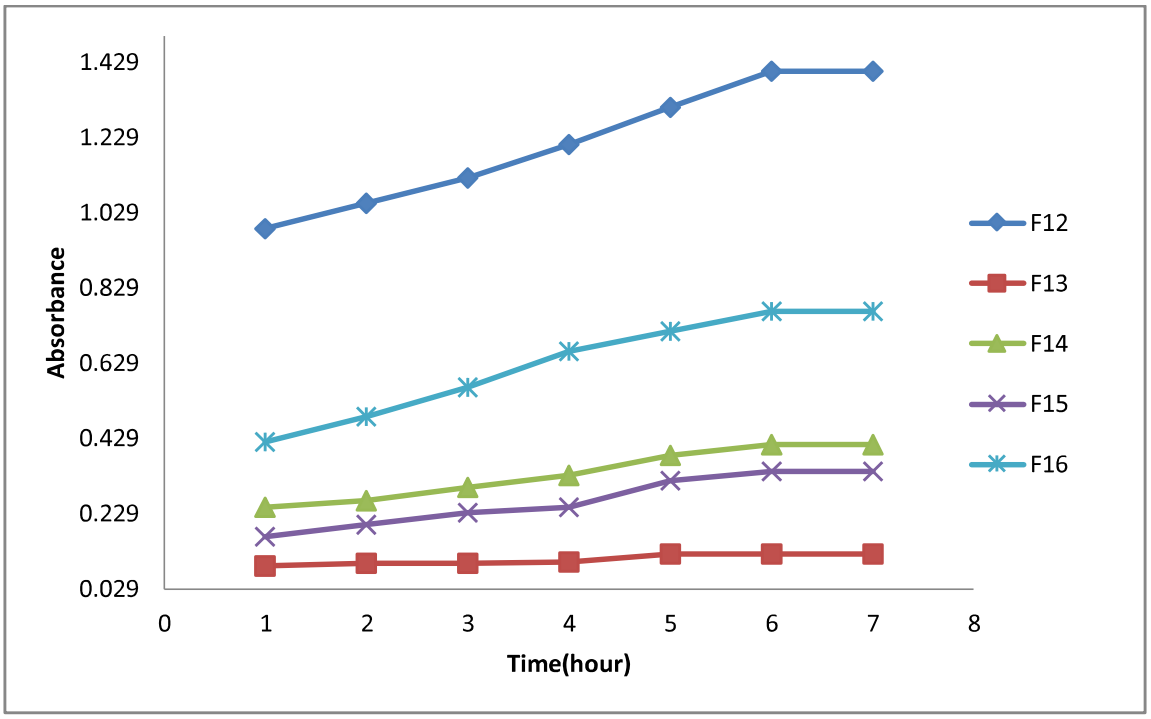


Figure (3-59): The drug release of hetero polymer in different hour in pH=7.0 at 37°C.

