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Studying the Possibility of a Novel Nano Co-Polymer as Drug Delivery

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Degree of Master in Chemistry Sciences

By

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وما تَكُونُ فِي شَأْنٍ وما تَتْلُوا مِنْهُ مِنْ قُرْآنٍ ولا تَعْمَلُونَ مِنْ عَمَلٍ إِلَّا كُنَّا عَلَيْكُمْ شُهُوداً إِذْ تُفِيضُونَ فِيهِ وما يَعْزُبُ عَنْم رَبِّكَ مِنْ مِثْقالِ ذَرَّةٍ فِي الأَرْضِ ولا فِي السَّماءِ ولا أَصْغَرَ مِنْ ذلِكَ ولا أَكْبَرَ إِلَّا فِي كِتابٍ مُبِينٍ.

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Dedication

To whom is the Reason of My Existence;

To Those Who Brighten My Future'

To Those Who Encourage Me to get the Best in Life;

To the Owners of Compassionate Hearts and Hidden Pearls;

To the Most Magnificent Persons in My Opinion;

To My family

Maha mahdi

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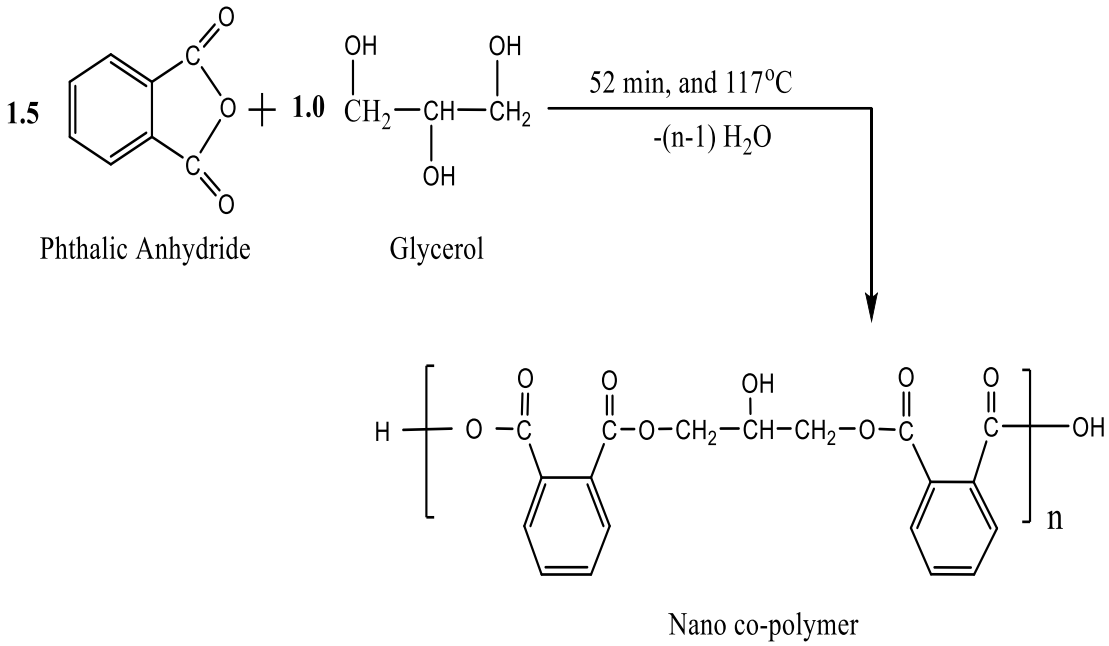
The work on this thesis would not have been completed without their help

Maha

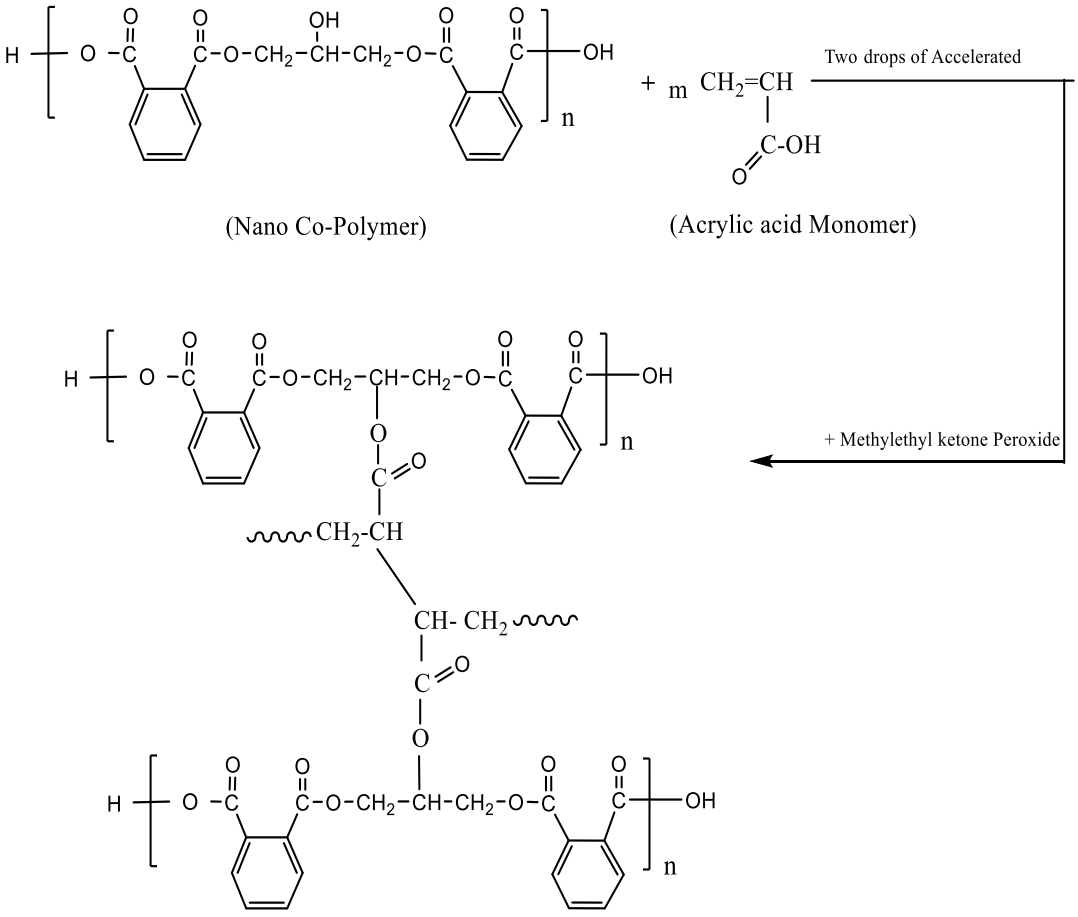
Abstract

In the current work, a novel nano co-polymer was produced via reacting 1.5 mole of phthalic anhydride to one mole of glycerol in specific conditions, as is shown in the following reaction. The prepared nano co-polymer was discriminated using (FT-IR, 1HMNR, DSC, AFM, XRD, and TEM) techniques.



(Linear nano co-polymer)

Then three asymmetrical moles from the acrylic acid monomer (0.15, 0.25, and 0.35 moles) have been adding in order to prepare three new nano co-polymer, as is shown in the following reaction.



(Nano Co-Polymer) (Acrylic acid Monomer)

(Cross-Linked Graft Nano Co-Polymer)

The glutathione protein was loaded in a specific polymeric matrix by submerging the hydrogel nano co-polymer within buffer solution (pH=2.2) also (pH=8.0) and at a steady temperature (310K) then allowed to load. The concentration of loaded and released glutathione was evaluated by using a UV-Vis spectrophotometer.

The studies of drug release from the glutathione loaded hydrogel nano co-polymer were examined in two various PH media (2.2, 8.0) in steady temperature (310K) as a function of time. We noticed that when drug concentration has increased the process of the release will increase as a result.

The obtained results show that the loading and releasing process of protein to the basic medium (pH=8.0) is greater than to the acidic medium (pH=2.2). For example, the maximum absorbance for releasing Glutathione per time (hour and day) of containing 0.15 mole of acrylic acid monomer in (pH=2.2) is 0.307 nm, while the maximum absorbance for releasing the same sample in (pH=8.0) is 0.398 nm.

It seems that the effectiveness of the nano-co-polymer in releasing the protein in the acidic medium (pH=2.2) is lower than that in basic medium (pH=8.0), which means the combined nano-copolymer is selective/sensitive in the medium.

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Abbreviations	
Abbreviation	**Full name**
3D	Three-dimensional
LCST	Lower critical solution temperature
CGPs	Chain-Growth Polymerizations
SGPs	Step-Growth Polymerizations
ASTM	American Section of the International Association for Testing Materials
MEKP	Methyl Ethyl Ketone Peroxide
DMSO	Dimethyl Sulfoxide
UV-Vis	Ultraviolet-Visible
FT-IR	Fourier Transformer Infra-Red
AFM	Atomic Force Microscope
DSC	Differential Scanning Calorimetry
XRD	X-Ray Diffraction
TEM	Transmission Electron Microscope
SFM	Scanning Force Microscopy
Tg	Glass Transition temperature
Tc	Crystallization temperature
Tm	Melting temperature
RMS	Root Mean Square

CHAPTER ONE

Introduction

1. INTRODUCTION

1.1 Overview of General polymer

Polymers represent a highly significant materials class, life seems almost impossible without polymers especially in this ever-increasing technological world, where the science of polymers plays a major role in providing solutions to critical challenges that may face applications related to energy, food, clean water, air, and health in general. Therefore, polymers are found in every application around us during our daily life such as plastics, rubbers, resins, and tapes for binders and adhesives, soils, etc. [1].

Furthermore, the fact that molecular biology, biomedicine, biochemistry, pharmacology, and biophysics are the domains in which polymers and polymer chemistry play a major role in the development of their new fields. It is all this clear why the study of big molecules is one of the topics of scientific research that is most attended and fastest-growing. As a result, it appears that polymer is not only an interdisciplinary discipline or a chemical science branch [2].

The Greek word polys meaning "many" and meros, which means "part" is the one from which the term "Polymer" is derived . It was first presented by the Swedish chemist Jöns Jakob Berzelius in 1883[3]. Despite it had just been one year since the word "isomer" introduced (derived from the Greek word isos mean "equal" and meros mean "part") in order to represent substances that have various properties but the same combinations [2]. The polymer's modern concept as covalently linked macromolecular structures was Submitted by Hermann Staudinger in 1920, who spent the following decade collecting experimental proof for this hypothesis, and thus the polymer's history is closely related to his name [4].

In the 1920s, DuPont continued to focus on the science of materials, Hired 1928, Wallace Carothers, for working on polymers. Also on November 3, 1931, Carothers created neoprene, a synthetic rubber that was considered the first polyester super polymer [5]. DuPont is an American company headquartered in Wilmington, Delaware, in the state in which it was incorporated since the establishment of the ancient DuPont in 1802. It is considered one of the biggest public corporations in the United States [6].

Polymers are large molecules that have a great molecular weight, therefore named macromolecules that accumulate by binding a huge number of small molecules termed monomers with each other. The chemical reaction that combines two or more monomers, with present any of heat, water, or whatever other solvent, to create a large molecular weight molecule (polymer). The aforementioned reaction is termed polymerization [7]. As a result, their high molecular mass compare to tiny molecule compounds gives unprecedented physical characteristics, such as viscoelasticity, toughness , etc.[8].

1.1.1 Polymers Classification.

It is not possible to categorized polymers based on one category due to their wide applications, various behaviors, and complex structures, so polymers have been classified depending on various basis into different types as in the following enumeration[8]:

1- Classification of polymers according to the availability source:

Polymers are classified according to their presence or source into three types[9]:

- **Natural polymers:** A class of polymers that referred to polymers, which are naturally obtained such as from plants or animals, for example. Cellulose, Lignin, RNA and DNA [10].

- **Semi-synthetic polymers:** These are a class of polymers obtained by simple chemical modified of natural fibers, for example. Ethyl Cellulose (EC), and Methylcellulose (MC) concerning pharmaceutical purposes [11].
- **Synthetic Polymers:** It is also a class of polymers obtained from linking monomers which the made through the chemical synthesis. For example, Poly acrylate, Poly Vinyl Alcohol (PVA), Poly Ethylene (PE), etc.[11].

2- Classification of polymers according to the monomer chain structures:

Polymers are classified according to The monomers binding way into three types [8][12]:

- **Linear polymers:** In this class of polymers, the monomers are bonded to other and form a long straight chain. There is not branches coming out of the chain. For example, Nylon, Polyethylene, PVC, etc.
- **Branched polymers:** In this class of polymers, they have a long straight chain with different side chains, for example, Amylopectin and low-density polythene.
- **Cross-linked polymers:** In this class, the monomers are linked together to form a three-dimensional network, for example, Vulcanized Rubber, Bakelite, etc.

3- Classifications of polymers according to the polymerization process:

Polymers can be classified according to the type of polymerization process into two groups**[8][13]**:

- Addition Polymerization or Chain-Growth Polymerizations **(CGPs)**; In this class of polymers, these polymers created via the serial addition of monomer units frequently without other products co-creation. The monomers interact exclusively with the ends of the active chain, but they really do never interact with one another. For example, Teflon, Orion,

Polyethylene, PVC, Polypropylene, in general, Alkenes, and their derivatives are mono units for it.

- Condensation polymers (Step-Growth Polymerizations) **(SGPs)**; This class of polymers is created by combining the two monomers are combined by removing tiny molecules such as water, NH3, or alcohol. Therefore, the monomers interact with one another and further interact with every type of oligomers plus polymers that have active ends, but on one condition that the polymeric and Oligomeric chains are not very stiff. For example; Polyamide (nylon), Polyurethane, Polyester.

4- Classification of polymers according to the monomer types:

Polymers can be classified according to the type of monomer process into following [14][15]:

- **Homopolymer:** This class of polymers derived from a single type of monomer. The structural framework of homopolymer hydrogels is subject to polymerization technology, the cross-linker, and the nature of the monomer, etc. For example, polystyrene (PS), polyethylene (PE), and polyethylene glycol (PEG).
- **Heteropolymer or co-polymer:** This class of polymers is derived from more than one type of monomer. At least one of these monomers should be naturally hydrophilic (the hydrophilic monomer swells the hydrogel's profile). For example, Nylon 6-6, polyethylene oxide (PEO), and this class is divided into four different types of copolymer structures that have been based on the different monomers arrangement method as shown in Figure (1-1):

I. Random copolymer: The repeating units randomly distributed along the polymer backbone in this type.

II. Alternating copolymer: This type contains only two various kinds of repeating units that are found in alternating locations along the polymer backbone.

III. Block copolymer: These copolymers are linear, wherein the repeating units are found solely in long sequences or blocks of the same type.

IV. Graft copolymer: are polymers that are branched through a repeating unit, in which the branch units have a various chemical structure than the units in the main chain.

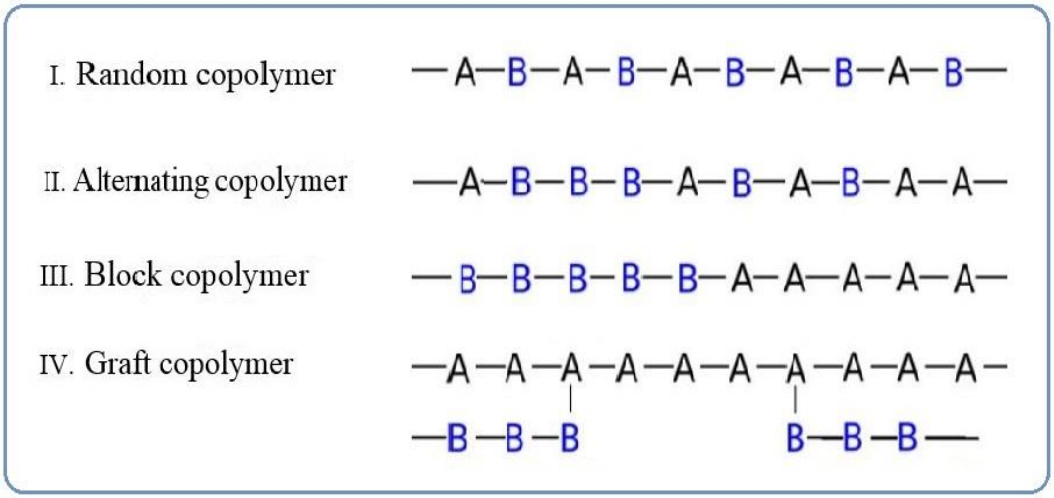


Figure (1-1): Types of Heteropolymer or Co-polymer structures.

5- Classification of polymers according to the molecular forces:

The mechanical characteristics of polymers such as elasticity, stiffness, and tensile strength based mainly on intermolecular forces such as van der Waals forces and also hydrogen bonding. Therefore, it is mainly classified according to these forces into[14][16]:

- **Elastomers:** This class of polymers that the polymer chains are suspended by the weakest forces of attraction. These polymers are flexible so they can be easily stretched into long stretches which quickly restore their first dimensions when the stress that applied is cleared, for example, Vulcanized Rubber, and Neoprene.

- **Thermoplastic polymers:** This class is polymers with intermolecular forces among elastomers and fibers that get liquid phase when heat is applied. It can be modified (and reshaped) into almost every shape utilizing the processing techniques like injection moulding and extrusion. For example PVC, Polystyrene, Polythene.
- **Thermosetting polymers:** These polymers are stiff, lattice materials in which the motion of the chain is very limited through a great degree of impenetrable cross-linking upon heating. , For example. Bakelite.
- **Fibers:** This class of polymers has a great intermolecular attraction force as H-bonding. It has large tensile strength, for example. Terylene, Nylon-6, and Nylon-66.

1.2 Nano polymers

1.2.1 Nanotechnology

Nanotechnology is regarded as the study that includes both science, engineering, medicine, and technology at a nano-level [17] . The term “nano” is a Greek word that implies dwarf [18]. Nanomaterials can be clearly described as the material with sizes among (1-100) nm[19]. The nanotechnology adventure begins with Nobel Prize winner Richard Feynman's lecture “There’s Plenty of Room at the Bottom” at the American Physical Society gathering at Caltech on December 29, 1959 [18]. This has informed the scientific community of the untapped possibilities from nanomaterials [18].

Nanotechnology provides a pathway for entirely new classes of noble-engineered nano-carriers, biosensors, and systems that have changed modern drug delivery methods dramatically [20]. Researchers nowadays are trying to reach undiscovered biological localities by reducing the transporter's sizes without affecting drug loading to provide better and more rapid therapy, like the central nervous system (CNS) [21]. Therefore, a diversity of organic and inorganic

materials have been developed through researchers, in order to enhance the drug delivery systems, and these nano-sized particles display advanced mechanical, chemical, structural, biological, magnetic, and electrical characteristics for biodistribution [21].

Since nanoparticles include atomic or molecular-level materials, nanoparticles are generally small-sized nano spheres [22]. Hence, nanoparticles can travel more easily inside the human body if compared to materials with larger sizes, and the materials fabrication and engineering on a molecular size empower us to penetrate biological sites where blood does not circulate into it, like Blood-Brain Barrier (BBB) [21].

Nanomedicines have recently become appreciated because of the fact that nanostructures can be utilized through encapsulating drugs as delivery agents, or attaching and delivering therapeutic drugs to purpose tissues [19][23]. Which is affecting the borders of nanomedicine that is beginning at first from Biosensors, Microfluidics, Drug transfer, and Microarray testing to Tissue engineering [24].

additionally, there is two main strategies are employed to synthesize nanomaterial (nanopolymer) top-down and bottom-up processes [25]. In top-down approach, nanomaterial can be synthesized using many processes to a deconstruction of larger structures into their smaller ones in nano-scale with keeping their original characteristics, while the bottom-up approach synthesizes nanomaterial by many processes to engineered from atoms structure piecing together to produce a nano-scale structure [26].

1.2.2 Nanoparticles

The “nanoparticles” term includes both nanocapsules and nanoshells, which are different in numerous major factors regarding to the size and morphology of the particles. Microscopic techniques like AFM, TEM, and SEM

can measure these factors [27]. Depending on the method of preparation and the organic phase composition, nanospheres or nanocapsules may be produced [28].

The nanocapsule particle has the shape of a core-shell with an oily or watery cavity, on the other ghand, the active composites are enclosed and surrounded by a polymer shell, the nanosphere has a polymeric matrix-like structure in which the active composites and polymer are evenly separated such that the medicine is maintained within or adsorbed on its surface [29]. These categories of polymeric nanoparticles (NPs) are known as reservoir system which is called as nanocapsule, and matrix system which is called as nanosphere, as shown in the Figure (1-2) [30].

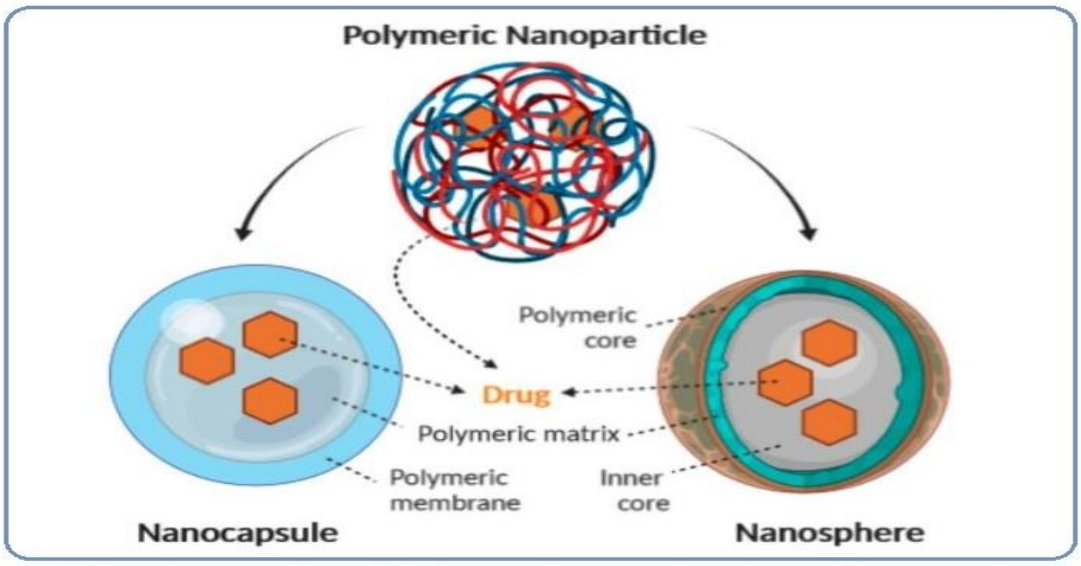


Figure (1-2): Schematic illustration of the structure of the nanocapsules and nanospheres (the arrow indicates the presence of a drug / bioactive inside the nanoparticles).