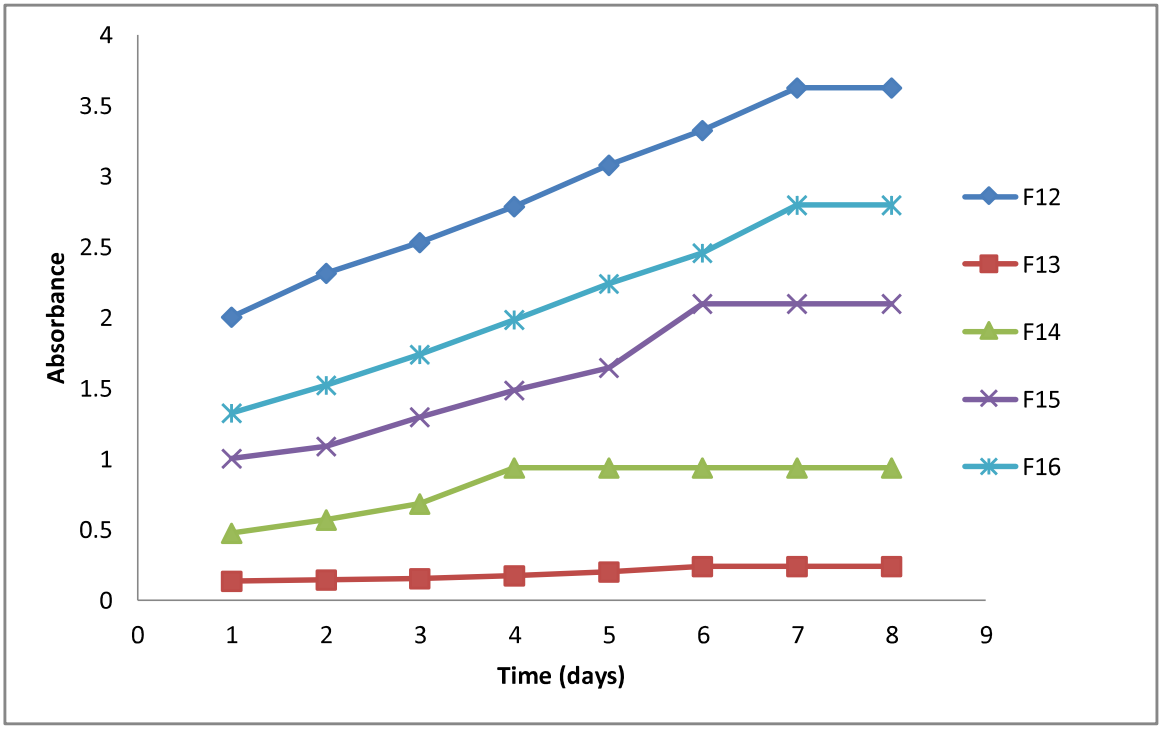


Figure (3-60): The drug release of hetero polymer in different days in pH=7.0 at 37°C.

Table (3-16): Release of drug for hetero polymer at pH=8.0 and 37ºC.

Time	Release of drug (Absorbance)				
	Types of drug				
Hour	F12	F13	F14	F15	F16
1	0.785	0.318	0.112	0.197	0.622
2	0.943	0.371	0.196	0.261	0.769
3	1.101	0.45	0.219	0.35	0.935
4	1.256	0.496	0.250	0.400	1.002
5	1.350	0.595	0.312	0.490	1.105
6	1.534	0.671	0.334	0.570	1.146
7	1.534	0.671	0.334	0.570	1.146
Day					
1	3.000	0.556	0.967	1.509	1.120
2	3.247	0.675	1.166	1.788	1.451
3	3.534	0.775	1.359	2.131	1.751
4	3.747	0.854	1.504	2.325	2.004
5	4.000	0.938	1.664	2.759	2.404
6	4.000	0.985	2.000	3.313	2.684
7	4.000	1.000	2.000	3.313	3.170
8	4.000	1.000	2.000	3.313	3.170

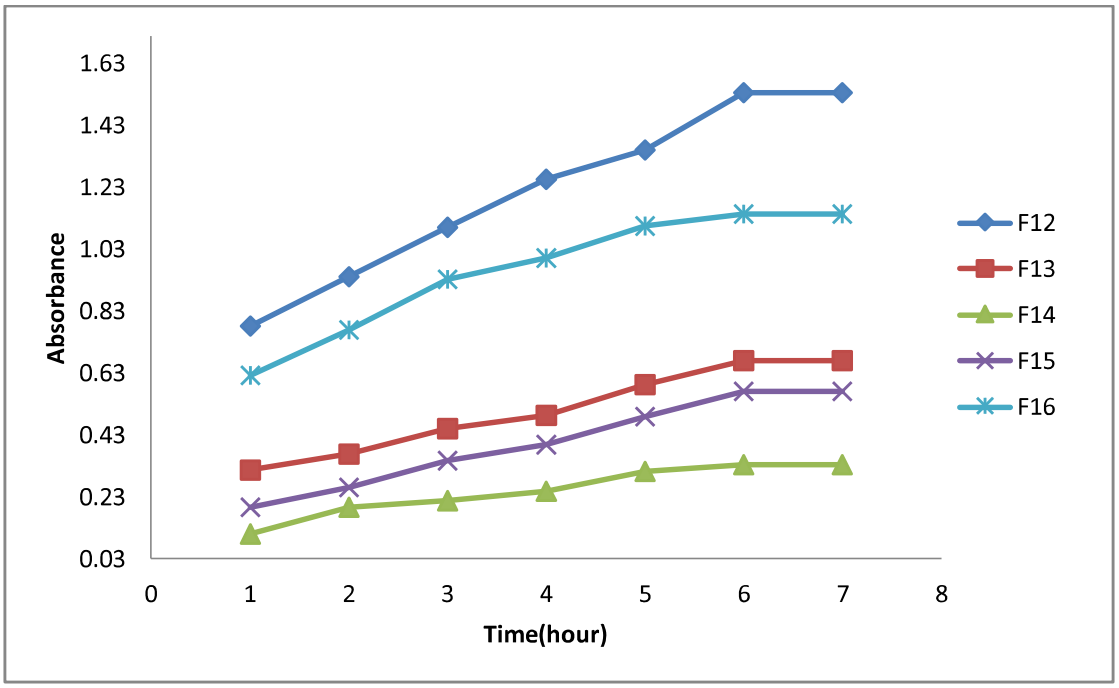


Figure (3-61): The drug release of hetero polymer in different hour in pH=8.0 at 37°C.

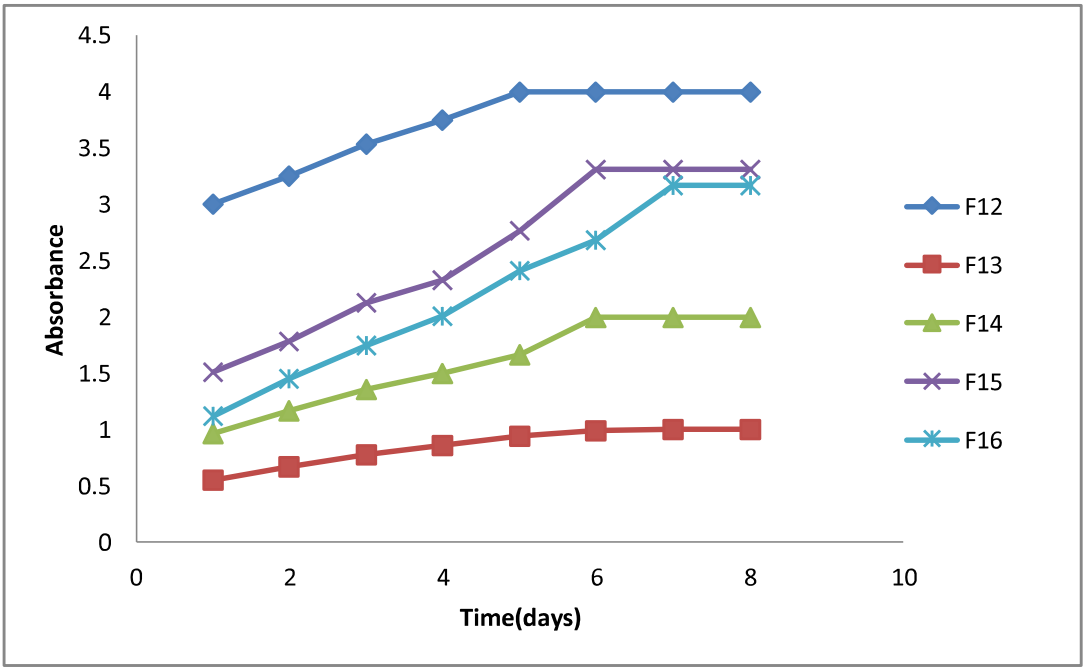


Figure (3-62): The drug release of hetero polymer in different days in pH=8.0 at 37°C.

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 F7, F9, and F12, against the breast cancer cell lines. Based on cytotoxicity analyses, it can be concluded that F_7, F_9, and F_{12} 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 F_{12} (IC50=18.32) in comparison with pure drugs and induced apoptotic cell death pathway. The results of this study suggest that the F_{12} might be used for medical applications and offer a beneficial formulation for chemotherapy. The IC50 value of F7 and F9 are 41.93 and 38.42 respectively [Figures (3-63) – (3-65)].