Various methods may be utilized to prepare polymeric nanoparticles according to the kind of drug to occur loaded into the polymeric nanoparticles, it needs an appropriate administration route, and the drug's physical and chemical properties [31]. Table (1-1) shows a list of the most commonly used techniques [32][33].

Table (1-1): Different methods for the production of polymeric nanoparticles.

Polymeric Nanoparticles	Production Method
Nanospheres	Solvent evaporation Emulsification/solvent diffusion Nanoprecipitation Emulsification/reverse salting-out
Nanocapsules	Nanoprecipitation

In most technologies that need the usage of preformed polymers, organic solvents are often applied in the initial step in order to polymer dissolution [25]. These solvents may cause toxicity issues and environmental hazards. Moreover, the solvent residues should be eliminated from the finished product. Whichever preparation method is utilized, the products are generally produced as hydrocolloid suspensions [34].

1.2.3 Basic Properties Nano Drug Delivery

Traditional systems of drug delivery that using large-sized materials for drug delivery show several critical issues related to sensitive toxicity. In poor bioavailability, vivo instability, problems with targeted delivery, drug resistance generation, and potential adverse influences of bad quality drugs, that significantly reduces the treatment efficacy of several drug systems [35]. Accordingly, the use of new systems for drug delivery like the nanopolymer system to target drugs to particular parts of the body may be a useful option since these previous critical issues could solve, because it possesses the following essential properties that make current medication delivery more efficient [24].

First, enhance bioavailability, and acceptability with extremely weak cytotoxicity through boosting drug circulation time of highly loaded drug, lower toxicity [36].

Second, the hydrophobic drug delivery [37], due to the natural immune reaction of the body's to strange substances, the higher hydrophobic of these substances, the more probable they are removed [38]. Since the hydrophobic nanoparticles (NPs) are easily removed. It looks reasonable to expect that making their hydrophilic surface will enhance their circulation time inside the body. Actually, coating nanoparticles by surfactants or polymers, or forming copolymers such as Polyethylene glycol (PEG, reduces opsonization and prevents localization to the hepatic and splenic), Polyethylene oxide, poloxamine. Polyethylene glycol is hydrophilic and moderately inert polymer, and when it is integrated onto the surface of nanoparticles. It obstructs the plasma protein binding (Opsonization), therefore avoiding a significant loss of the administered dose [39].

Third, features of nanoscale can be utilized to improve cell permeability therefore therapeutic delivery will increase [40]. Drug transport over biological barriers, including stratum corneum, endothelial barriers and tight epithelial, etc.[41]. The cell absorption of drugs can also be supported via binding targeted ligands or changing the size, shape, and surface features of nano deliveries [42]. Thus, modifying surface properties is another possibility to create the perfect system, additionally, to generate a perfect drug delivery system from nanoparticles. It is important to integrate suitable targeting bondings, surface curvature. Also, reaction event is also crucial to treatment the aggregation inhibition, receptor binding, stability, and succeeding pharmacological influences of a drug [38].

Fourth, nanotechnology offers the opportunity to control releasing, multimodality, and extreme precision for targeted delivery, through

accumulating the information about the relations among the physical and chemical characteristics of nanomaterials and biological activities of the microenvironment that surround it [40]. Their degradation rates and drug release rates may be changed utilizing different polymers [43].

Fifth, reduce the amount and frequency of dosages [40], delivering drugs with a spatial/temporal controlled way to the target areas and with a lower dosage frequency [35].

Finally, companies will not just thrive on developing new creations of their "intellectual property", but will be motivated by patent expirations [44]. The advantage of pharmaceutical companies using this modern technology would be that nanotechnology provides a new beginning to those drugs which were beforehand regarded as non-marketable because of their limited solubility and bioavailability, extraordinary toxicity, and notable side effects [45].

1.2.4 Nanogels (Nano-sized hydro-gels)

Nanogels are particles in nanoscale generated in three-dimensional networks using crosslinking polymers [46] [47].Nanogels own structure with porous feature that could swell in water or in biological fluids and also retain large amounts of drug and oligonucleotide inside their 3D network [46][48]. Nano-size hydrogel react more quickly to stimuli and also possess larger exchange rates every volume unit [49], properties of nanogels involve great surface area Compare to volume , biodegradability, biocompatibility, extremely low toxicity, specific steady structure, softness and flexibility [50][51][52].

Nanogels could be generated of natural polysaccharides, natural proteins, or synthetic polymers [46][53]. For example, the natural polymers that have been utilized in manufacturing nanogels are derivative from cellulose known as sodium carboxymethyl cellulose (CMC) [54].

Nanogels are very sensitive toward ambient condition such as pH, temperature, light, and magnetic field, that are suitable for drug release control inside target cells [46][48][50].

N-isopropylacrylamide (NIPAM) monomer is used to achieve the temperature sensitivity for the nanogels [46][48]. The existence of some groups like poly acrylic acid (PAA) and N, N-di ethyl amino ethyl meth acrylate (DMA) makes nanogel sensitive to pH, which is manages the drug release within definite organs or cells [46][48].

In addition, several efforts have been made to improve nanogels performance, after identification them as drug delivery systems, for instance, in tuberculosis therapy, particles of nanogel were designed through a structure in micron-scale in order to develop loading and drug delivery, thus through merging drug with these nanogels, dry powders were produced that could have been applied easily through the respiratory tract and then deposited within lungs[55]. Drug release behaviors studies have also demonstrated that binary nanogel-hydrogel system have increased kinetic release of drug, and long-term drug-release sustainability [56][57].

The hydrogel-nanogel system was illustrated using IR, SEM, TEM, and UV spectrophotometry techniques. The drug-loaded amount was calculated [58]. To assess this system sensitivity toward temperature and pH, drug release was examined at various temperatures and acidity levels [59].

1.3 Hydrogel

1.3.1 General Consideration

Hydrogels are a three dimensional hydrophilic polymer generated of a polymeric network including chemical and/or physical crosslinks which absorbs and maintains large amounts of water in its pores without degrading within the

aqueous environment [60][61], which its swells and preserving its mechanical strength, structure, and flexibility [62]. The earliest reporting hydrogel was produced in 1960, when Lim and Wichterle both manufactured poly(2-hydroxy ethyl methacrylate) (PHEMA) and applied it in the production of contact lenses with the capability to absorb moisture while confirming their network structure, indicative of presently hydrogels [63][64].

Hydrogels could be modified easily through functional groups and show pores of well-distinct sizes which is can be modulated via crosslinking density, and these can be also sensitive to external parameters like temperature, pH, and magnetic field [65]. Polymer chains in a hydrogel generate a special hree-dimensional matrix with interfacial gaps competent of holding aquatic liquids like the physiological fluids [66]. Furthermore, the high water content offers an environment for the diffusion of nutrients, oxygen, and other small molecules that are essential for cell growth and proliferation [67].

Additionally, various drug molecules can be combined in to the hydrogel and spread into the biological medium from the interstitial spaces, enabling it to be utilized as a reservoir for applications of controlled release. Therefore, over the years, hydrogels have become major players in the field of biomedicine in general (clinical practice and experimental medicine for a wide range of applications [68]. Involving regenerative medicine and tissue engineering [69], diagnostics [70], and pharmaceutical research and development in special [68].

Hydrogel is generally applied in another fields like horticulture, agriculture, biosensors, and pharmaceuticals, is capable to form it into a variety of physical forms, involving fine particles, panels, nanoparticles, films, and coatings [61][49].

1.3.2 Hydrogel structure and water content

In hydrogels, the ubiquity of water represents a key role in the total penetration of active components inside and outside the gel. Water could be attached to every hydrogel structure in four ways as illustrated in Figure (1-3) [71].

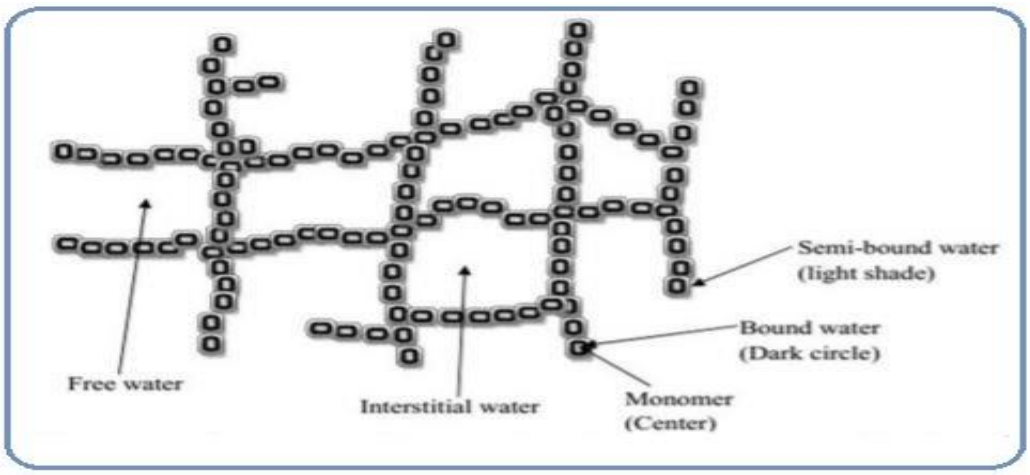


Figure (1-3): Diagrammatic diagram for the molecular structure of a hydrogel network with various water types.

The hydrogel-associated water types are [15] [71]:

1- **Bound water (primary and secondary):** During the dry hydrogel gets into touch with water, water will absorption into a matrix begins. Initially, the molecules of water will adhere immediately to the hydrophilic groups when it is reaching inside the matrix, creating primary bound water or hydrophilic bound water. Due to the full hydration of polar groups, the polymeric network will swell resulting in the hydrophobic group exposure. In addition, these exposed groups react with the molecules of water, resulting in the 'secondary bound water' or hydrophobically linked water, in other words, chemically bound water dissolves or hydrates functional moieties (ions or groups) and binds directly to the polymeric chain. Only under severe circumstances can this type of water be removed from the hydrogel, since it remains like the integrated unit of the hydrogel structure.

2- **Semibound water:** Subsequent the hydrophobic and hydrophilic groups are saturated, the extra water that is because of the network chain osmotic driving force is named bulk water or free water. This type of water, present in the outer area. This can be simply removable from the hydrogel in normal circumstances.

3- **Interstitial water:** is an aqueous layer, that present among the bound water which is on the surface of the polymer monomer. The free water, which is can quickly identify and characterize by utilized DSC thermo gram.

4- **Free water or bulk water:** This type of water presents in the vacuoles of the hydrated polymeric network, which is physically confined but not connected to the hydrogel network.

1.3.3 Hydrogels and Cross-linking

The hydrogel is a massive molecular polymer gel constructed from a cross-linked network of polymer chains that a water-insoluble, and also capable of absorbing vast quantities of water [72]. It is made from cross-linking hydrophilic monomers through chain or step-growth with a functional cross-linker in order to support network building, natural polymers or synthetic polymers, in both homopolymers or copolymers, are employed via molecular interweaving or chemical cross-linking of water to produce a three-dimension network as shown in the Figure (1-4) [73] .

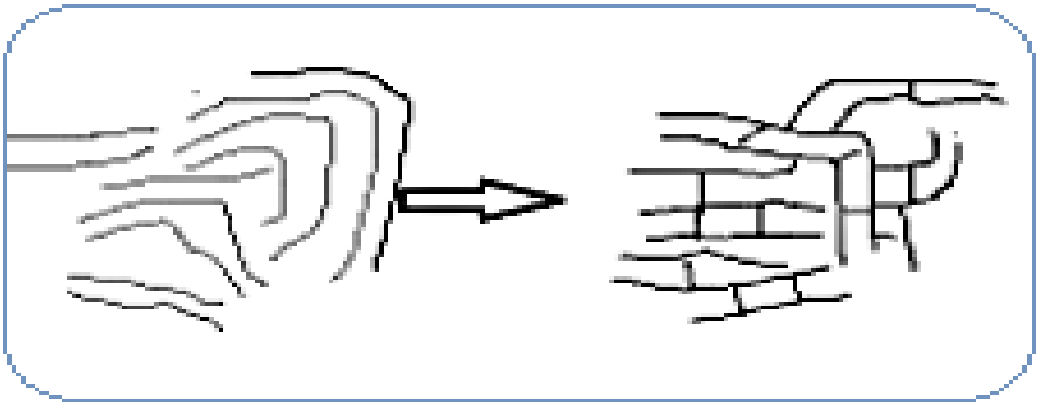


Figure (1-4): Cross-linking in polymer

Hydrogels can be classifies into several ways. However, since hydrogels are generated mainly by cross-linking networks, and thus, based on cross-linking, they are classified into two categories [74]:

(a) physically cross-linked or self-assembled hydrogel : This species has gained importance due to its relative ease of production and the advantage of not utilizing cross-linking factors during their synthesis protocol [75] . Which consist either of polymer chain crosslinking or physical interactions like hydrogen bonds, hydrophobic interactions, or ionic interactions. These physical crosslinks are maybe not stable in nature however, they enough to provide hydrogels insoluble character inside the aqueous medium are [73][76]. this field recently get a great interest in food, biomedical, and pharmaceutical, and the different methods introduced in the literature to production physically cross linked hydrogels are (Stereocomplex formation, Freeze-thawing, H-bonding, Ionic interaction Maturation heat-induced aggregation) [74].

(b) Chemically cross-linked hydrogel: In this kind, there are covalent links between various polymer chains. Accordingly. This hydrogel type is stable and also can't be easily dissolved in solvents which is why it’s termed irreversible or permanent [77]. The opposite of the previous type, in this one (chemical cross-linking) produces a network with comparably high mechanical strength moreover, according to chemical bond types in the cross-linkers and building blocks. It is likewise flexible for formation time, and also the chemical functionalization, gel pore size, and dissolution or degradation, thus comparably extended degradation periods can occur, and the different methods mentioned in the literature to production chemically cross-linked hydrogels are (chemical cross-linking, enzymatic reaction, radical polymerization, grafting, condensation reaction, and high energy irradiation) [74] [78].

There are other ways to classify hydrogels based on the various materials (types of polymers) parameters or involved, like physical structure in to (amorphous, supermolecules, semi-crystalline, hydrocolloid aggregates, and hydrogen bond-gels). On size to (Macrogels, Microgels, Nanogels), on the path of synthesis to (Homopolymas, co-polymers, Multipolymen), on the ionic charge to (anionic, cationic, neutral, ampholitic), on structural and mechanical characteristics to (Phantom, Affine) [79].

1.3.4 Hydrogels Properties

Hydrogels have attracted a lot of attention due to their special properties such as the following.

1- Mechanical Properties

For controlled drug administration and other general medical uses, the mechanical strength of hydrogels is particularly significant. For the hydrogel, it is vital that its physical strength be maintained for a specified time while the treatment chemicals are released. In addition, some polymers, co-monomers, cross linkers, and changes in the degree of crosslinking can be combined to achieve a strong gelatinous network, through which the desired mechanical properties of hydrogels are obtained [79]. Even so, a very high level of crosslinking will results in less elasticity, low elongation and with higher brittleness, elasticity is critical not only to provide greater flexibility but also to aid in incorporated therapeutic moieties movement. And that is why a better level of cross-linking is important to ensure that mechanical strength and flexibility are equal [80]. The viscosity characteristics of hydrogels may be verified using a technique called rheometer, and rheology may be described as "the science of distortion and flow of matter under pressure or stress, it is derived from the Greek terms“ rheo ”, which means flow, and“ –ology, ”to study [81].

Also, evaluation of the mechanical properties of hydrogels can be performed through many other techniques. Such as stress and tensile analysis, which can be performed by localized or unconfined indentation using a probe or dynamic mechanical analysis [79][82].

Fluid and solid perfect conduct were defined in a mathematical manner by the rules of Hooke's laws and Newton's. Nevertheless, there are a huge number of materials that have a transitional behavior among ideal fluids and solid, which cannot be explored using these traditional theories, in particular, that following by Maxwell and Wilhelm Weber's described behaviors of fluids and silk threads. Furthermore, Wilhelm Weber has discovered the non-ideal elastic conduct of silk thread; these materials were generally classed as viscoelastic and non-Newtonian materials. the viscosity of non-Newtonian materials depends on stress and time, while the Viscoelastic materials can be restored after a little deformation [83].

2- Swelling Properties

Hydrogels are particularly characterized by their swelling behavior in water or biological liquids, and as result of it hydrogels are commonly employed in numerous areas, such as drug delivery biomedical tissue engineering, sensors, and etc. [84]. Since the balanced swelling ratio affect the coefficient of the solute diffusion (drug), the surface movement, optical and mechanical characteristics of hydrogels [85].

The swelling ability of hydrogels occurs due to ionization, which enables hydrophilic functional groups connected to the backbone in the cross-linked polymer to absorb the resulting water as well as via difference in the swollen osmotic pressure among the solvent phase and the gel phase [84]. I.e. between both the expansion of hydrogel chains in melting state and the retracting force of their structure to pull the chain inward [86].

Swelling studies can be conducted via immersing totally dry hydrogels inside the swelling medium then extracting the hydrogel from the solution and weighing it after a surface excessive solution is wiped [87]. The properties of swelling are governed by many factors, such as type and structural composition of monomers, cross-link density, and other environmental parameters (temperature, pH, and ionic strength, etc.[85].

3- Biocompatibility Properties

Biocompatibility is a major area that first caught the attention of researchers in the 1940s in the context of medical implants and their interactions with the body. In 1987, the official definition of biocompatibility was "the ability of a biomaterial to perform with an appropriate host response in a specific application" [88].

In order to make it an excellent biological parameter, hydrogels must be biocompatible and non-toxic. most polymers utilized for this idea must therefore be follow both cytotoxicity and in vivo toxicity tests, biocompatibility comprises mostly of two parts [89]:

a. Biologic safety, i.e. appropriate systemic and local response, which is means surrounding tissue, avoidance cytotoxicity, mutagenesis, and carcinogenesis.

b. Biofunctionality i.e. the ability of the materials to fulfill the specific task for which it is particular purpose.

In addition, to eliminate harmful chemicals from the preformed gels, Specific purification processes such as washing with solvents or dialysis must be performed [90].

1.3.5 Important types of sensitive/responsive hydrogels

Hydrogels may exhibit swollen behavior related to the external environment, over the past 30 years, there has been great interest in studying developing and analyzing hydrogels that are environmentally or physiologically responsive to surrounding factors, the most important of which are the following[91].

1- pH-Responsive Hydrogels

PH-responsive hydrogels are one of the most widely studied types of hydrogels. All ionic substances exhibit pH sensitivity. They are swollen ionic networks that contain either acidic or basic suspended groups, and in aqueous media of suitable pH, the suspended groups can ionize and develop constant charges on the gel and thus cause an increase in swelling more than it is in those systems found in non-ionic substances [91].

An example of cationic hydrogels is chitosan and Poly (Ethylene Amine), which swell at a low pH, i.e. an acidic medium, and that due to the proton of the amine-groups, as the positively charged proton slits on the polymer chains cause repulsion and are thus accountable for the swelling, and these types of hydrogels may be used to deliver antibiotic drugs into the stomach during ulcer inflammation or as vectors for an injectable drug delivery system, and one of the examples of anionic hydrogels is the swelling of Carboxy Methyl Chitosan at a higher pH of any basic medium due to the ionization of acidic groups, as a result, negatively charged ionized pendant clusters on the polymer chains cause repulsion resulting in swelling so this This ability of hydrogels can be use for drug delivery at a pH of 7.4 in the intestine [92].

2- Thermal-Responsive Hydrogels

It is another important class of responsive hydrogel systems that have been extensively researched [91]. The common identification of thermo responsive polymers is the existence of various hydrophobic groups like Methyl, Ethyl, and Propyl [85].

Most polymers increase their solubility in water when the temperature increases. However, in some cases of these polymers, the solubility of water decreases with an increase in the inverse temperature or a negative dependence on temperature. This peculiar action generates a phenomenon of the transformation of the polymer phase. The temperature is elevated to a critical value dubbed LCST (lower critical solution temperature). So for hydrogels having negative temperature, water is an excellent polymer solvent immediately below the LCST, and hydrogen bonding interactions among the polymer and water molecules result in enhanced dissolution in water. While, these interactions are destroyed, and the polymer chains fall and then precipitate in the media, whenever the temperature is higher than the lower critical solution temperature (LCST) [93].

So from the above, due to this response to the change in the external environment temperature, the mechanical properties of the hydrogel also change, and as an example of polymers for temperature-responsive hydrogel is Poly N-Iso-Propyl Acryl Amide (PNIPAAm). Also, poly N, N-di Ethyl Acryl Amide (PDEAAm) which are frequently employed due to their lower critical solution and regulated drug delivery which is related to sol-gel phase conversion at the body temperature [85].

3- Photo-Light Responsive hydrogel

This type undergo a modified in their characteristics when radiated with light in suitable wavelength. They consist of a polymeric network and a photo-receptive moiety as that of the functional part side chains or along polymer backbone , the optical signal captured at first via the photochromic molecules which is convert the photo-irradiation to a chemical signal by a photo-reaction includes isomerization, dimerization , and cleavage. The latter signal is conveyed to the functional moiety of hydrogel and controls its properties, which is made it particularly appealing to biomedical applications [69] [93].

1.3.6 Synthetic Hydrogels

Hydrogel synthesis is a key step in development of novel structures with useful drug delivery characteristics. The structure of the hydrogel is dictated by hydration of the hydrophilic groups and the various polymer regions. These groups and their interrelated chain networks therefore establish 3D networks by interlacing to avoid their aqueous phase dissolution [94].

Standard synthesis procedures include polymerization and crosslinking, such as Physical cross-linking, chemical cross-linking, polymerase grafting, and radiation crosslinking, have been utilized for hydrogel preparation [79].

The polymerization process is part of the generation process, the structure and shape of the onset material affect the creation of soluble polymer networks, and the substance (starting material) from which the polymer is used is polymer monomers, prepolymers, or hydrophilic polymers. Furthermore, in the network development, the monomers and multi-functional components serve as linkers[94].

Conventional and controlled radical polymerization techniques enable the creation of various hydrogels, such as hollow core-shell particles, of varied composition, size and shapes [95][96].

In addition, crosslinking a variety of crosslinking techniques including click chemistry reactions, , image crosslinking, amide crosslinking, enzyme-mediated crosslinking, etc., have been utilized to manufacture hydrogels, in particular nanoparticles of polymer precursors [79]. All these previous methods might take place at the same time in one stage or in several steps one after the other [94].

1.3.7 Hydrogel for drug delivery

The crucial role of hydrogels in the production and development of drug delivery systems is demonstrated by the following characteristics [90][97]:

- Highest absorption ability (swelling of the maximum equilibrium) of the drug in saline or biological fluids.
- Because of its large water content, it possesses a degree of elasticity very similar to normal tissues.
- It can give the required absorption rate (recommended particle size and porosity) according to the requirements of the drug delivery system application.
- Hydrogels possess the capacity to discern changes in pH, temperature, or metabolite concentration and release their load in time as a consequence of such a change.
- Lowest in terms of the soluble content, remnant monomer and price.
- It has the highest biocompatible, ability to biodegrade and can be injected without creating any of the toxic species after degradation..
- The best durability and stability in the swelling environment as well as midst the storage.

- Equivalent in the pH value following swelling in the water.
- Hydrogels Have the ability to re-wetting (if needed), it must be able to sustain or restore the imbibed solution; According to the application requirements.
- Absolutely colorless, odorless and non-toxic.

Indeed, in practice, it is not possible for a hydrogel sample to achieve simultaneously all of the required features described above, as synthetic components to maximize some of these features will result in inefficiency of the rest. Hence, in practice, the production reaction variables have to be modified such that an appropriate balance may be achieved among it attributes. For example, the hydrogels utilized in drug delivery have to be porous and respond to either pH or temperature [76].

1.4 Glutathione

Glutathione (GSH) is a tripeptide comprising of glutamic acid, glycine, and cysteine, from the point of view of chemical structure, GSH is a sensitive compound that could oxidized to Formula GSSG, synthesizing GSH is has been in every cells for the living organisms [98]. Moreover, it plays a very important role in reducing oxidative stress, controlling redox balance, promoting detoxification of vital organisms, and regulating immune system response, etc.[99]. Whereas glutathione-mediated biotransformation (GSH) is the one of most popular liver detoxification strategies for the removal of small foreign materials especially since liver detoxification is a natural defence response that the body utilises , as it is the most abundant biothiol (~10 mM) in the liver, GSH is existent in every mammalian tissues and synthesized inside hepatocytes [100].

Several chronic diseases like cardiovascular disease, endotoxemia, and even cancer, are associated with suboptimal or deficient glutathione levels (i.e., dysregulation of GSH synthesis in the body) [98].

1.5 Drug delivery system

The advancement of Nano medicine, and the progress of drug discovery/ construct drug delivery systems, have led to the proposed many therapeutic procedures and conventional clinical diagnostic methods studied, to Improve medication specificity and accuracy in diagnosis. For example, novel medication delivery methods are being studied and their target actions in certain places are being ensured, therefore, improving their bioavailability and lowering their toxicity inside the organism [24].

Moreover, many studies and reviews were conducted in this field; They concentrate on the rational design for various molecules and demonstrate how important it is to investigate diverse drug release mechanisms [101]. Within that regard, drug development was a potential characteristic of the identification of novel delivery drugs based on the knowledge of a biological target. Advances in computer science and the development of experimental techniques for classifying and purifying proteins, peptides, and biological targets are important for this sector's growth and progress [24].

1.6 Aim of the work

There are four main aims of the study, the first of which is to prepare three new types of modified nano co-polymers, and Second, it is to study the swelling of these nano co-polymers at a constant temperature (310 K) for three distinct pH (2.2, 8.0) at a constant temperature (310 K). And the third is to study the ability of these copolymers to load and release the drug (glutathione) in acidic and basic media, at a constant temperature of 310 K.

As for the last aim, it is to calculate the efficient nano co-polymers created in transporting the drug (Glutathione).

CHAPTER TWO

Experimental

2. Experimental Part

2.1 Chemicals and Techniques

2.1.1 Chemicals

All the solid and liquid chemical materials, which are used in this work, are shown in table (2-1).

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

No.	Material	Company	Purities %
1	Malic anhydride	Fluka	95.5 %
2	Phthalic anhydride	ALPHA	99 %
3	Glycerol	BDH	99.5 %
4	p-xylene	MERCH	99 %
5	Ethanol absolute	BDH	99.9 %
6	Dimethyl Sulphxide	BDH	98.9 %
7	Borax	BDH	99 %
8	Potassium Chloride	BDH	99 %
9	Acrylic acid monomer	B.D.H	99.0 %
10	Hydrochloric acid	C.D.H	99.0 %
11	Glutathione	AVONCHEM	99.9 %
12	Cobalt Octoate 6 %	B.D.H	96.8 %

2.1.2 Techniques:

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

2- ^{1}H-NMR were recorded on a Bruker AC 400 NMR spectrometer, operating at 300 MHz for H-NMR. All chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) as reference (δ=0.0 ppm); Berta laboratory for laboratory investigations, Iran.

3- UV-Vis. Spectrometer, (Jenway Genova Plus), Department of Chemistry / College of Education for Pure Sciences/ University of Kerbala.

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

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

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

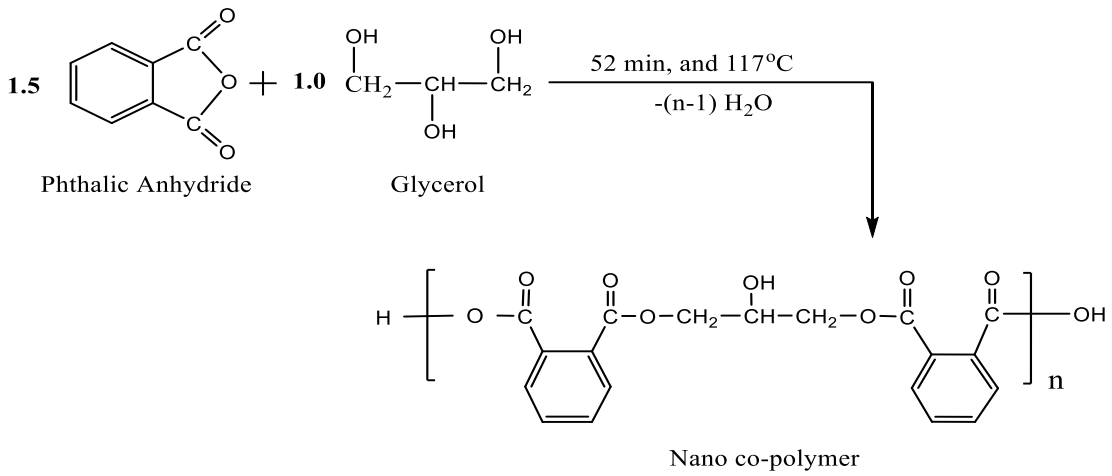
7- Transmission Electron Microscopy (TEM), Philips, CM30, Netherland, Berta laboratory for laboratory investigations, Iran.

2.2 Synthesis of co-polymer nanoparticle

The process that used to Synthesis the nano co-polymers is the esterification process; where the method of preparing is described below:

In 200 mL beaker, (1.5 mole, 222 g) of Phthalic Anhydride and (33 mL) of DMSO, were mixed together. This beaker was equipped with a thermometer.

The mixture warmed carefully with a hot plate magnetic stirrer to 70°C until clear liquor is formed. 1.0 mole, 92 g of glycerol was then added to the solution. The mixture warmed carefully to 100°C then 10 mL of p-xylene was added carefully to the reaction beaker, in the form of batch (three drops in each batch), withdrawal of water formed by the esterification process, and the beaker was gently heated. Heating was stopped after (52 min, at 117°C), until no more water came off to prepare the nano co-polymer. Then add the cold distilled water, where the suspension solution is formed. Leave the suspension solution to precipitate overnight, then filtrated and wash with distilled water and leave to dry.



Equation (2-1): Synthesis of nano co-polymer

The prepared nano co-polymer was characterized using FT-IR, ^{1}HNMR, DSC, AFM, XRD and TEM techniques.

2.3 Preparation of Polymeric Specimens:

Polymer samples have been formed with the addition of several amounts of moles of the Acrylic acid monomer (0.15, 0.25, and 0.35 moles) with a continuous stirrer to the nano co-polymer, as well as applying both Methyl Ethyl

Ketone Peroxide (MEKP) which serves as a hardener (the technique of initiator cross-linking), and Cobalt octoate 6% which acts as an accelerator. Three various copolymers were produced, each of which has a different number of moles of the acrylic acid monomer.

Following polymeric samples preparation, all were emptied in matrixes glasses for molded, wherein polymers have hardened, measuring (110 x 50 x 30) mm, and after that were cutting like a disc with sizes (thickness = 3.0 mm & diameter = 1.0 cm) based on ASTM: D-2849.

All sample discs were utilized in the study of swelling, with dry xerogel discs weighted were exactly 0.4 gram for each one.

2.4 Differential scanning calorimetry (DSC)

It is a very effective method of studying thermal analysis parameters for the nano materials. It is one of the most popular methods of thermal analysis utilized because of simplicity and speed [102]. This technique includes the process of determine heat transfer by comparing a test substance sample to a reference. While maintaining a steady rate of heating or cooling during that measurement process [103]. Basically, the calorimeter evaluates the heat or energy which is taken up or released by the sample while exposed to the defined temperature pathway, with chemical reactions and physical transformations occur, heat is generated concurrently (exothermic reaction) or consumed (endothermic reaction). This process provides a heat flux that works as a signal that is detected with the DSC device [104].

DSC is utilized to identify the polymeric materials depending on their characteristics like glass transition temperature (Tg), melting point (Tm), and crystallization temperature (Tc) [100], although it is not possible to utilize thermal techniques alone for identification, so other complementary techniques are used.

In addition, the crystallization levels are very significant to determine the characteristics of polymers. Crystallinity grades can be determined using Infrared spectroscopy, density measurements, and thermal methods. DSC is one of the easiest ways in which crystallinity levels are measured and the amorphous content levels are determined in polymers [102].

2.5 Atomic Force Microscope (AFM)

It is a very high-resolution instrument, that utilized to recognize sample morphology and quantitatively assess atomic resolution mechanical properties. In the family of (SPM) scanning probe microscopy, AFM is the highest resolution and utilized member, with a vertical resolution of 0.01 nm, a horizontal resolution of 0.1 nm. It reaches beyond the precision limits of microscopes that use electron and light wavelengths [105].

This type of microscopy plays an important role quantitative determination of the physical and chemical features of the surfaces of polymer, and under broad variety, such as measurement of intermolecular forces, etc.[106].

The principle of action of this technique is based on the utilize of a micrometer tip. Appropriately mounted on a cantilever, which is brought close to the surface of the sample. The interatomic interaction between the tip-forming atoms and the surface is assessed. As the tip scans the surface of the sample, tip vibrations occur as a result of changes in the surface topography. Therefore, recording potential interatomic differences. In specifically, by observing the cantilever deflection [107]. Where the deflection of the cantilever is identified utilizing a laser beam. The deflection of the cantilever makes the direction of the reflected laser beam change slightly. It traced by using a photo-sensitive photodiode. While maintaining a steady laser position through restraining the tip's height over the surface during scanning, hence allows the AFM to provide a topographic map in high accuracy for surface characteristics [108].

2.6 X-Ray Diffraction (XRD)

This technique is one of the most widely utilized methods for characterizing NPs. it is usually gives information concerning the crystal grain size, crystal structure, lattice parameters, and nature of the phase [109].

X-rays are high energy, wave-length electromagnetic waves among (10^{-3}, 10^{-1}) nanometers, when X-ray photons strike material, an elastic Scattering happens among photons and electrons circling the nucleus of an atom. In this instance, the scattered wave energy does not change and maintains its phase relation with the incident wave. Therefore, the X-ray photons that collide on every atom of the radiating volume are scattered in several directions as destructive or constructive radiation, resulting in a special diffraction phenomenon that can be studied in order to verify the material's crystal structure. The methods principle that depending on X-ray diffraction through periodic and angular atomic levels or energy detection of the diffracted signal [110].

W.L. Bragg has provided the geometrical understanding of the XRD (constructive interferences) phenomena through his following law:

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

where **n** is an integer, **d** is the spacing among diffraction levels, **λ** is the wavelength of the X-ray beam, and **θ** is the angle between the incident ray and the surface of the reflecting crystal lattice [111].

This law explains the relation connecting the wavelength of electromagnetic radiation produced and the lattice spacing of the crystal sample and the angle of diffraction. The intensity and position of the reflection are related to the position and identity of the atoms inside the unit cell [112].

2.7 Transmission Electron Microscopy (TEM)

The most prominent approach for the characterization of nanomaterial's in electron microscopy is transmission electron microscopy (TEM). This technique provides chemical information and pictures of nanomaterial's with a spatial resolution similar to the level of atomic dimensions. The exact particle size canbe provided by TEM, which gives details about the nanoparticles where it uses energetic electrons to give data concerning morphological, crystallographic, and structural [113].

Its working principle is, the incident beam of the electron is transmitted through a thin sample (it necessity be thin enough to transfer enough electrons to create images). This incident electrons interacting with the sample are converted into non-scattered electrons; elastic scattered electrons or scattered electrons not flexible. Then it focuses the scattered or non-scattered electrons, through electromagnetic lenses series and next projected onto a screen in order to create image or electron diffraction changing basing on the non-scattered electrons density [114].

2.8 Swelling Measurement

The swelling ratio has been determined by utilizing dried hydrogel discs. Where it was delimited through immersing the xerogel discs (0.4 g) inside 50 ml of two pH (pH=2.2, pH=8.0) and allowed them to soak at constant temperature (310 K) for 5 h and 5 days.

The hydrogel discs were extracted from water, after every one hour and 24 hours as well, and dried by using filter paper in order to eliminate surface water. Then it have been weighed .while the swelling percentage was calculated utilizing the following equation [115]

$$\text{Swelling ratio (\%)} = \frac{\text{(wt. of hydrogel-wt. xerogel)}}{\text{(wt. of hydrogel)}} \times 100 \quad \text{.....(3)}$$

The buffer solutions prepared method was [116]:

1- pH = 2.2

Mixing 50 ml from 0.2 M of KCl and 7.8 ml from 0.2 M of HCl was done to prepared this solution.

2- pH = 8.0

Mixing 100 ml from 0.025 M of Borax with 41 ml from 0.1 M of HCl was done to prepare this solution.

2.9 Preparation of standard calibration curve [117] [118]

The standard curves of glutathione were delimited with various formulation solutions with concentrations of glutathione using range (0.3–0.8%). Deionized water was used as a solvent for previous solutions. Then it has been measured the absorbance of the finding solutions at λmax equal to 224.0 nm and through deionized water which was acting as a vacuum on a Shimadzu UV-1800PC spectrophotometer. Figure (2-1) shows the linear relationship between the absorbance and the concentration of the glutathione.

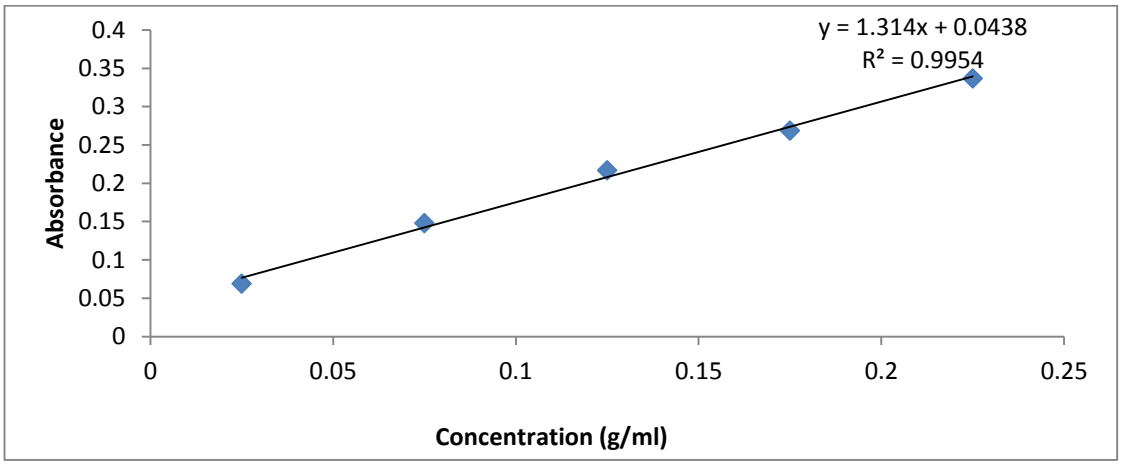


Figure (2-1): Calibration curve of Glutathione at λ max equal to 224.0 nm

2.10 Drug (glutathione) loaded [119]

The loaded process of glutathione in a buffer solution has been done through the immersed xerogel disc into each pH (pH=2.2, pH=8.0) which has special weights of the glutathione material and at a steady temperature of (310 K). It was loaded each hour, each hour subsequently, the samples were extracted from a buffer solution, dried by using filter paper in order to eliminate surface water. Determined the glutathione content percentage via applying equation (1).

Meanwhile, the concentration of glutathione in the buffer solutions was estimated utilizing an ultraviolet spectrophotometer at λmax equal to 224.0 nm. The process of measurement has been lasting till each sample repeated a consistent disc content.

2.11 Drug (glutathione) Release [120]

Following achieving disc equilibrium state through stabilizing the content of the disc in a buffer solution soaked in it. At steady temperatures (310K), the loaded hydrogel disc was submerged within the solution of buffer at pH (pH=2.2 and pH=8.0) respectively. Then it has been evaluated the quantity of glutathione release, every hour and day, by utilizing UV-spectrophotometer at λ max equal to 398.0 nm. The process of measurement has been lasting till each sample repeated a consistent disc content.

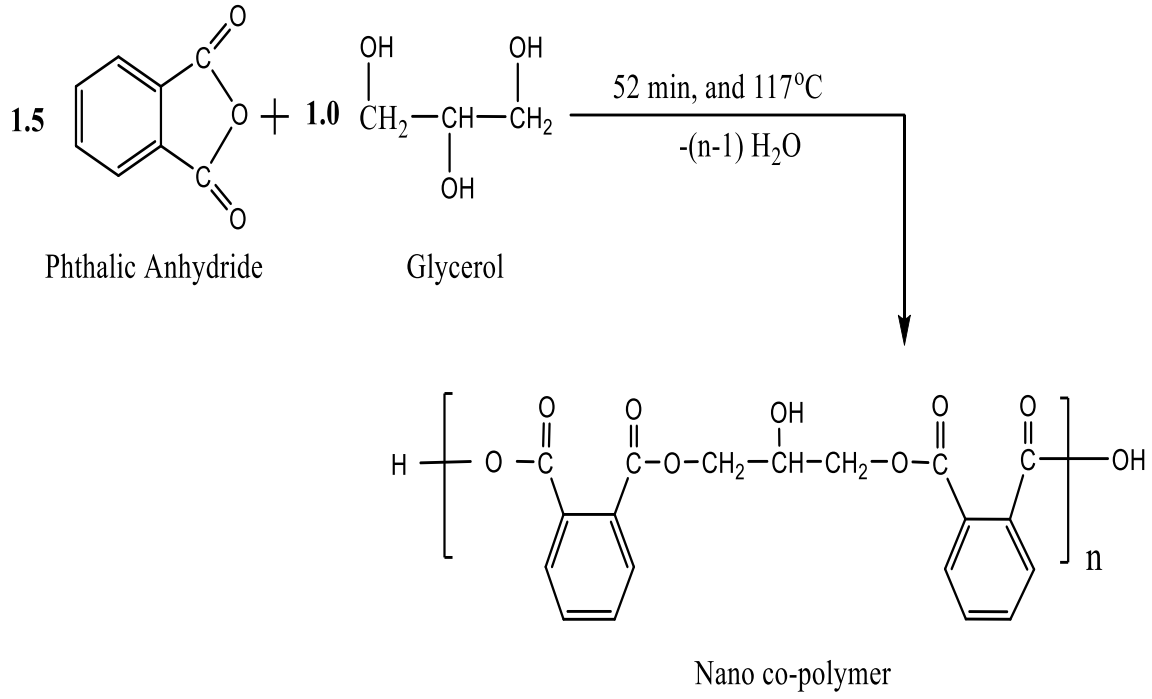
CHAPTER THREE

Results & Discussion

3. Results & Discussion

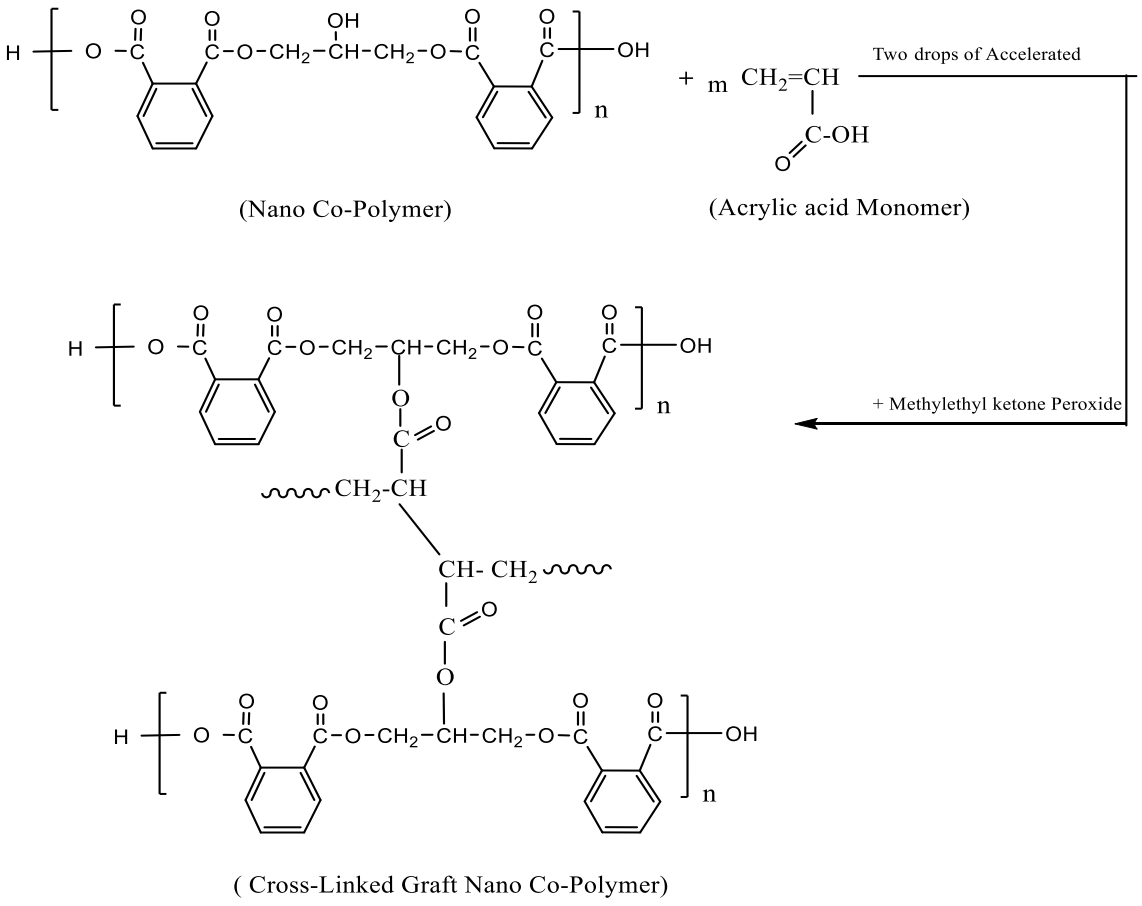
3.1 Synthesis of nano co-polymers

The co-polymer nano particle was synthesized using solubilization process by condensation polymerization from the reaction of one mole of glycerol with 1.5 mole of phthalic anhydride at constant temperature and time with releasing of water as by-product, as showed in Equations (3-1) .