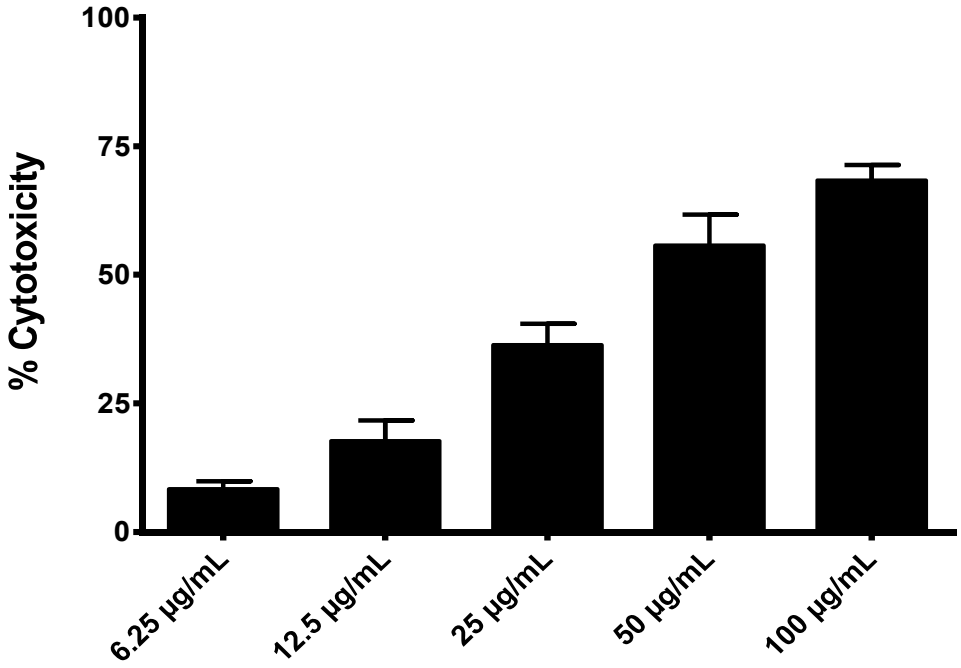


Figure 3-63: Cytotoxicity effect of F-7 in MCF-7 cells. IC50=41.93

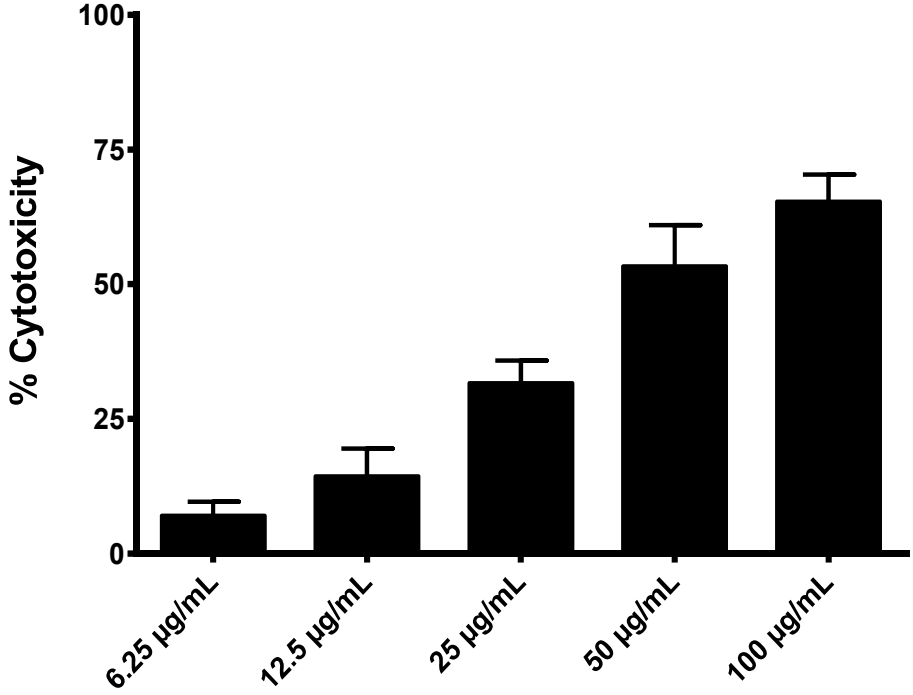


Figure 3-64: Cytotoxicity effect of F-9 in MCF-7 cells. IC50=38.42

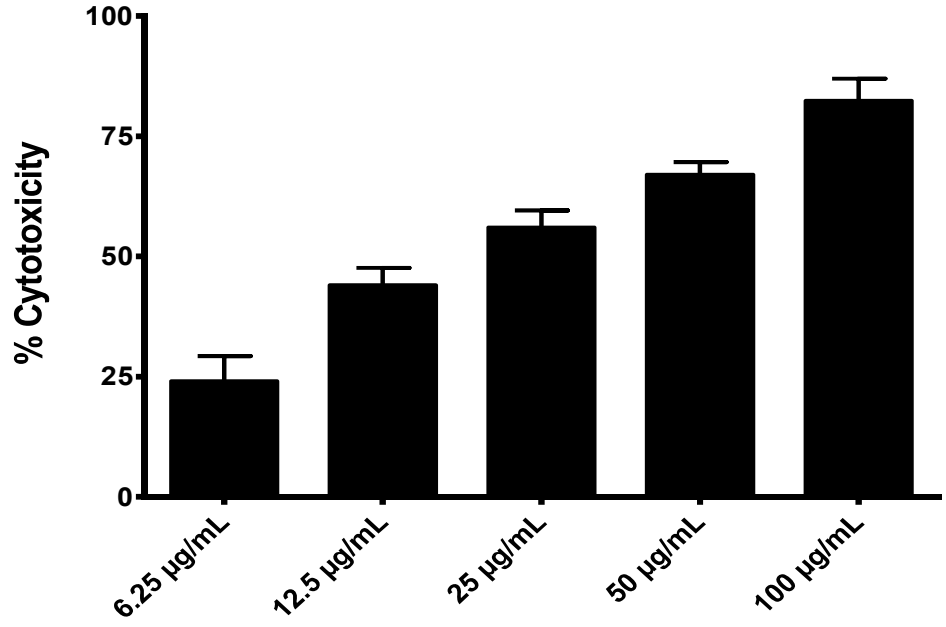


Figure 3-65: Cytotoxicity effect of F-12 in MCF-7 cells. IC50=18.32

3.7 Antioxidant activity

DPPH radicals scavenging assay

Antioxidant activity of (x-substance) was measured using stable DPPH radicals with minor adjustments[120]. (F10, F15, and F16) were used to investigate the scavenging activity. The samples were mixed with 450 µl of DPPH solution and then complete the volume of mixture to one ml using absolute ethanol. Ascorbic acid was used as a positive control at concentration 10 µg/ml . The samples and control are left in dark at room temperature for 30 minute. The absorbance was measured at 517 nm.