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

Then three asymmetrical moles from the acrylic acid monomer (0.15, 0.25, and 0.35 moles) have been adding in order to prepare three new nano co-polymer, as is shown in the following in Equations (3-2):



Equation (3-2): Reaction of cross-linked nano co-polymer

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

Figure (3-1) is FT-IR spectrum which shows weak broadband at the frequency (3074 cm^{-1}) due to the alcoholic (OH) bond and H bond. Also, displayed a band of stretching at the frequency (3000 cm^{-1}) because of the aromatic (CH) bond, whilst display two stretching bands at (2810, 2879 cm^{-1}) which is due to bands (CH) symmetric and asymmetric, a powerful stretching band at (1670 cm^{-1}) was absorbed because of the ester (C = O), and also showed at the frequencies (1400, 1494, and 1584 cm^{-1}) stretching bands due to (C = C) aromatic, moreover, an ester peak (C-O) appears at around (1069 cm^{-1}), also at the frequency (735 & 898 cm^{-1}) shows bands that due to the aromatic ring di-substitution.

Figure (3-2) displays the spectrum of ^{1}H-NMR, which explains at 13.07 ppm a singlet signal for the specific proton in the carboxylic acid group. Furthermore, the multiplier into the area 7.56 - 7.70 ppm is due to every proton within the aromatic ring, also display at 4.29 - 4.30 ppm signals which are back to four methylene protons into the structure of copolymer, while at 4.13 ppm show multiplier because of protons of the methyl, and at 3.48 ppm singlet signal attributed to the protonation of aliphatic alcohol.

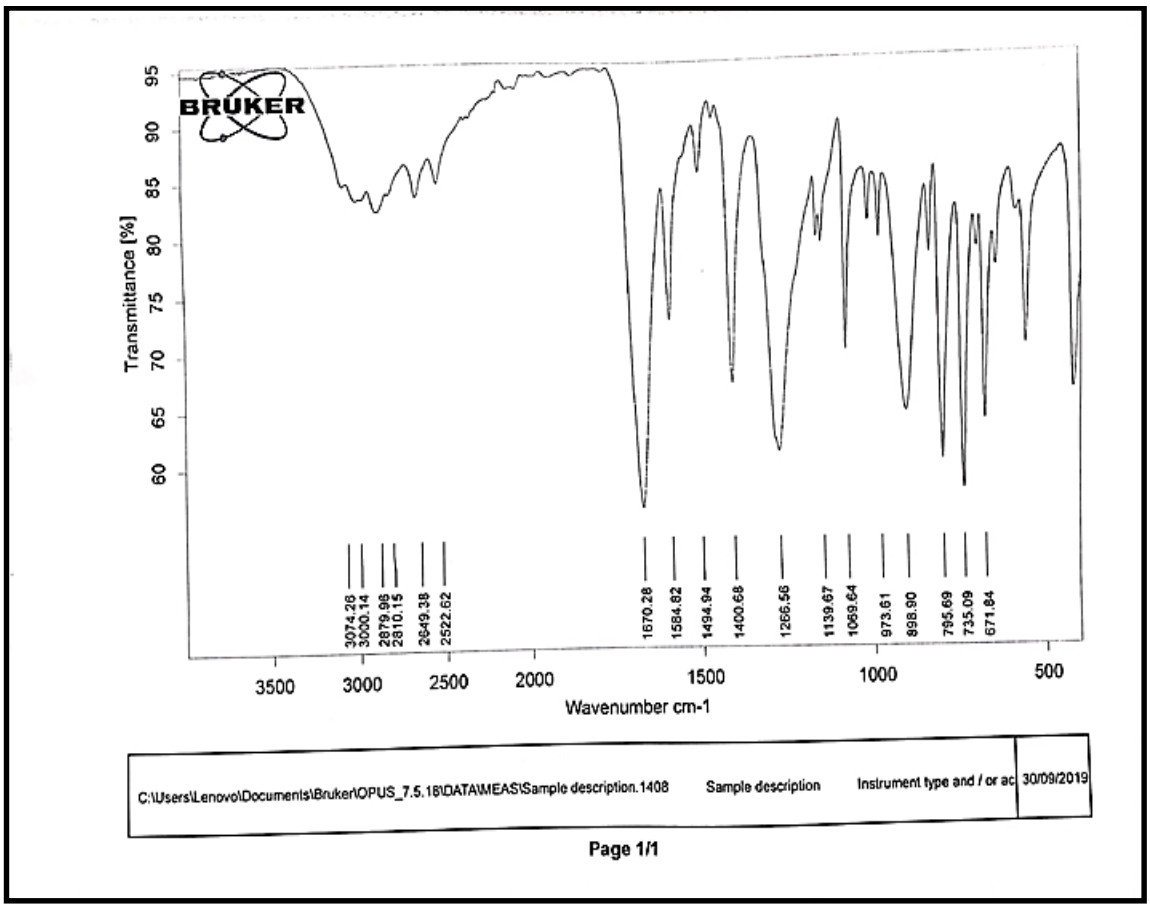


Figure (3-1): FT-IR spectrum for nano co-polymer

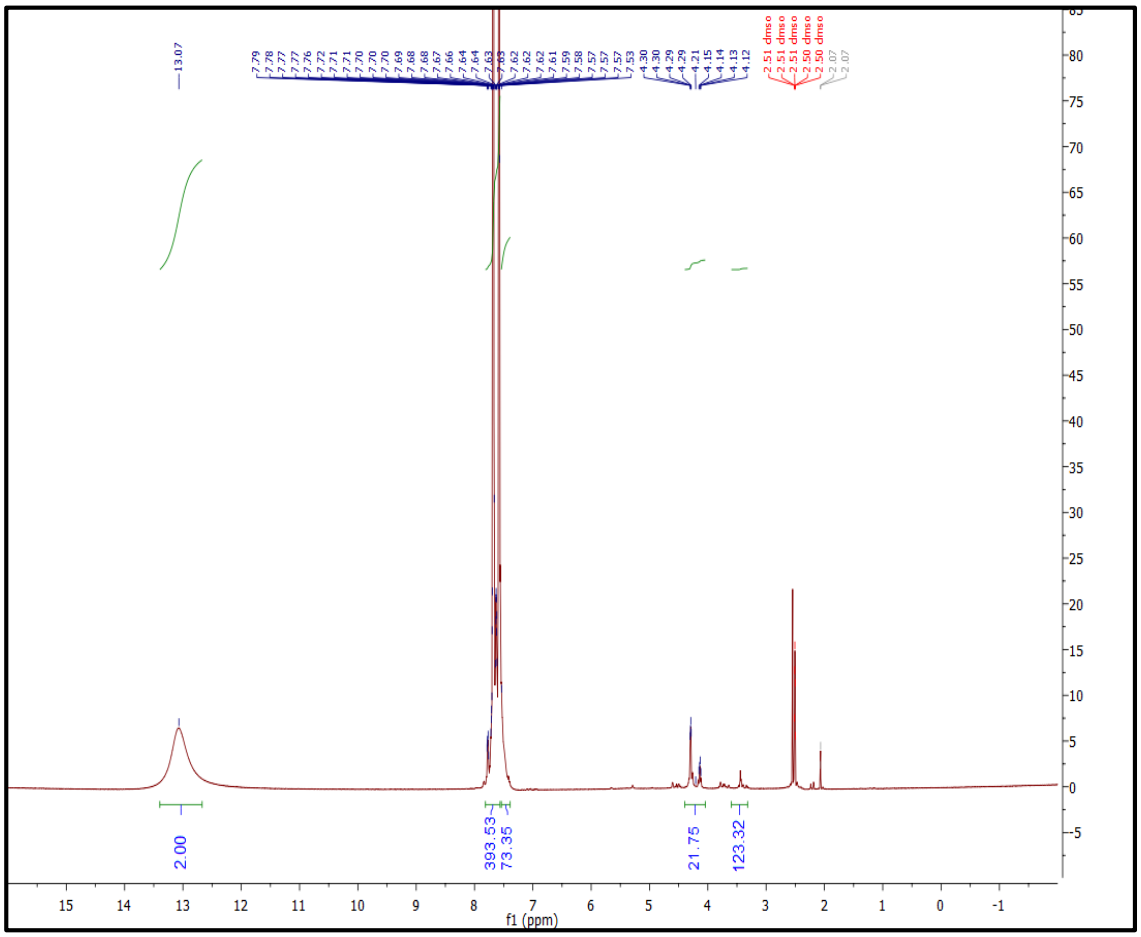


Figure (3-2): The ^{1}H-NMR spectrum of nano co-polymer

Figure (3-3a, b, c) shows the exterior surface for the copolymer nanoparticles. The copolymer surface roughness modulus was equal to 1.05 nm and the RMS was 1.27 nm, which demonstrates that the dark size for the nanoparticles takes a major role in the surface roughness, surface homogeneity, and regular crystal system. In addition, as shown in Figure (3-3 a), the average particle height was 5.48 nm. Table (3-1) showing both the overall rate and various proportions for the sizes of the common nanoparticles, findings showing that co-polymer nanoparticles had a molecular size of 85.31 nm. Figure (3-4) shows the arrangement of the various ratios for the particle sizes in the co-polymer nanoparticles.

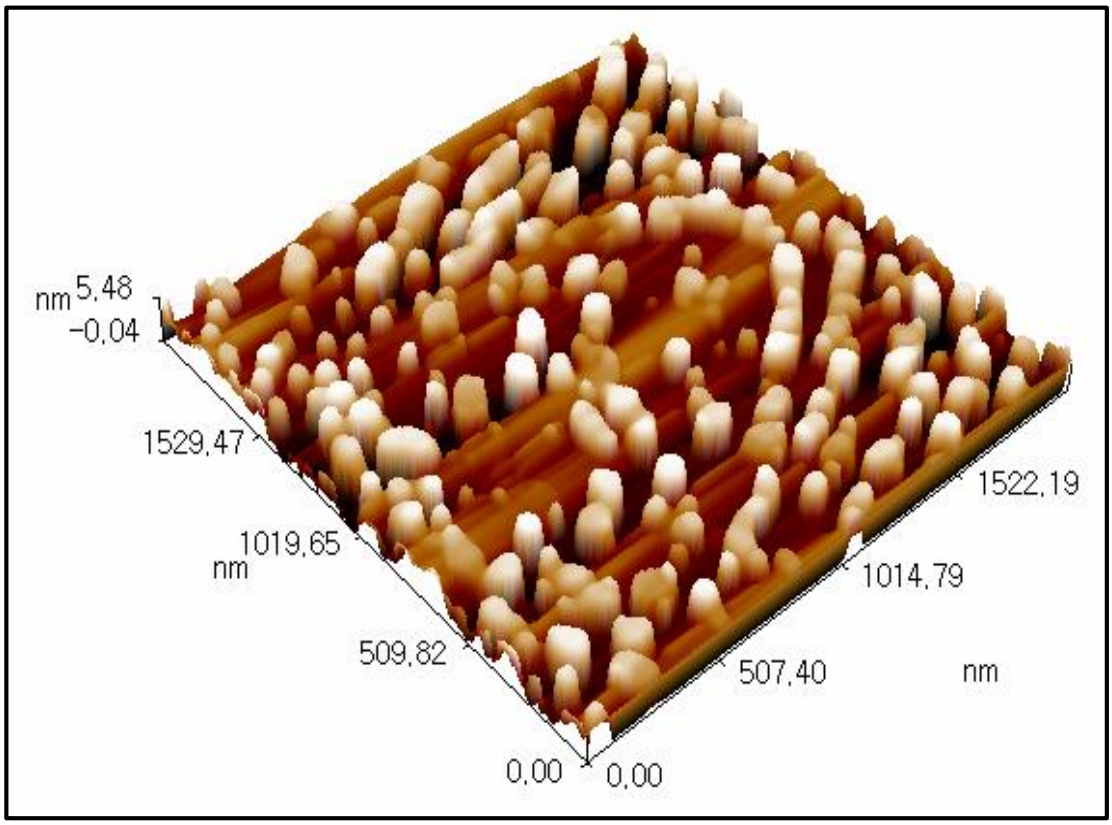


Figure (3-3 a): Atomic Force Microscope (AFM) Image of nano co-polymer display 3D Image.

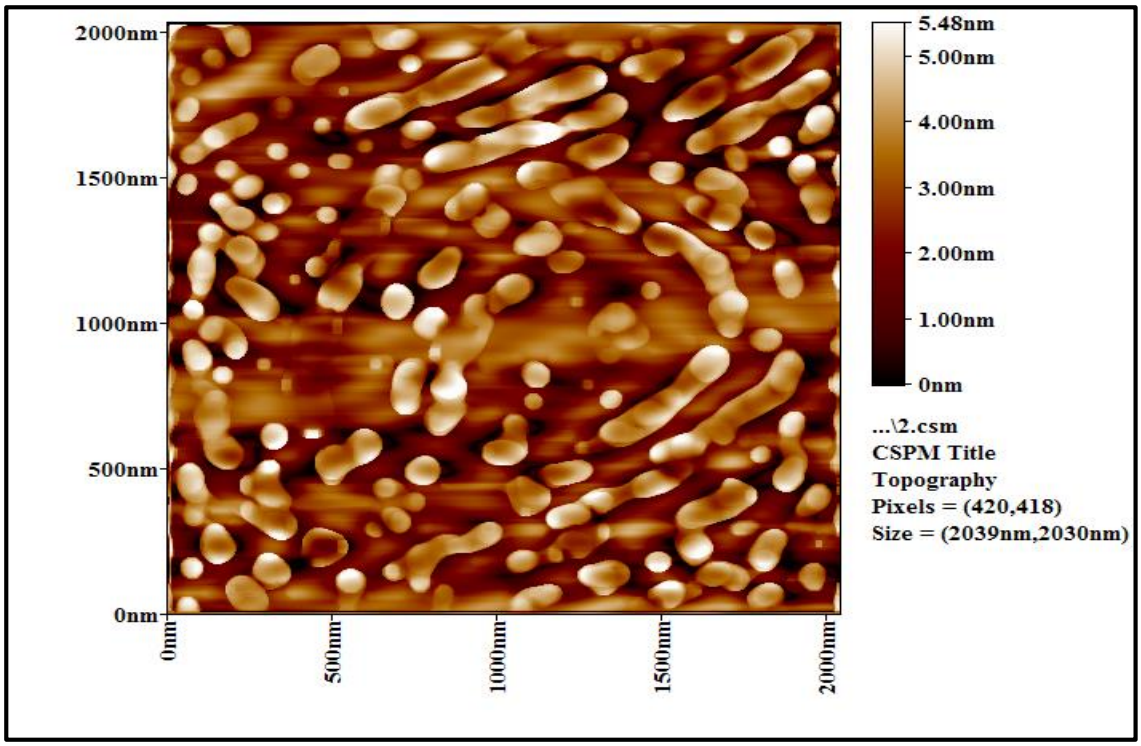


Figure (3-3 b): Atomic Force Microscope (AFM) Image of nano co-polymer display 2D Image

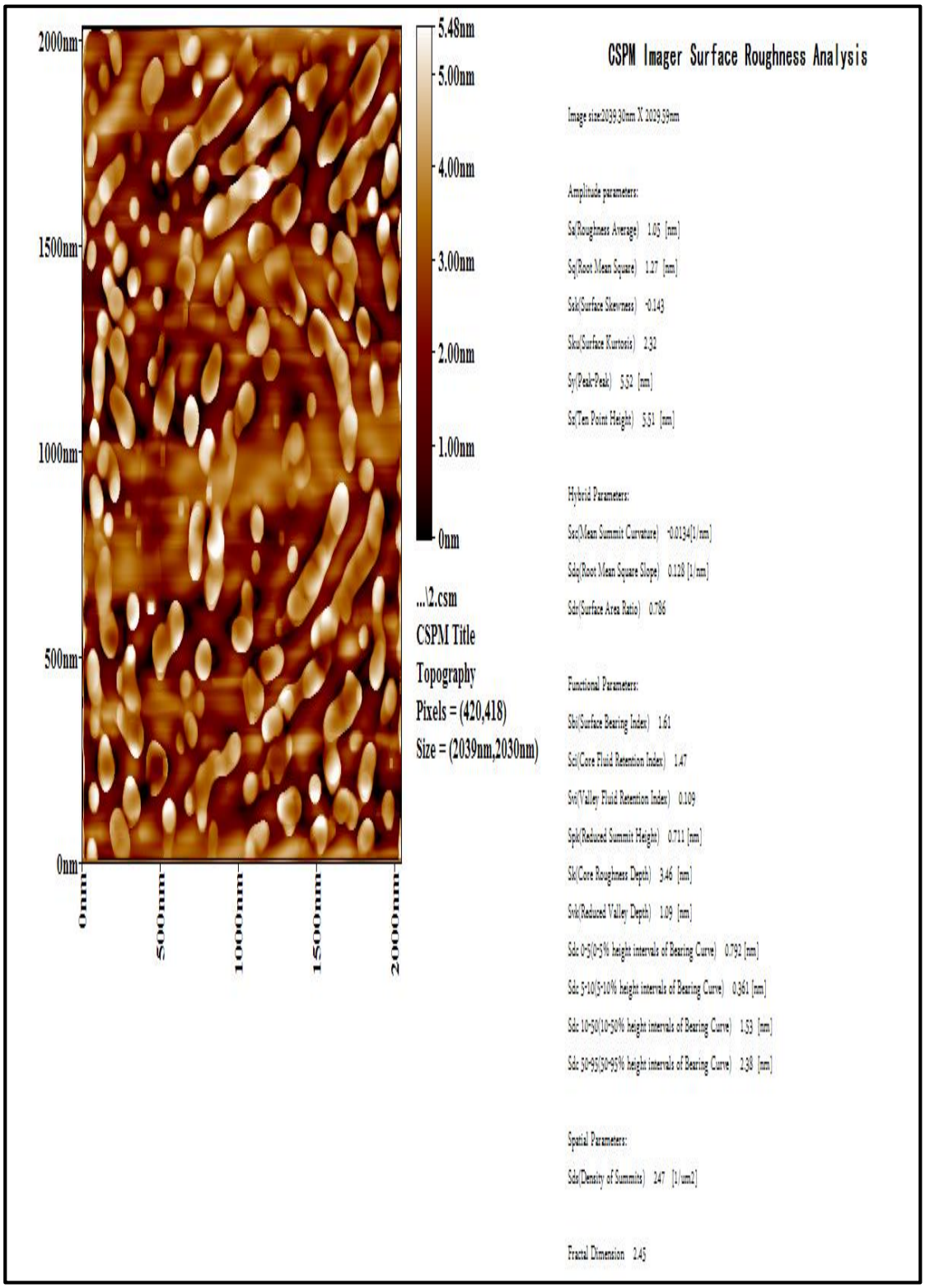


Figure (3-3 c): Atomic Force Microscope (AFM) image of nano co-polymer display 3D Image and showing every details of the particles

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

Sample: 2	**Code:** Sample Code
Line No.: lineno	**Grain No.:**151
Instrument: CSPM	**Date:** 2019-09-24

Avg. Diameter: 85.31 nm	**<=10% Diameter:60.00 nm**
<=50% Diameter: 80.00 nm	**<=90% Diameter:110.00 nm**

Diameter (nm)<	Volume (%)	Cumulation (%)	Diameter (nm)<	Volume (%)	Cumulation (%)	Diameter (nm)<	Volume (%)	Cumulation (%)
60.00	5.96	5.96	85.00	9.27	50.33	110.00	5.96	89.40
65.00	6.62	12.58	90.00	17.22	67.55	115.00	4.64	94.04
70.00	6.62	19.21	95.00	6.62	74.17	120.00	5.96	100.00
75.00	9.27	28.48	100.00	5.30	79.47			
80.00	12.58	41.06	105.00	3.97	83.44			

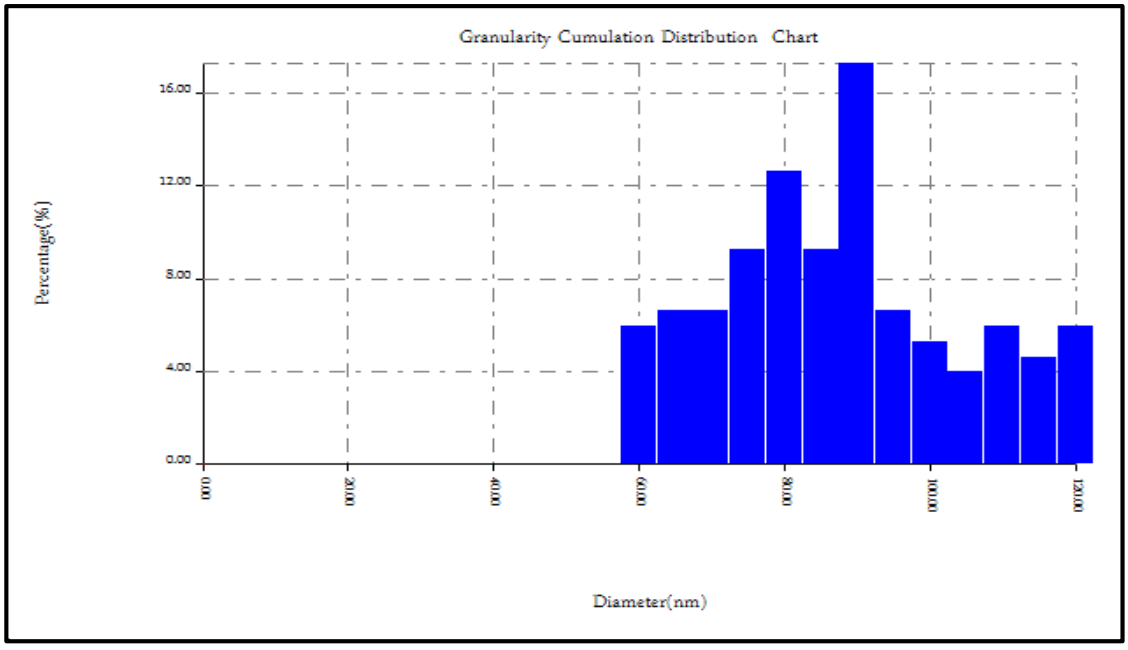


Figure (3-4): Distribution of the various proportions of particle sizes for the nano co-polymer

Figure (3-5) the x-ray diffraction (XRD) within the nanoparticles for the co-polymer peaks at 2θ values of (15.4°, 18.5°, 21.1°, 22.2°, 26.9°, and 30.5°). These previous peaks intimated that the novel copolymer was formed like a crystalline composite containing fewer carbon amorphous atoms. Through utilizing the origin program, the mean spacing among atoms (dhkl) was equal to 0.415 nm based on Bragg's law

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

The average total crystal size was equal to 85.13 nm according to the Scherrer's equation:

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

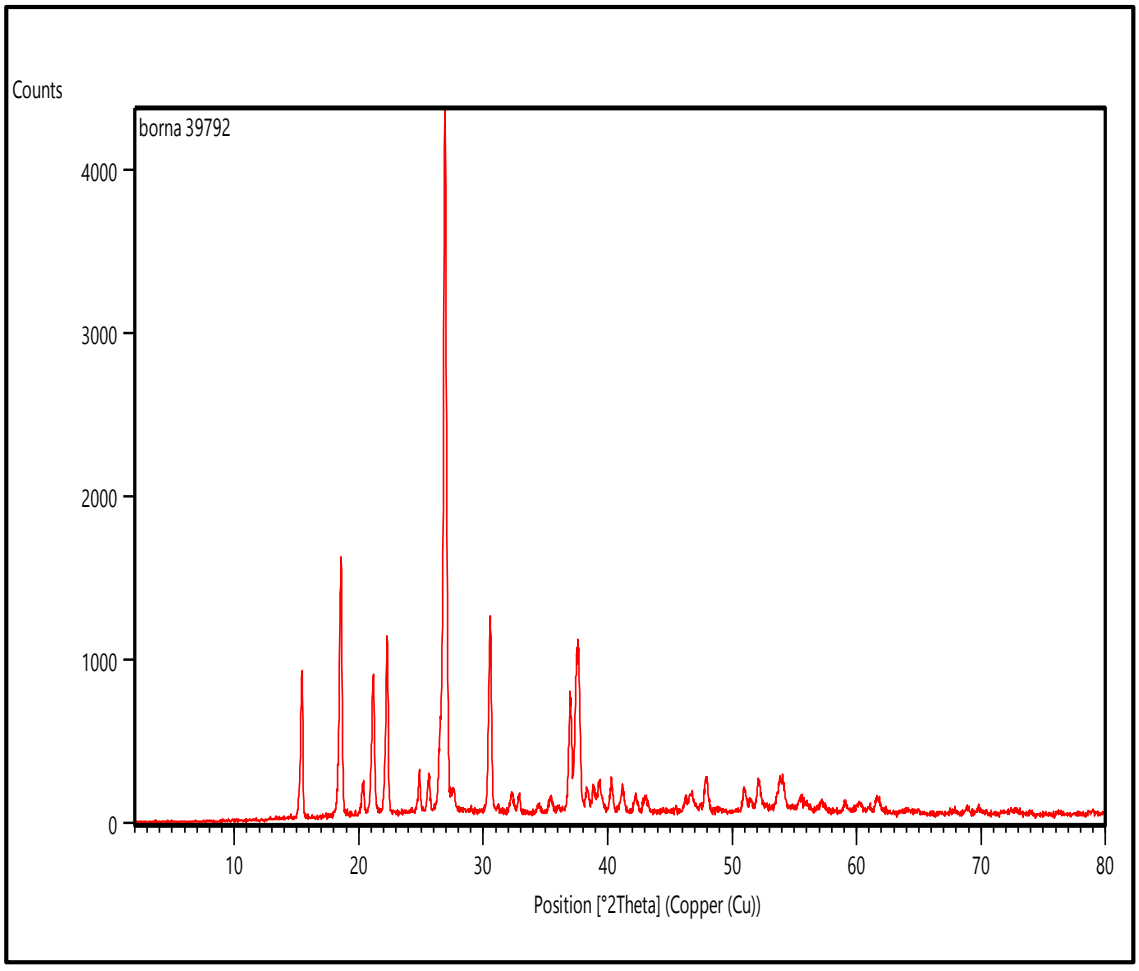


Figure (3-5): X-ray diffraction (XRD) into the co-polymer nanoparticle

Table (3-2): Ratios, crystal sizes, and d-spacing (distances among atoms) into nano co-polymer

2 θ	θ	FWHM	D nm	d_{hkl} nm	D (Av.) nm	d_{hkl} (Av.) nm
15.4185	7.70925	0.077372	103.6135	0.574224	**85.1369**	**0.4156**
18.55062	9.27531	0.096004	83.84597	0.477917		
21.15168	10.57584	0.10133	79.75537	0.419698		
22.26306	11.13153	0.088563	91.42186	0.398991		
26.93032	13.46516	0.118207	69.10626	0.330808		
30.55521	15.27761	0.099126	83.07896	0.292338		

Figure (3-6) exhibited the transmission electron microscopy (TEM) micrographs of co-polymer nanoparticles that have diverse sizes and forms ranging from normal spherical interconnected shapes, semi-spherical shapes, transparent plate shapes, and also annular disc shapes. In the nanoparticle co-polymer, the average nanoparticle size was equal to **84.84 nm**.

Table (3-3) displays the ratios of angles and diameters, and standard deviations for the nano co-polymer utilizing software image-J, moreover, Figure (3-7) depicts histogram of the size distribution of various ratios of the particle volumes for the nano co-polymer.

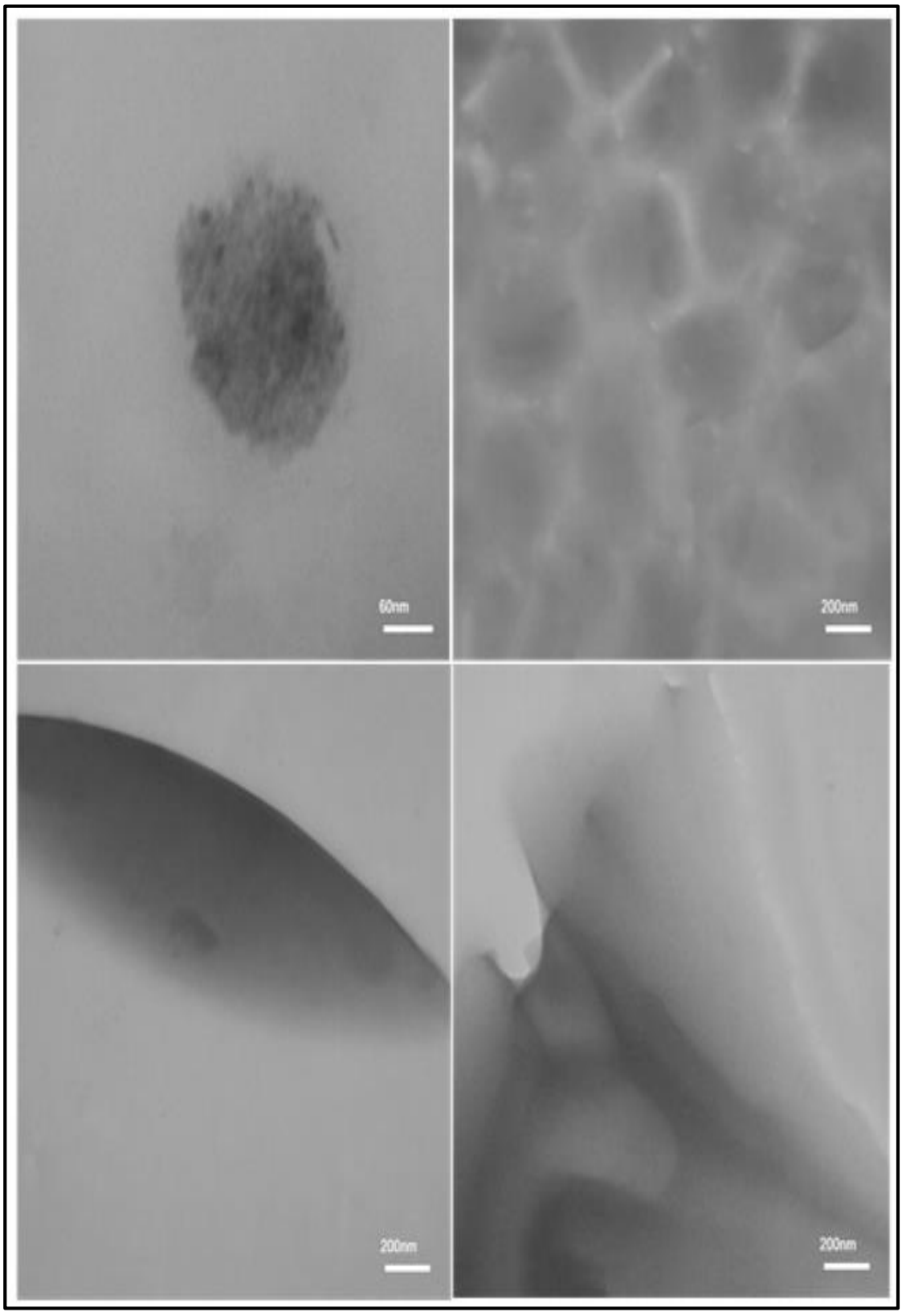


Figure (3-6): TEM micrographs of the nanoparticles co-polymer

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

Area	StdDev	Angle	Diameter nm	D(av.) nm
45.931	6.678	-104.036	47.421	**84.844**
58.792	5.776	-18.435	60.618	
63.385	7.13	-28.072	65.174	
70.419	6.292	-90	72.172	
70.734	7.488	-47.121	73.244	
81.757	11.515	-92.603	84.43	
84.513	8.473	-138.576	86.918	
84.408	8.733	63.435	87.153	
87.059	10.392	-83.66	89.433	
90.025	7.765	-65.556	92.648	
91.862	10.224	-58.241	94.688	
91.862	8.501	180	95.845	
49.211	9.778	-55.713	102.082	
109.316	7.685	-144.689	112.755	
123.095	9.302	-131.348	127.671	
127.688	11.611	-35.538	131.918	

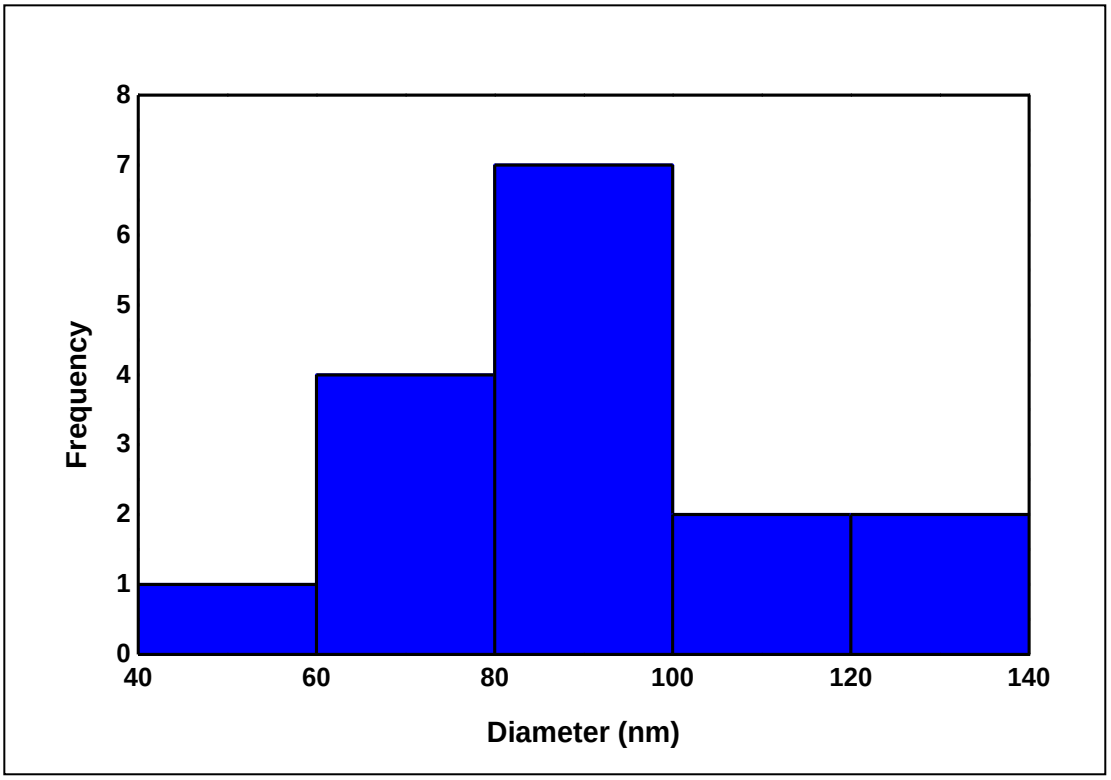


Figure (3-7): Size distribution of the nano co-polymer

Figure (3-8) shows the Differential scanning calorimetry (DSC) thermal grams of the nano co-polymer, at the peak (99.77 °C) is the first thermal transition which represents the glass transition temperature (Tg), and at the peak (243.37 °C) is the second transition which expresses the crystallization temperature (Tc), while transitions at the peaks (250.54 and 314.31 °C) are third and fourth, which are represent the melting temperature (Tm1 and Tm2) respectively for the nano co-polymer.

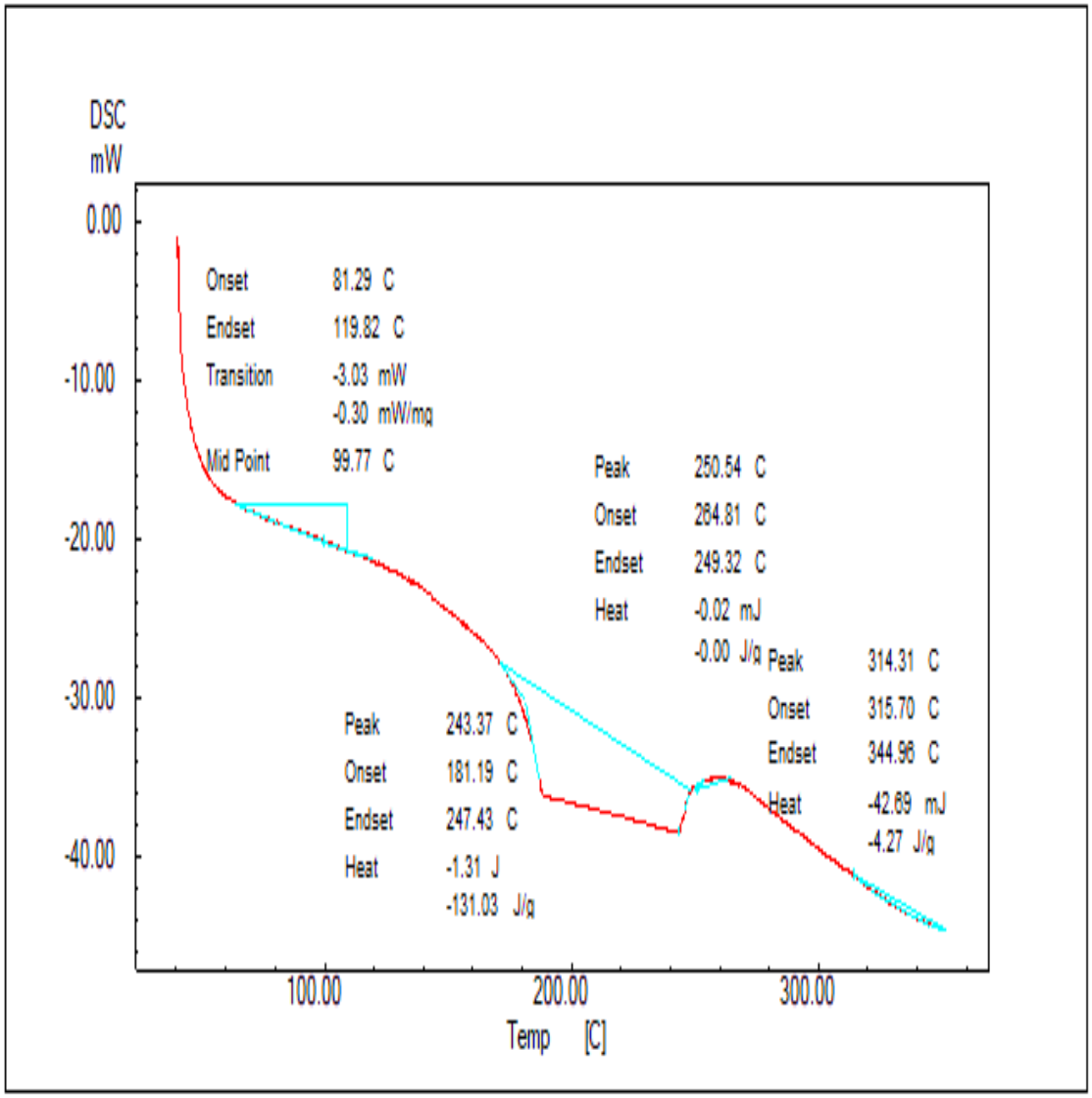


Figure (3-8): DSC thermo grams for the nano co-polymer

3.2 Loaded Protein (glutathione)

A plot of glutathione content (percent) against time demonstrated the nano-polymer curves for various three numbers of moles of acrylic acid formulations ranging from 0.15, 0.25, and 0.35 mole, versus time of loaded (hour and day). At a steady temperature (310 K) and the dry discs dimension was; thickness (3.0 mm), diameter (10.0 mm) and weight (0.4 gm) of each sample were utilized.

Tables (3-4) to (3-6) and Figures (3-9) to (3-20) show result recorder measured for pH=2.2, while tables (3-7) to (3-9) and Figures (3-21) to (3-32) at pH=8.0.

UV-spectrophotometer was used to determine the absorption of these solutions. It is conceivable to notice that the loading of the protein in the acidic medium achieves the equilibrium state faster than in the acid solution (4 hours). However, after 24 hours we observe an uptick in the loading of the protein until after (6 days) of submerged by the solution, the equilibrium status is reached.

In the basic medium, the load of the protein achieves an equilibrium state after a maximum of (5 hours). However, after (24 hours) the load progress till it achieves the equilibrium state after a maximum period of (9 days).

From all this, it has been inferred that acidic media loading is less effective than the basic medium for loading.