As shown in Figure 3-66, the antioxidant activities of F10, F15, and F16 were monitored using two different concentrations. The results demonstrated a higher free radical scavenging activity of modified drug than pure drug and a concentration-dependent inhibition was observed. Accordingly, these results agreed with the findings that indicated F10, F15, and F16 enhanced antioxidant activity of drugs. The enhanced antioxidant activity of modified drugs could be attributed to the enhanced solubility and dissolution rate.

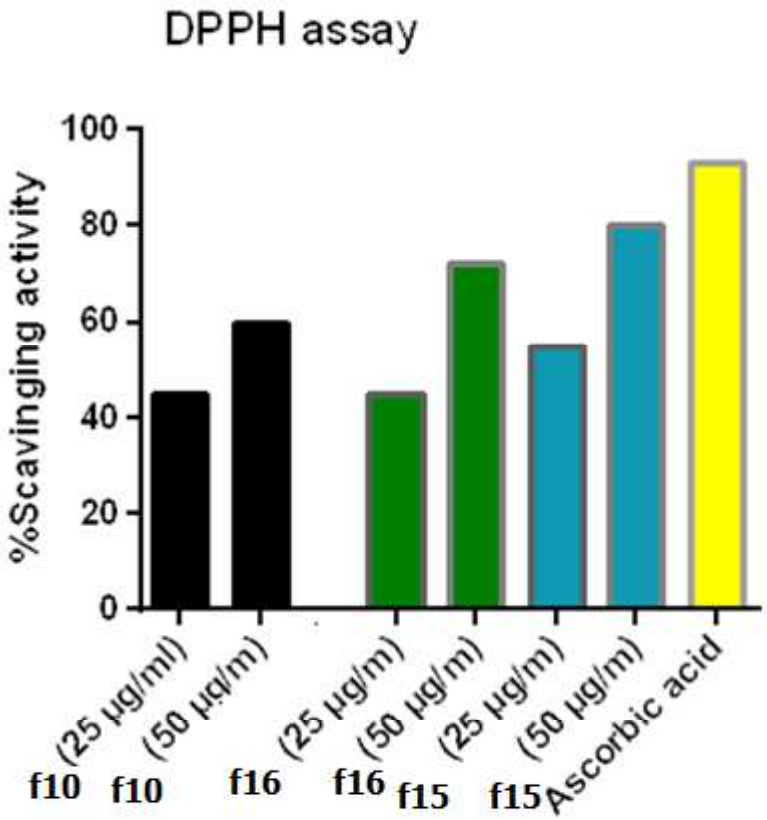


Figure 3-66. DPPH free radical scavenging activity of F10,F15,and F16 at different concentrations (25, and 50µg/mL_1). The values represent the mean ± SD of three experiments. Vit. C: vitamin C was used as positive control.

3.8 Conclusion

New 4-aminobenzoic acid substituted with amino drug molecules based on maleimide were synthesized and characterized. New homo polymers based on maleimide and drugs chloride monomers which loaded with medical properties to extend the controlled drug were synthesized and characterized. Also, new hetero polymers based on maleimide and drugs chloride monomers with acrylic acid which loaded with medical properties to extend the controlled drug were synthesized and characterized. All these prepared monomers and polymers were characterized by FT-IR , ^{1}H-NMR and ^{13}C-NMR techniques and displayed characteristic bands proving the formation of the desired target molecules from the starting material. The physical properties of all prepared monomers and polymers were studied. Synthesized monomers, homo polymers, and copolymers are soluble in Acetone, DMSO, and partial in ethanol, diethyl ether, toluene, chloroform, and H_2O. Viscosity measurements in acetone were carried out at one concentration of homo polymers and copolymers in acetone at 25 ºC using an Ostowalled viscometer with a capillary diameter of 0.49 mm. The rapid release of prepared polymers was studied. Acid and base functions were used where hydrolysis gradually. As a pharmaceutical unit of the hydrolysis of the polymer loaded with the drug where pH = 2.2, pH = 7.0 and pH= 8.0 and the process of medical liberation after five hours, and appears that the medical release in the basic environment faster than the acid. We evaluated the anti-proliferating effect of drug-loading F_7, F_9, and F_{12} against the breast cancer cell lines. Based on cytotoxicity analyses, it can be concluded that F_7, F_9, and F_{12} may be an appropriate and promising strategy for developing effective drug delivery system to clinical application against breast cancers. The results of antioxidant agreed with

the findings that indicated F_{10}, F_{15}, and F_{16} enhanced antioxidant activity of drugs. The enhanced antioxidant activity of modified drugs could be attributed to then hanced solubility and dissolution rate.

3.9 The Future work

1. Synthesis and characterization of new monomers from the prepared starting material using another drugs.
2. Synthesis and characterization a new homo and copolymers from the new drug monomers.
3. Study of biological activity for the other prepared polymers.
4. Study the size of the prepared polymer particle due to high possibility to be nanoparticles.
5. The prepared fluorescent compounds may a number of application such as biofluorescence, bioluminescence and biophosphoresences.