Table (3-4): Glutathione content (%) and solution absorption (Abs.) per hour and day, of nano polymer containing 0.15 mole of acrylic acid monomer in pH=2.2, Temp.=310K

Time (hour)	Concentration of Glutathione											
	0.3		0.4		0. 5		0.6		0.7		0.8	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	13.17	0.288	15.19	0.378	17.17	0.464	19.27	0.528	21.21	0.649	23.19	0.729
2	14.22	0.271	16.25	0.36	18.27	0.443	20.34	0.506	22.32	0.621	24.22	0.708
3	15.31	0.261	17.38	0.345	19.33	0.424	21.38	0.483	23.38	0.609	25.31	0.689
4	15.31	0.261	17.38	0.345	19.33	0.424	21.38	0.483	23.38	0.609	25.31	0.689
(Day)												
1	16.21	0.25	18.24	0.322	20.19	0.411	22.21	0.471	24.21	0.589	26.19	0.669
2	17.22	0.24	19.31	0.31	21.22	0.391	23.28	0.458	25.26	0.566	27.24	0.648
3	18.25	0.23	20.35	0.3	22.27	0.374	24.31	0.439	26.31	0.548	28.29	0.629
4	19.52	0.22	21.41	0.29	23.31	0.351	25.36	0.418	27.37	0.529	29.32	0.604
5	21.36	0.21	23.46	0.277	25.34	0.334	27.41	0.398	29.41	0.509	30.37	0.589
6	21.36	0.21	23.46	0.277	25.34	0.334	27.41	0.398	29.41	0.509	30.37	0.589

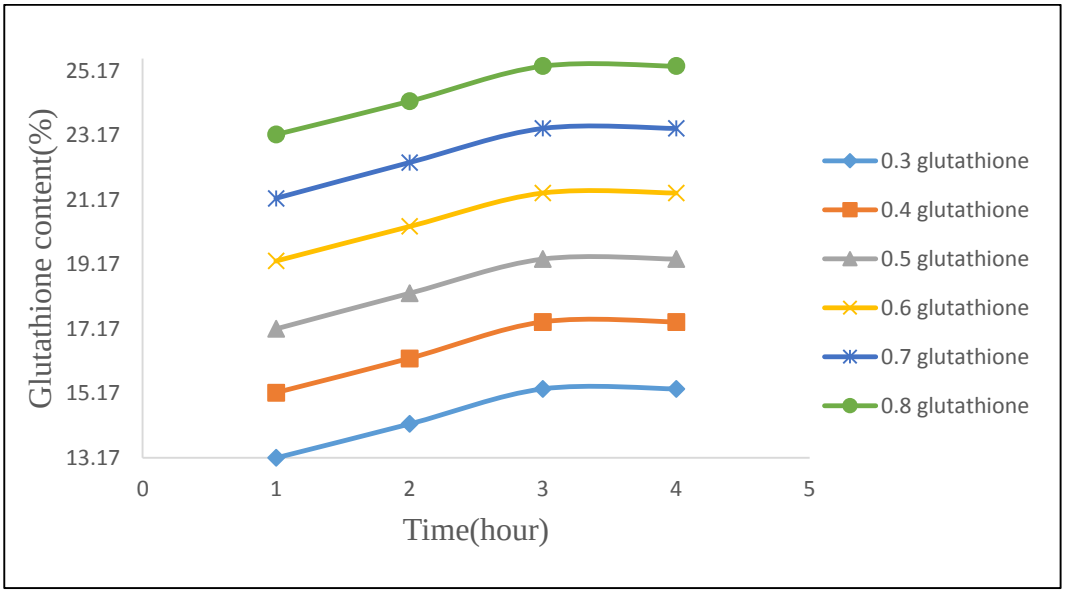


Figure (3-9): Glutathione content (%) curves and time (hour), of the hydrogel nano co-polymer containing 0.15 mole of acrylic acid monomer in pH=2.2, Temp.=310K

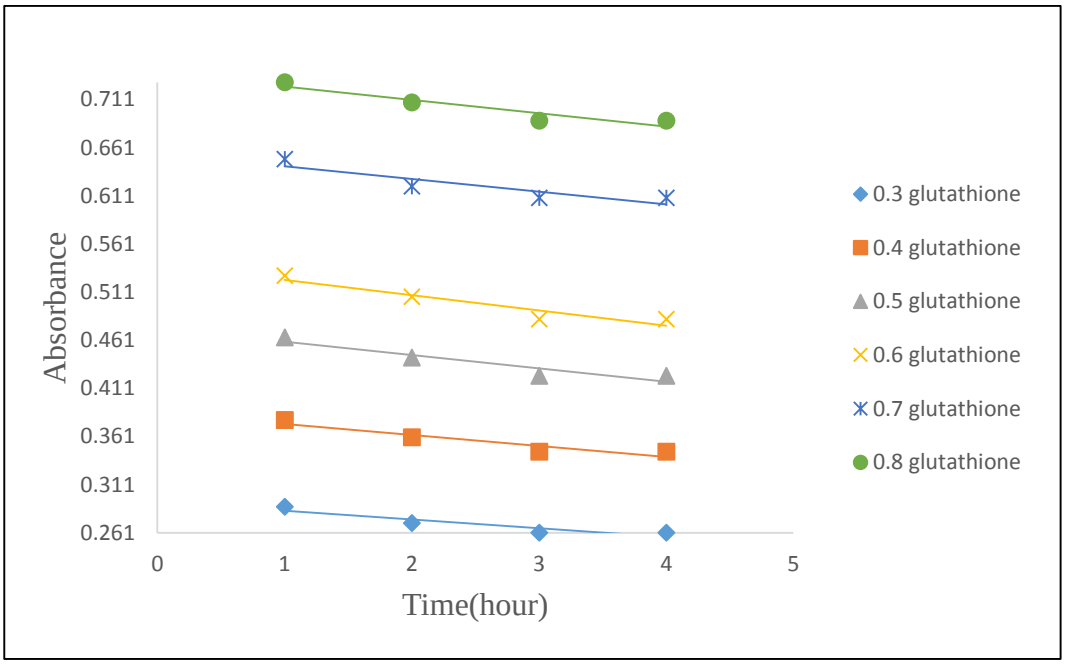


Figure (3-10): Absorbance (Abs.) curves and time (hour), of the hydrogel nano co-polymer containing 0.15 mole of acrylic acid monomer in pH=2.2, Temp.=310K

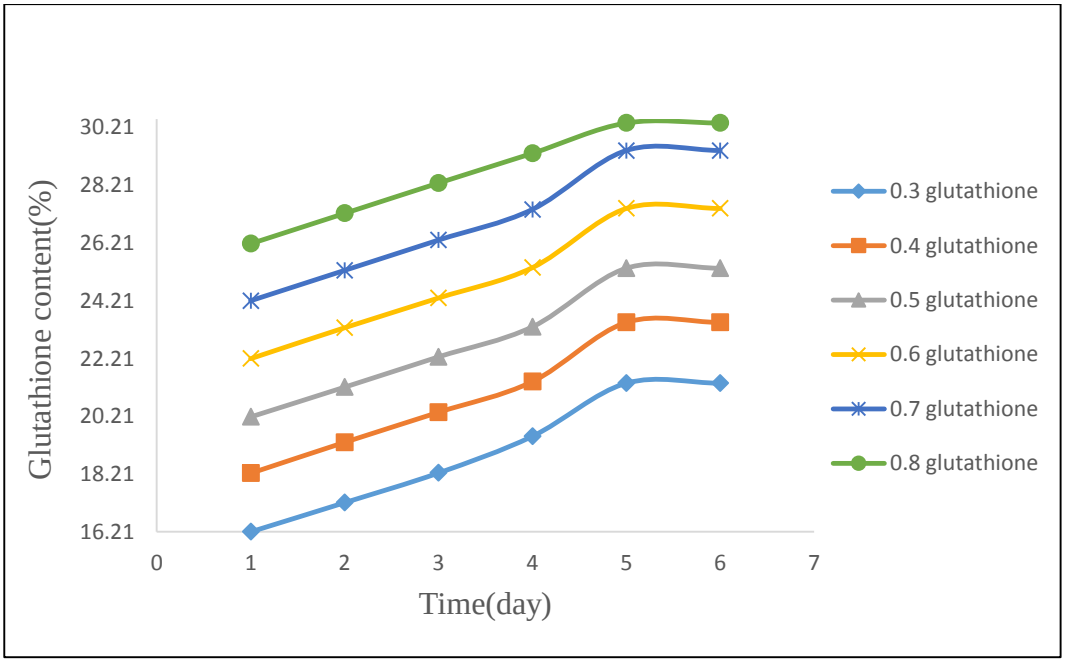


Figure (3-11): Glutathione content (%) curves and time (day), of the hydrogel nano co-polymer containing0.15 mole of acrylic acid monomer in pH=2.2, Temp.=310K

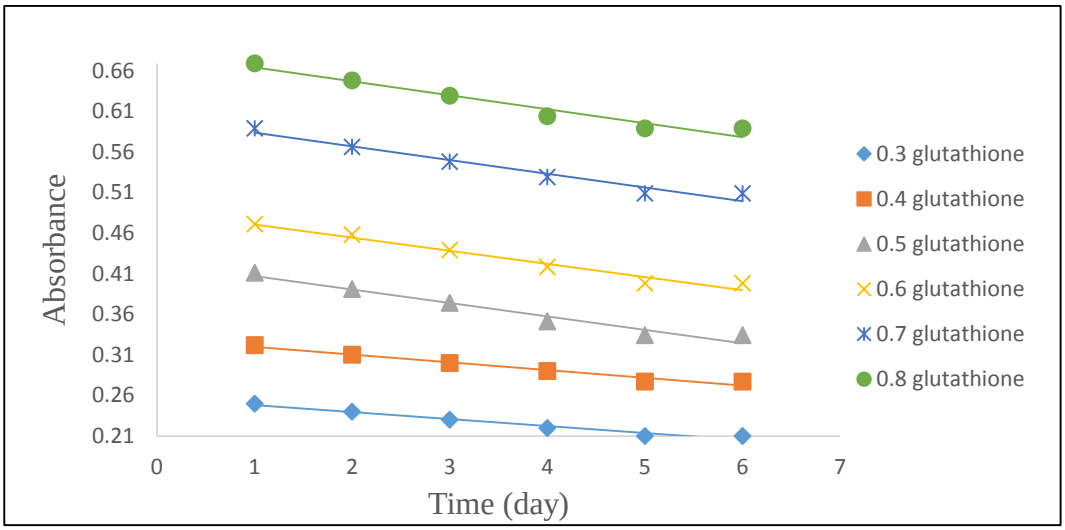


Figure (3-12): Absorbance (Abs.) curves and time (day), of the hydrogel nano co-polymer containing 0.15 mole of acrylic acid monomer in pH=2.2, Temp.=310K

Table (3-5): Glutathione content (%) and solution absorption (Abs.) per hour and day, of nano polymer containing 0.25 mole of acrylic acid monomer in pH=2.2, Temp.=310K

Time (hour)	Concentration of Glutathione											
	0.3		0.4		0. 5		0.6		0.7		0.8	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	14.17	0.279	16.19	0.366	18.21	0.448	20.31	0.516	22.29	0.633	24.31	0.713
2	15.22	0.261	17.22	0.351	19.28	0.434	21.38	0.498	23.34	0.613	25.39	0.696
3	16.31	0.25	18.31	0.334	20.32	0.415	22.4	0.472	24.41	0.598	26.43	0.673
4	16.31	0.25	18.31	0.334	20.32	0.415	22.4	0.472	24.41	0.598	26.43	0.673
(Day)												
1	17.19	0.241	19.21	0.318	21.19	0.401	23.18	0.461	25.19	0.572	27.21	0.651
2	18.25	0.231	20.29	0.301	22.29	0.381	24.22	0.448	26.28	0.553	28.29	0.635
3	19.31	0.22	21.32	0.291	23.32	0.362	25.28	0.424	27.32	0.532	29.32	0.614
4	20.38	0.21	22.34	0.28	24.41	0.341	26.31	0.402	28.38	0.513	30.37	0.595
5	22.41	0.2	24.41	0.262	26.44	0.322	28.38	0.382	30.41	0.494	32.41	0.574
6	22.41	0.2	24.41	0.262	26.44	0.322	28.38	0.382	30.41	0.494	32.41	0.574

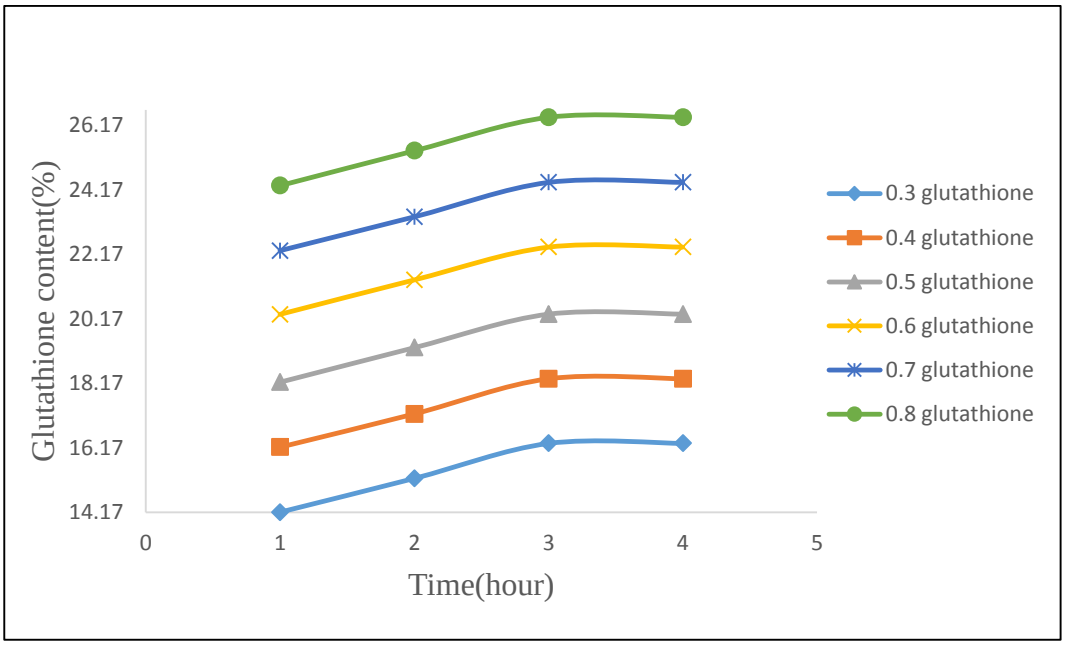


Figure (3-13): Glutathione content (%) curves and time (hour), the hydrogel nano co-polymer containing 0.25 mole of acrylic acid monomer in pH=2.2, Temp.=310K

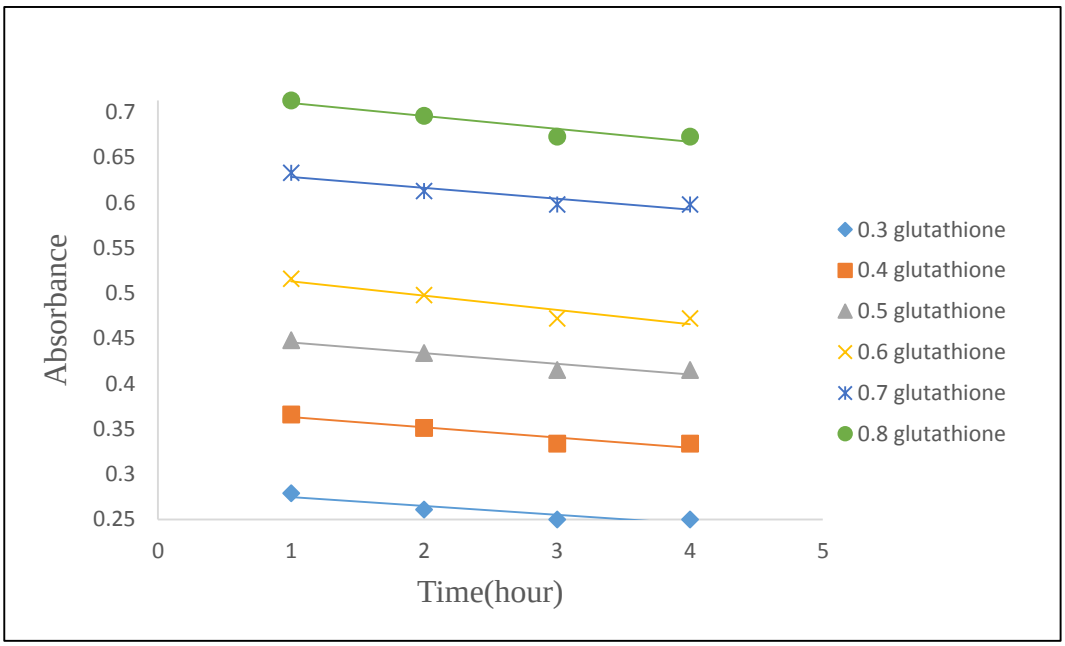


Figure (3-14): Absorbance (Abs.) curves and time (hour), of the hydrogel nano co-polymer containing 0.25 mole of acrylic acid monomer in pH=2.2, Temp.=310K

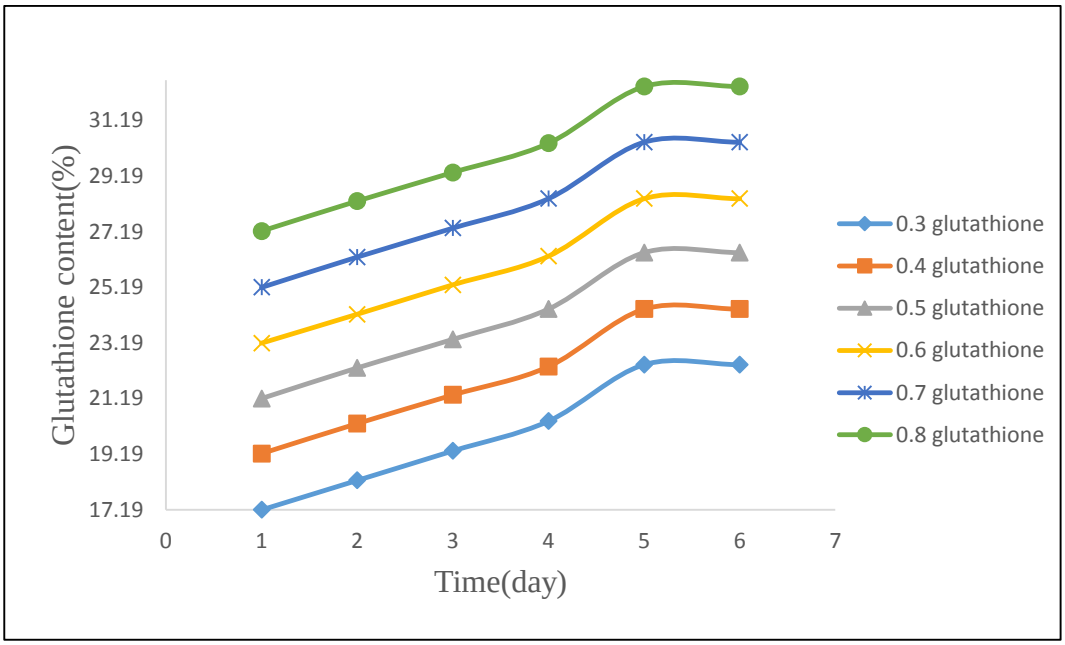


Figure (3-15): Glutathione content (%) curves and time (day), of the hydrogel nano co-polymer containing0.25 mole of acrylic acid monomer in pH=2.2, Temp.=310K

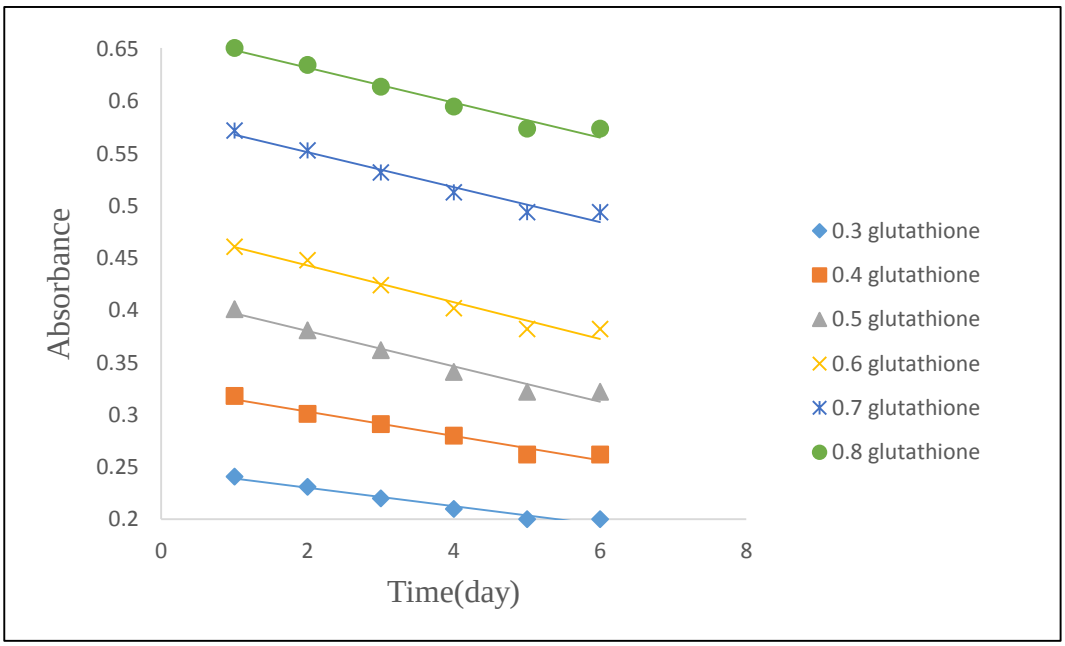


Figure (3-16): Absorbance (Abs.) curves and time (day), of the hydrogel nano co-polymer containing 0.25 mole of acrylic acid monomer in pH=2.2, Temp.=310K

Table (3-6): Glutathione content (%) and solution absorption (Abs.) per hour and day, of nano polymer containing 0.35 mole of acrylic acid monomer at pH=2.2, Temp.=310K

Time (hour)	Concentration of Glutathione											
	0.3		0.4		0. 5		0.6		0.7		0.8	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	16.21	0.262	18.24	0.358	20.19	0.441	22.21	0.501	24.29	0.621	26.31	0.702
2	17.24	0.25	19.32	0.341	21.25	0.422	23.29	0.483	25.32	0.603	27.39	0.684
3	18.31	0.241	20.41	0.325	22.34	0.403	24.33	0.461	26.39	0.582	28.42	0.665
4	18.31	0.241	20.41	0.325	22.34	0.403	24.33	0.461	26.39	0.582	28.42	0.665
(Day)												
1	19.18	0.231	21.19	0.301	23.21	0.382	25.23	0.441	27.21	0.562	29.19	0.649
2	20.22	0.221	22.28	0.291	24.24	0.361	26.29	0.424	28.28	0.542	30.29	0.622
3	21.29	0.21	23.31	0.281	25.32	0.344	27.34	0.403	29.32	0.524	31.31	0.602
4	22.31	0.2	24.38	0.271	26.38	0.325	28.41	0.385	30.37	0.503	32.35	0.582
5	24.36	0.19	26.41	0.251	28.41	0.306	30.46	0.365	32.41	0.484	34.41	0.561
6	24.36	0.19	26.41	0.251	28.41	0.306	30.46	0.365	32.41	0.484	34.41	0.561