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الخلاصة :

في هذا العمل ، تم تحضيرخمسة مونومرات دوائية معوضة جديدة وبوليمرات جديدة متجانسة وغير متجانسة محملة بالدواء حيث تكون ذات خواص طبية لغرض تنظيم تحرر الدواء.

تضمن البحث المسارات التالية :-

المسار الاول: تتضمن الخطـــوة الأولى تحضير حامض ماليميك (F1) عن طريق تفـاعل أنهيدريد ماليـك مع ٤- امينو حامض بنزويك. ثم تم تحويل المركب (F1) إلى مشتق كلوريد الأسيل (mF1) والذي فوعل مع ادوية أمينية مختلفة (سلفادزين، كلورورديازيبوكساید، باراسيتامول، ثيوفيلين ، سودافدرين) لتنتج المونومرات (F2-F6).

المسار الثاني:حضرت البوليمرات المتجانسة (F7-F11) من خلال تفاعل البلمرة للجذورالحرة للمونومرات (F2-F6) تحت النيتروجين باستخدام (MEKP) بادئاً للتفاعل.

المسار الثالث:حضرت البوليمرات غير المتجانسة (F12-F16) من خلال تفاعل البلمرة للجذور الحرة للمونومرات (F2-F6) بشكل منفصل مع حمض الأكريليك تحت النيتروجين باستخدام (MEKP) بادئاً للتفاعل.

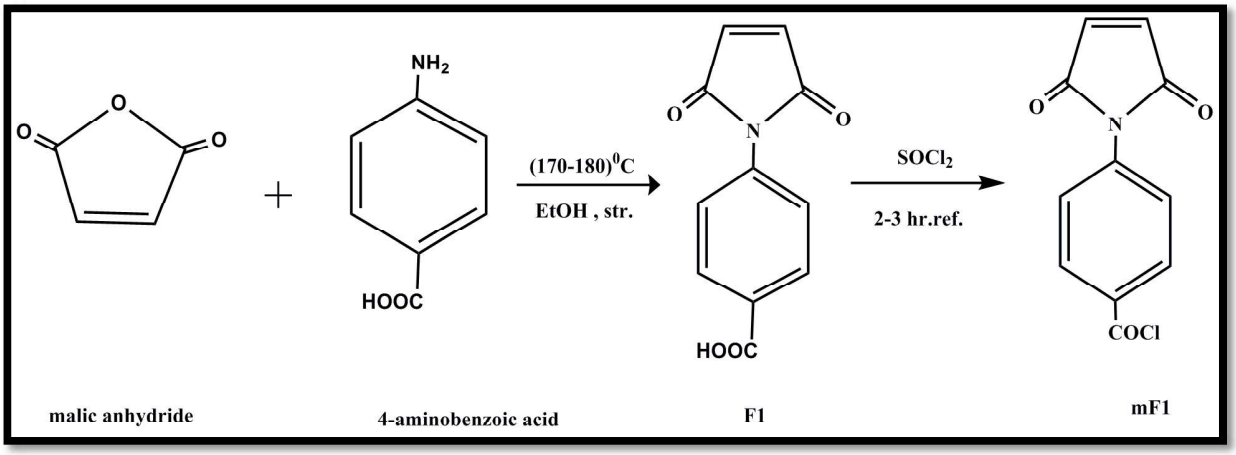
المسار الرابع: جميع هذه المونيمرات والبوليمرات المحضرة شخصت بوساطة تقنيات TF-IR ، ^{1}H-NMR ، ^{13}C-NMR. تمت دراسة التحرر الدوائي المحكم والانتفاخ في قيم pH مختلفة في درجة حرارة ٣٧ درجة مئوية . تم قياس اللزوجة الجوهرية عند ٢٥ درجة مئوية باستخدام مقياس استوالد ودرست خاصية قابلية الذوبان لهذه البوليمرات، تمت دراسة بعض الخواص الفيزيائية للمونيمرات والبوليمرات المحضرة .