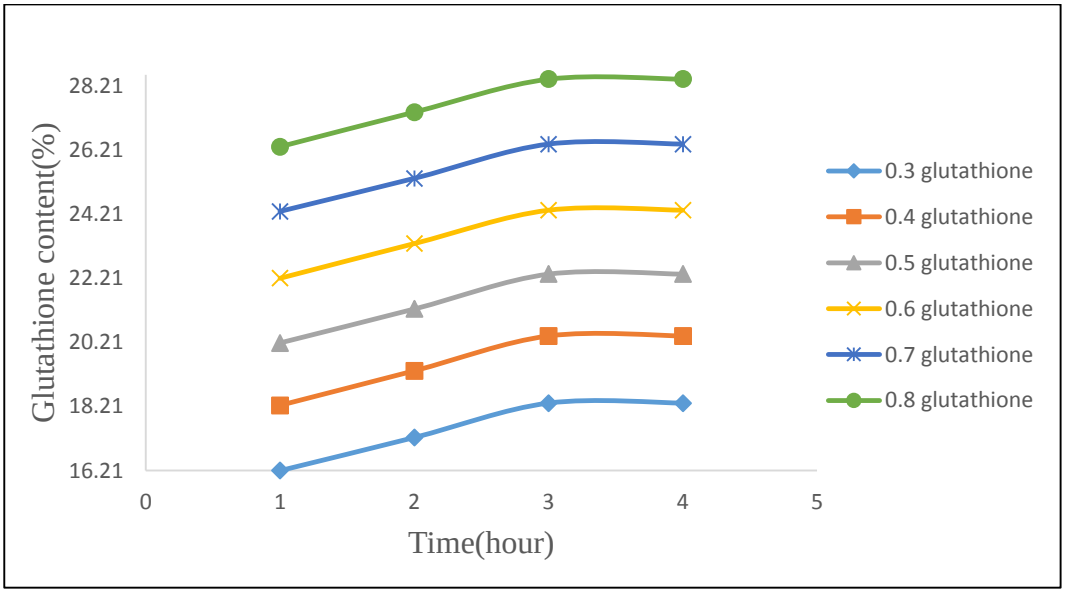


Figure (3-17): Glutathione content (%) curves and time (hour), of the hydrogel nano co-polymer containing0.35 mole of acrylic acid monomer in pH=2.2, Temp.=310K

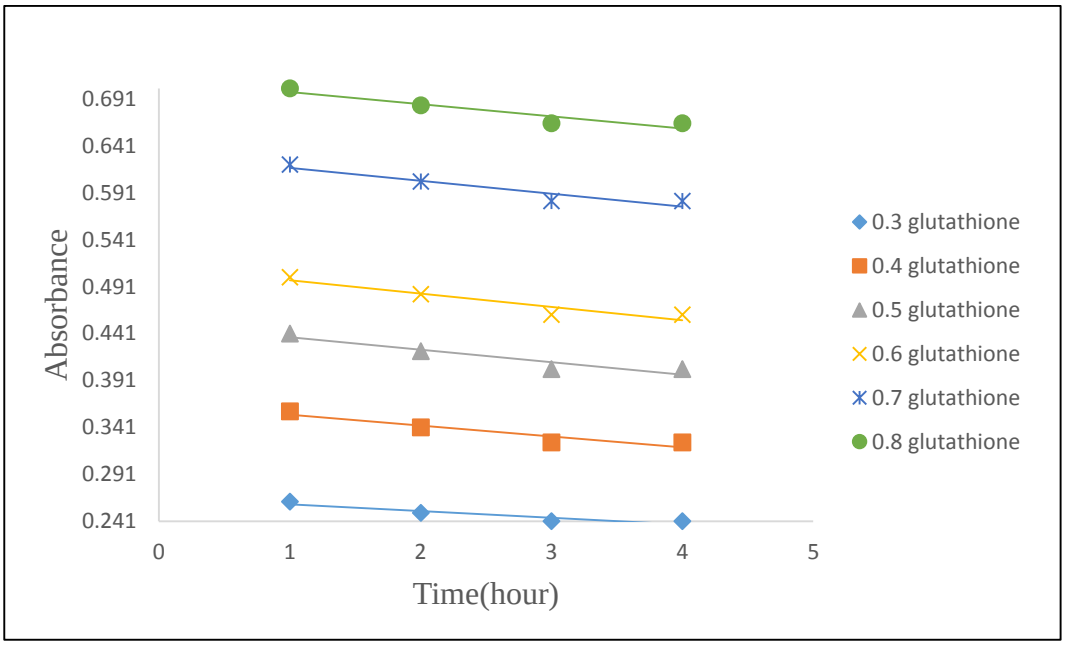


Figure (3-18): Absorbance (Abs.) curves and time (hour), of the hydrogel nano co-polymer containing 0.35 mole of acrylic acid monomer in pH=2.2, Temp.=310K

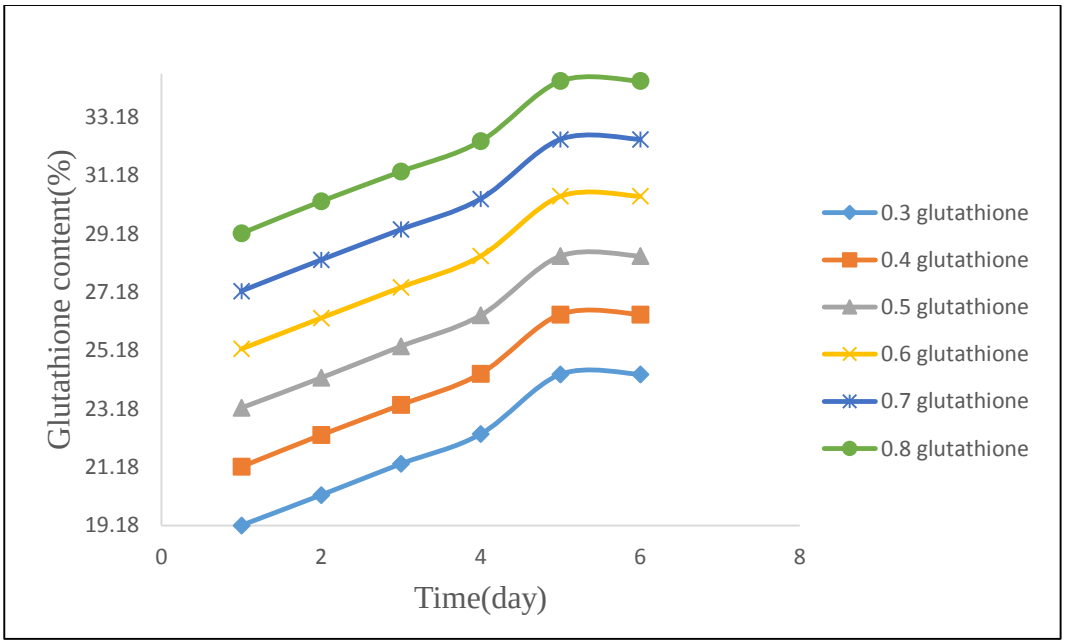


Figure (3-19): Glutathione content (%) curves and time (day), of the hydrogel nano co-polymer containing0.35 mole of acrylic acid monomer in pH=2.2, Temp.=310K

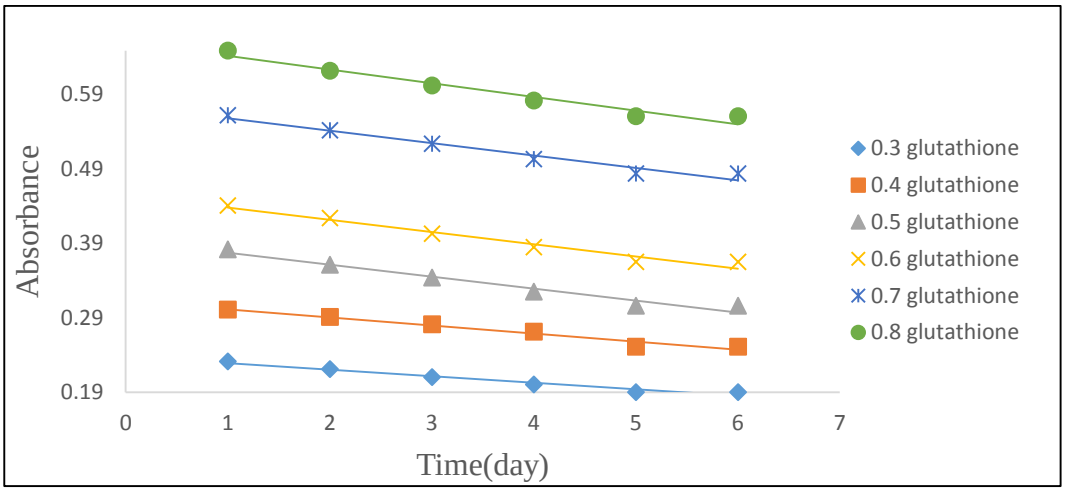


Figure (3-20): Absorbance (Abs.) curves and time (day), of the hydrogel nano co-polymer containing 0.35 mole of acrylic acid monomer in pH=2.2, Temp.=310K

Table (3-7): Glutathione content (%) and solution absorption (Abs.) per hour and day, of nano polymer containing 0.15 mole of acrylic acid monomer in pH=8, Temp.=310K

Time (hour)	Concentration of Glutathione											
	0.3		0.4		0. 5		0.6		0.7		0.8	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	18.21	0.229	20.17	0.319	22.29	0.408	24.21	0.469	26.31	0.589	28.29	0.669
2	19.29	0.21	21.29	0.301	23.33	0.389	25.34	0.448	27.39	0.569	29.32	0.648
3	20.31	0.2	22.34	0.292	24.41	0.369	26.41	0.429	28.45	0.548	30.44	0.629
4	21.39	0.193	23.41	0.27	25.49	0.348	27.48	0.408	29.51	0.528	31.51	0.608
5	21.39	0.193	23.41	0.27	25.49	0.348	27.48	0.408	29.51	0.528	31.51	0.608
(Day)												
1	22.21	0.18	24.19	0.251	26.25	0.32	28.21	0.389	30.25	0.501	32.29	0.582
2	23.29	0.171	25.25	0.241	27.31	0.308	29.29	0.369	31.31	0.486	33.36	0.561
3	24.31	0.161	26.31	0.23	28.39	0.284	30.32	0.345	32.39	0.461	34.44	0.542
4	25.36	0.15	27.37	0.22	29.43	0.261	31.41	0.324	33.44	0.443	35.56	0.524
5	26.41	0.14	28.41	0.21	30.51	0.248	32.52	0.305	34.51	0.424	36.63	0.503
6	27.48	0.13	29.46	0.2	31.58	0.229	33.59	0.286	35.59	0.408	37.69	0.484
7	29.51	0.121	31.5	0.183	33.61	0.208	35.66	0.263	37.62	0.384	39.75	0.466
8	31.59	0.11	33.59	0.162	35.69	0.187	37.75	0.249	39.71	0.366	41.81	0.448
9	31.59	0.11	33.59	0.162	35.69	0.187	37.75	0.249	39.71	0.366	41.81	0.448

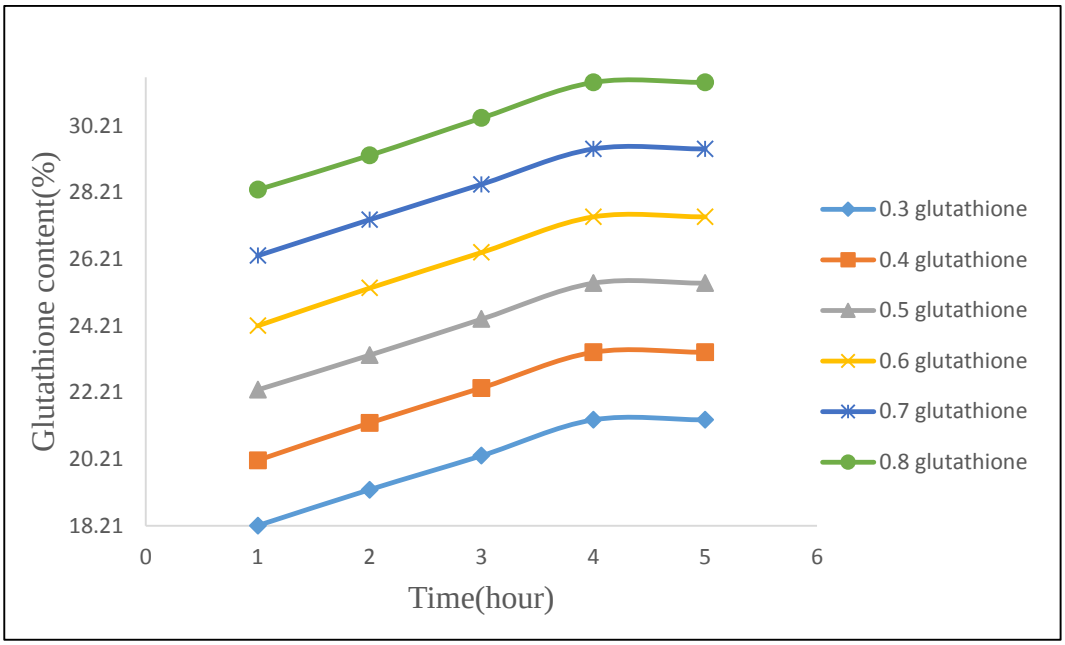


Figure (3-21): Glutathione content (%) curves and time (hour), of the hydrogel nano co-polymer containing0.15 mole of acrylic acid monomer in pH=8.0, Temp.=310K

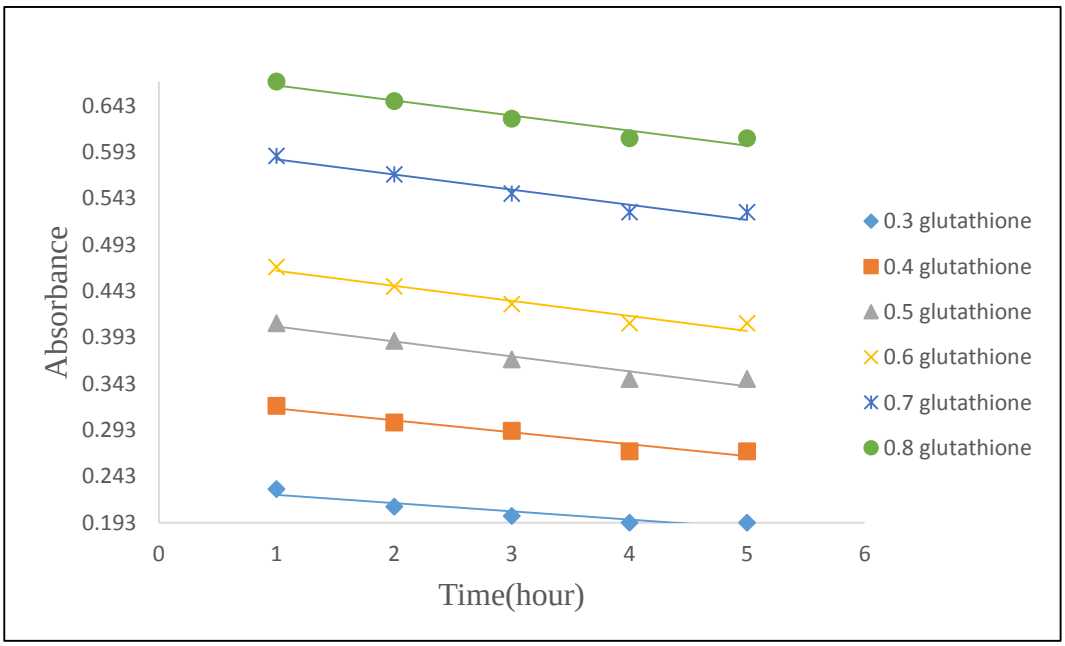


Figure (3-22): Absorbance (Abs.) curves and time (hour), of the hydrogel nano co-polymer containing 0.15 mole of acrylic acid monomer in pH=8.0, Temp.=310K

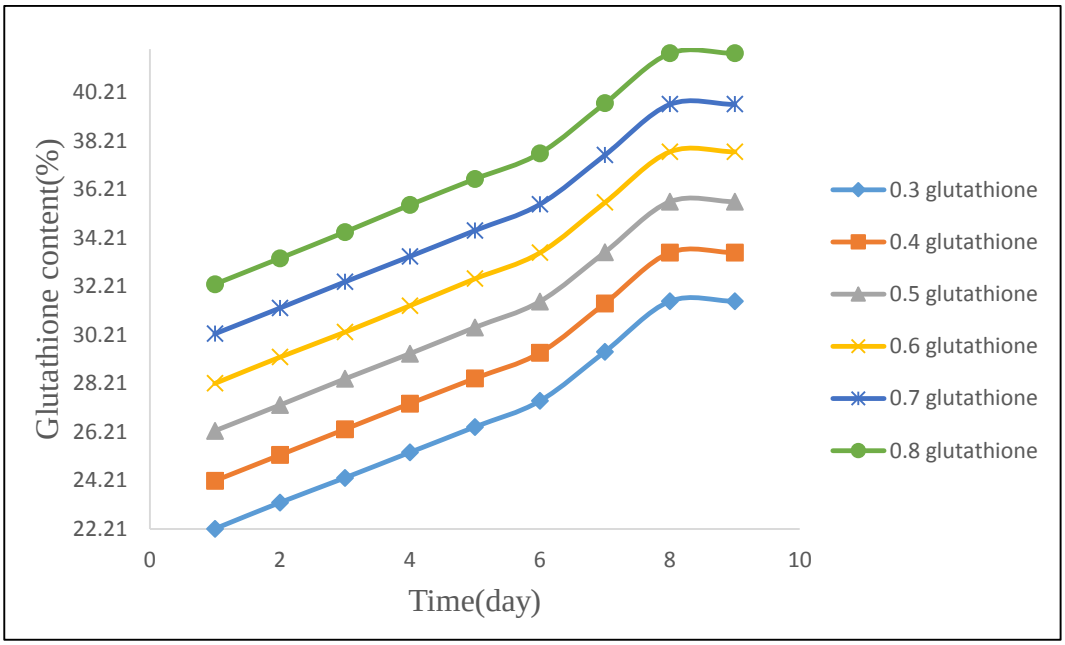


Figure (3-23): Glutathione content (%) curves and time (day), of the hydrogel nano co-polymer containing0.15 mole of acrylic acid monomer in pH=8.0, Temp.=310K

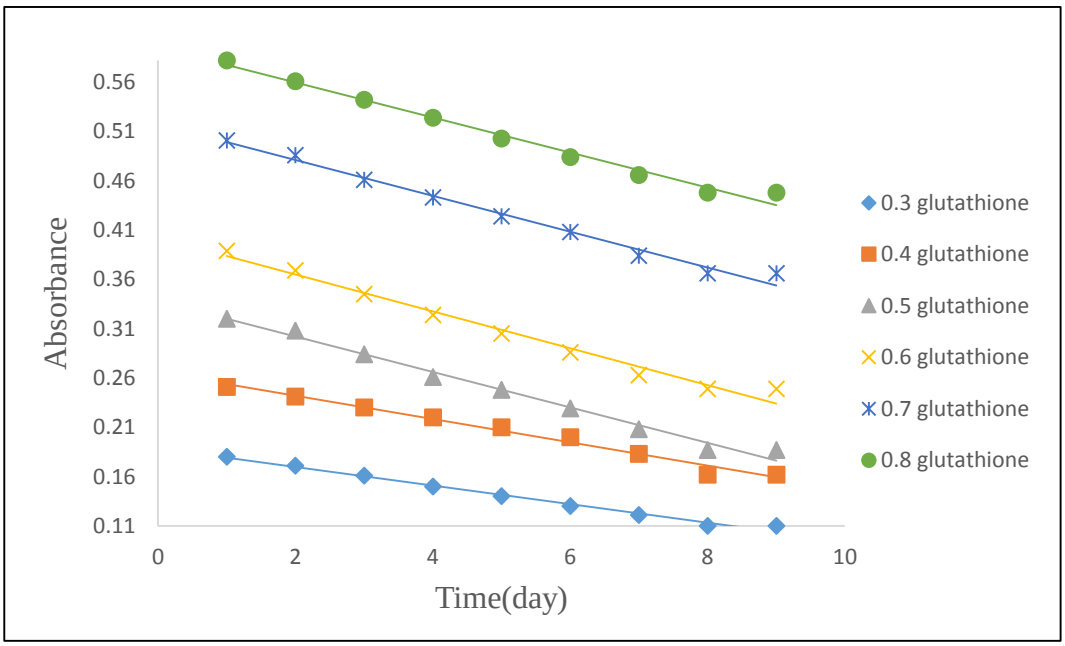


Figure (3-24): Absorbance (Abs.) curves and time (day), of the hydrogel nano co-polymer containing 0.15 mole of acrylic acid monomer in pH=2.2, Temp.=310K

Table (3-8): Glutathione content (%) and solution absorption (Abs.) per hour and day, of nano polymer containing 0.25 mole of acrylic acid monomer in pH=8, Temp.=310K

Time (hour)	Concentration of Glutathione											
	0.3		0.4		0. 5		0.6		0.7		0.8	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	20.21	0.211	22.19	0.302	24.29	0.392	26.18	0.452	28.18	0.573	30.21	0.651
2	21.18	0.2	23.22	0.29	25.31	0.373	27.22	0.432	29.25	0.553	31.29	0.636
3	22.24	0.192	24.25	0.281	26.34	0.352	28.29	0.414	30.34	0.532	32.32	0.615
4	23.29	0.18	25.31	0.261	27.38	0.333	29.32	0.392	31.39	0.516	33.39	0.595
5	23.29	0.18	25.31	0.261	27.38	0.333	29.32	0.392	31.39	0.516	33.39	0.595
(Day)												
1	24.19	0.17	26.18	0.241	28.21	0.311	30.19	0.372	32.21	0.494	34.19	0.577
2	25.24	0.161	27.25	0.23	29.25	0.295	31.22	0.355	33.26	0.474	35.25	0.553
3	26.31	0.15	28.32	0.221	30.31	0.273	32.26	0.333	34.31	0.452	36.32	0.538
4	27.39	0.14	29.36	0.21	31.37	0.255	33.32	0.316	35.36	0.437	37.39	0.514
5	28.4	0.13	30.42	0.201	32.42	0.236	34.37	0.294	36.41	0.415	38.42	0.493
6	29.46	0.12	31.44	0.192	33.48	0.216	35.42	0.276	37.49	0.394	39.48	0.473
7	31.51	0.111	33.5	0.179	35.52	0.199	37.48	0.254	39.52	0.372	41.53	0.455
8	33.56	0.1	35.55	0.155	37.56	0.177	39.51	0.235	41.53	0.354	43.59	0.435
9	33.56	0.1	35.55	0.155	37.56	0.177	39.51	0.235	41.53	0.354	43.59	0.435