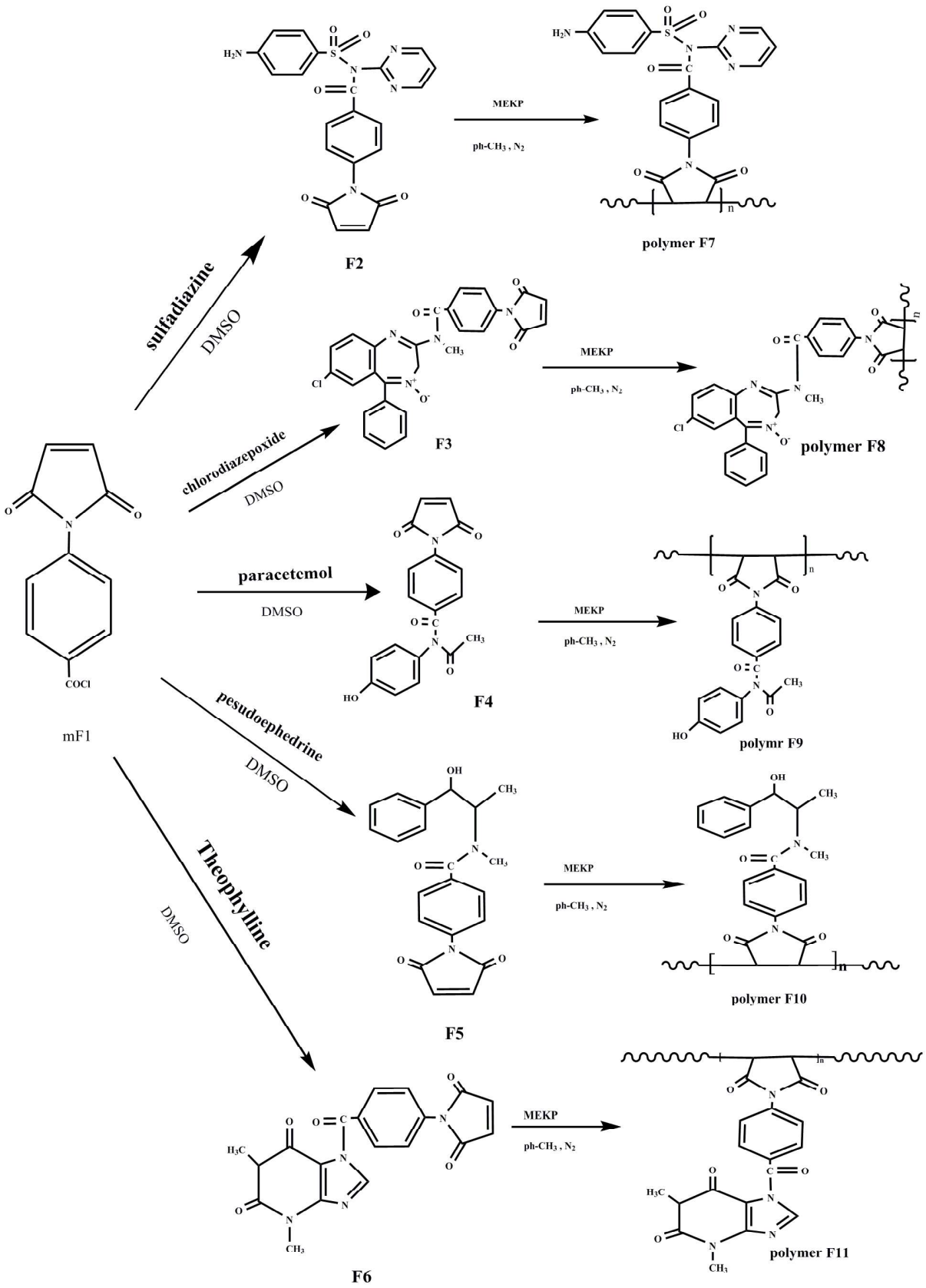
المسار الخامس: تحليلات السمية الخلوية والاكسدة

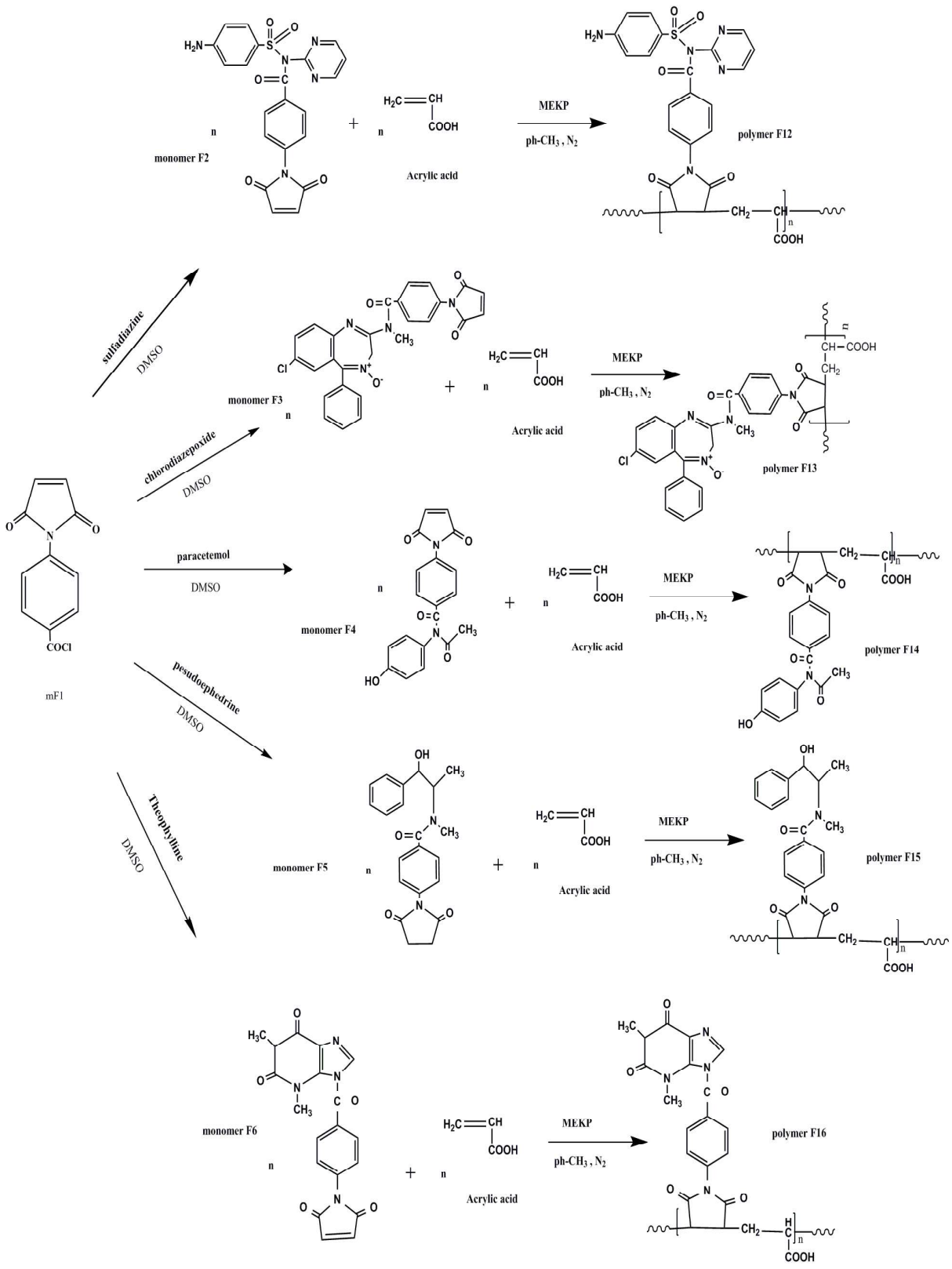
درست خصائص الفعالية البايولوجية لقسم من البوليمرات الدوائية المحضرة حيث تم تقييم تأثير مكافحة التكاثر للبوليمرات الدوائية المحضرة F7 ، F9 و F12 ضد خطوط الخلايا سرطان الثدي. استناداً إلى تحليلات السمية الخلوية ، يمكن الاستنتاج أنF7 ، F9 و F12 قد تكون استراتيجية مناسبة وواعدة لتطوير

نظام فعال لتوصيل الدواء إلى التطبيق السريري ضد سرطان الثدي. توافقت نتائج مضادات الأكسدة مع النتائج للبوليمرات F10، F15 و F16 التي أشارت لزيادة النشاط المضاد للأكسدة للادوية المحملة على البوليمرات. يمكن أن يعزى النشاط المضاد للأكسدة المعزز للأدوية المحورة إلى الذوبان المعزز ومعدل الذوبان.

وفيما يلي خطوات تحضير المركبات :




sulfadiazine
DMSO
F2
MEKP
ph-CH3 , N2
polymer F7
chlorodiazepoxide
DMSO
F3
MEKP
ph-CH3 , N2
polymer F8
paracetemol
DMSO
F4
MEKP
ph-CH3 , N2
polymr F9
mF1
pesudoephedrine
DMSO
F5
MEKP
ph-CH3 , N2
polymer F10
Theophylline
DMSO
F6
MEKP
ph-CH3 , N2
polymer F11


monomer F2
Acrylic acid
MEKP
ph-CH3 , N2
polymer F12
sulfadiazine
DMSO
monomer F3
chlorodiazepoxide
DMSO
Acrylic acid
MEKP
ph-CH3 , N2
polymer F13
mF1
paracetemol
DMSO
monomer F4
Acrylic acid
MEKP
ph-CH3 , N2
polymer F14
pesudoephedrine
DMSO
monomer F5
Acrylic acid
MEKP
ph-CH3 , N2
polymer F15
Theophylline
DMSO
monomer F6
Acrylic acid
MEKP
ph-CH3 , N2
polymer F16

جمهورية العراق
وزارة التعليم العالي و البحث العلمي
جامعــة كربـلاء
كليــة التربيــة للعلــوم الصرفــة
قسـم الكيميـاء

تحضير بوليمرات مشتـــركة جديدة من المالئميـــد كنظام ناقــل للدواء ودراســة فعاليتها ضـــــد السرطان

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

من قبل

فاطمة عبد الرزاق مجيد

بكالوريوس كيمياء / جامعة كربلاء (2013)

بإشـــــراف

أ.د.محمد ناظم بهجت

أ.م.د.مهند موسى كريم

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