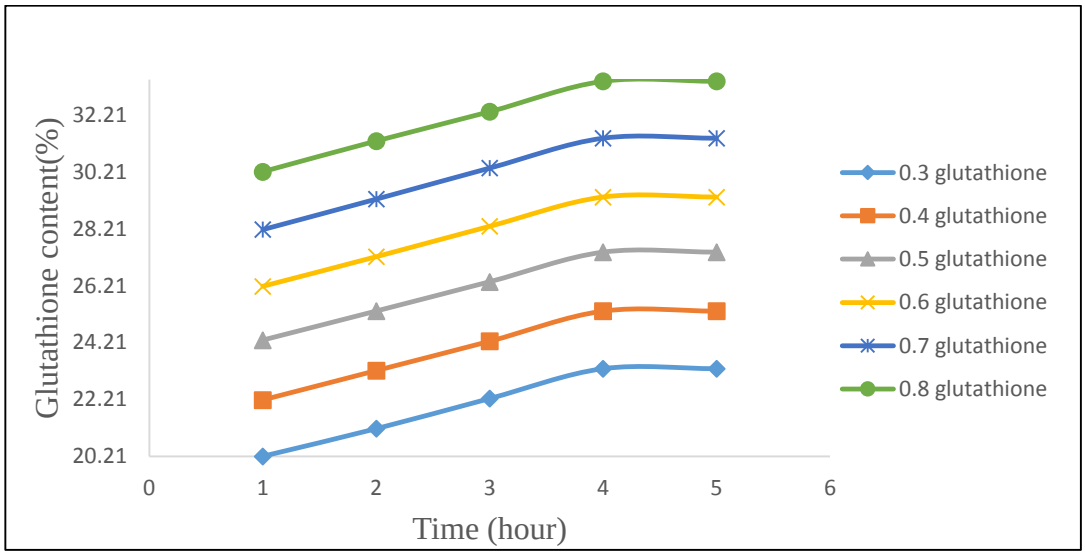


Figure (3-25): Glutathione content (%) curves and time (hour), of the hydrogel nano co-polymer containing0.25 mole of acrylic acid monomer in pH=8.0, Temp.=310K

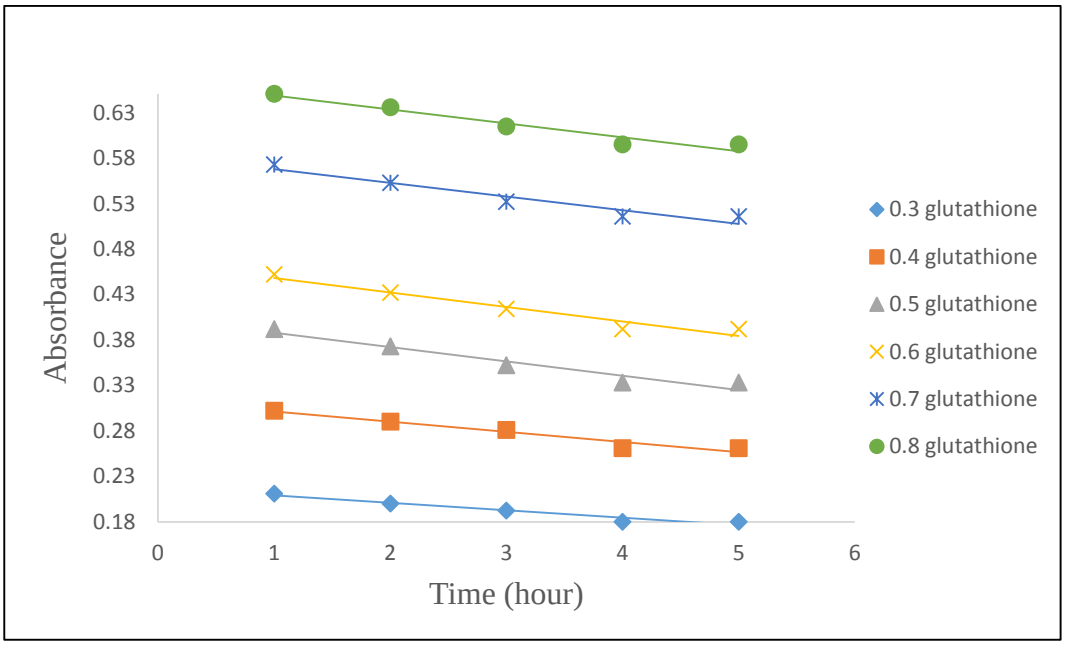


Figure (3-26): Absorbance (Abs.) curves and time (hour), of the hydrogel nano co-polymer containing 0.25 mole of acrylic acid monomer in pH=8.0, Temp.=310K

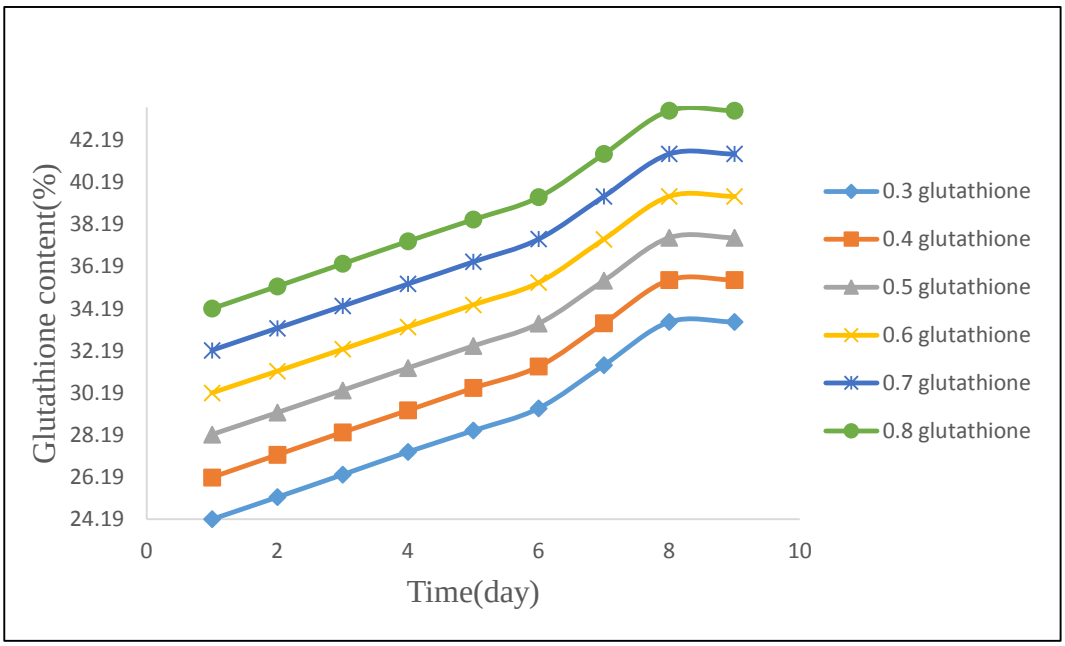


Figure (3-27): Glutathione content (%) curves and time (day), of the hydrogel nano co-polymer containing0.25 mole of acrylic acid monomer in pH=8.0, Temp.=310K

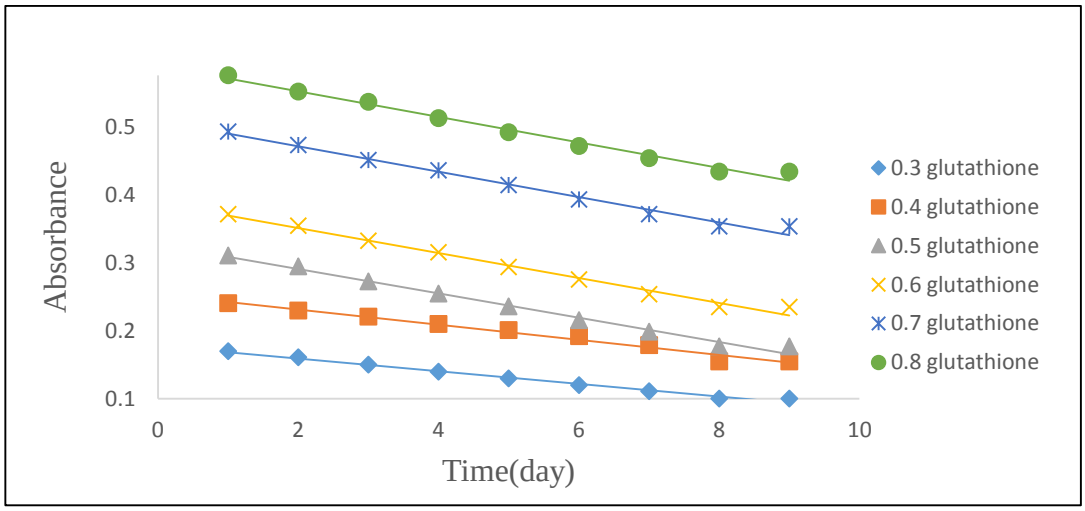


Figure (3-28): Absorbance (Abs.) curves and time (day), of the hydrogel nano co-polymer containing 0.25 mole of acrylic acid monomer in pH=8.0, Temp.=310K

Table (3-9): Glutathione content (%) and solution absorption (Abs.) per hour and day, of nano polymer containing 0.35 mole of acrylic acid monomer in pH=8, Temp.=310K

Time (hour)	Concentration of Glutathione											
	0.3		0.4		0. 5		0.6		0.7		0.8	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	22.19	0.195	24.21	0.286	26.22	0.375	28.24	0.436	30.29	0.557	32.29	0.634
2	23.28	0.182	25.29	0.272	27.29	0.356	29.34	0.417	31.31	0.536	33.32	0.616
3	24.31	0.17	26.34	0.26	28.31	0.335	30.41	0.396	32.39	0.517	34.41	0.595
4	25.37	0.16	27.38	0.245	29.37	0.316	31.48	0.375	33.41	0.495	35.46	0.575
5	25.37	0.16	27.38	0.245	29.37	0.316	31.48	0.375	33.41	0.495	35.46	0.575
(Day)												
1	26.16	0.149	28.18	0.224	30.21	0.299	32.22	0.358	34.19	0.477	36.21	0.559
2	27.25	0.135	29.22	0.217	31.34	0.275	33.32	0.337	35.29	0.455	37.29	0.538
3	28.32	0.123	30.29	0.206	32.41	0.256	34.39	0.315	36.33	0.434	38.32	0.516
4	29.42	0.111	31.32	0.195	33.48	0.234	35.41	0.294	37.39	0.415	39.38	0.497
5	30.49	0.1	32.39	0.183	34.52	0.213	36.49	0.273	38.42	0.396	40.42	0.475
6	31.52	0.097	33.42	0.166	35.59	0.195	37.52	0.252	39.49	0.373	41.49	0.454
7	33.59	0.094	35.48	0.144	37.62	0.172	39.58	0.232	41.53	0.354	43.53	0.433
8	35.61	0.091	37.53	0.126	39.61	0.156	41.62	0.211	43.61	0.336	45.77	0.412
9	35.61	0.091	37.53	0.126	39.61	0.156	41.62	0.211	43.61	0.336	45.77	0.412

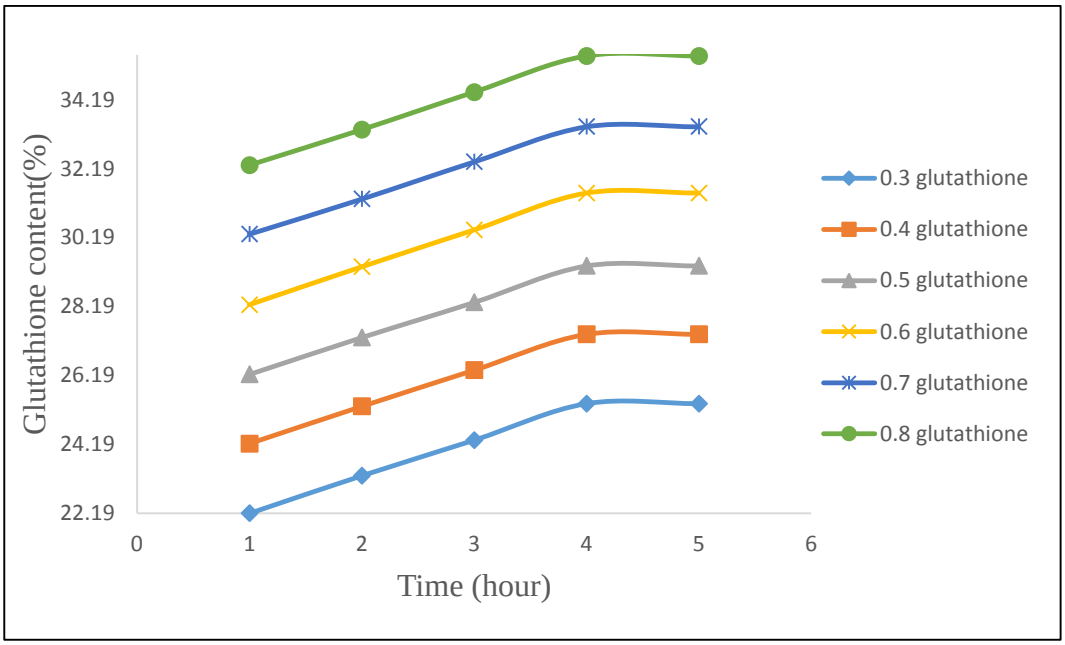


Figure (3-29): Glutathione content (%) curves and time (hour), of the hydrogel nano co-polymer containing0.35 mole of acrylic acid monomer in pH=8.0, Temp.=310K

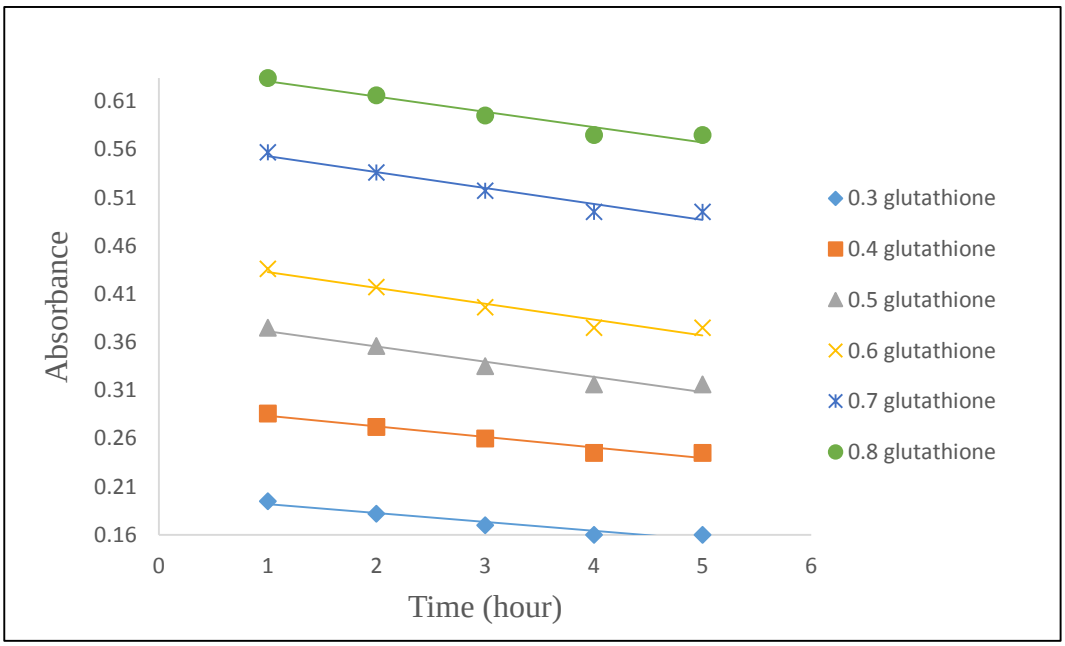


Figure (3-30): Absorbance (Abs.) curves and time (hour), of the hydrogel nano co-polymer containing 0.35 mole of acrylic acid monomer in pH=8.0, Temp.=310K

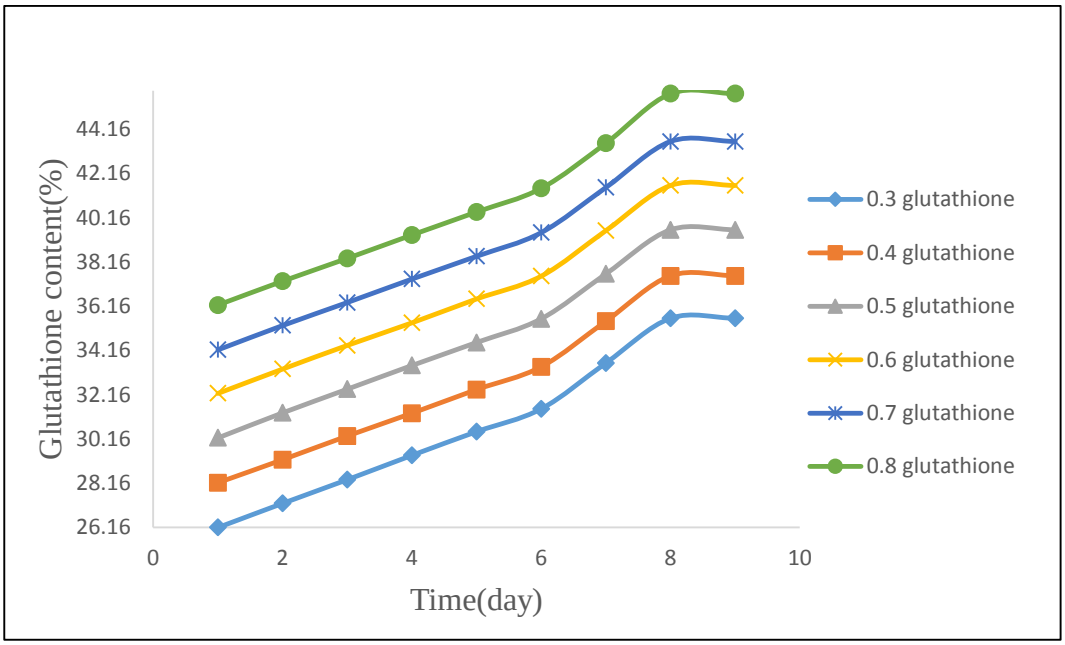


Figure (3-31): Glutathione content (%) curves and time (day), of the hydrogel nano co-polymer containing0.35 mole of acrylic acid monomer in pH=8.0, Temp.=310K

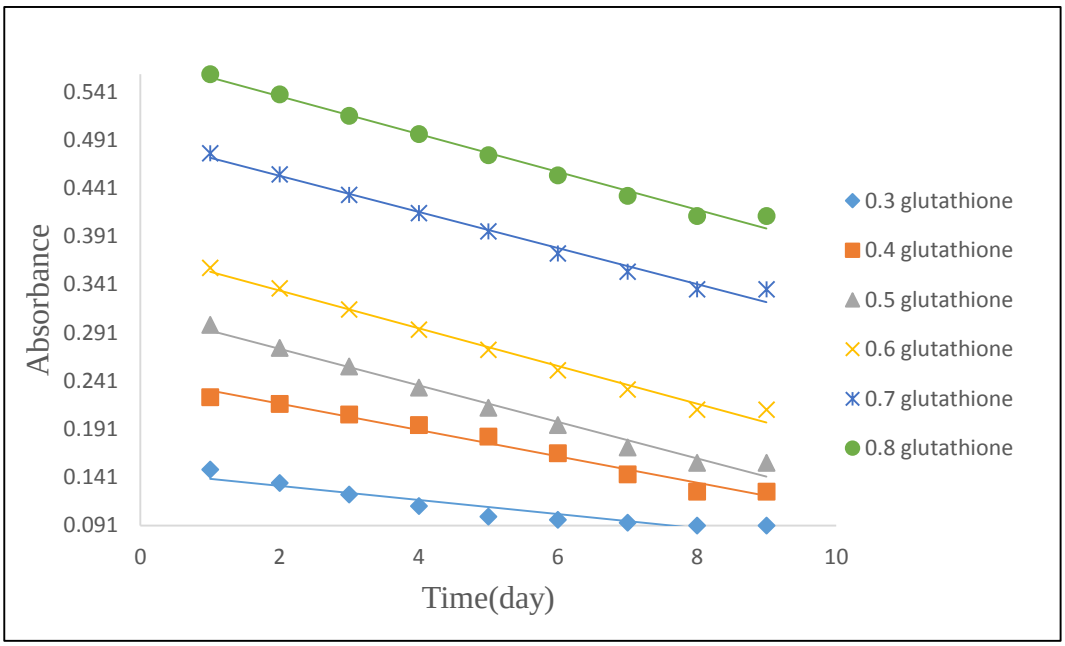


Figure (3-32): Absorbance (Abs.) curves and time (day), of the hydrogel nano co-polymer containing 0.35 mole of acrylic acid monomer in pH=8.0, Temp.=310K

3.3 Release of glutathione

Tables (3-10) to (3-12) and Figures (3-33) to (3-38) depict glutathione release from samples measured at acidic medium pH = 2.2, while Tables (3-13) to (3-15) and Figures (3-39) to (3-44), depict glutathione release from samples measured at basic mean pH = 8.0

It can be seen that the release of glutathione protein in the acidic medium pH = 2.2 is lower than that in the basic medium pH = 8.0, which means that the effectiveness of the nano-co-polymer in releasing the protein in the acidic medium pH = 2.2 lower than at the basic medium pH = 8.0

Table (3-10): Release of Glutathione per time (hour and day) of containing 0.15 mole of acrylic acid monomer in pH=2.2, Temp.=310K

Time (hour)	Absorbance					
	Concentration of glutathione					
	0.3	0.4	0. 5	0.6	0.7	0.8
1	0.09	0.098	0.152	0.181	0.212	0.233
2	0.091	0.099	0.164	0.194	0.224	0.245
3	0.092	0.105	0.179	0.206	0.238	0.257
4	0.092	0.105	0.179	0.206	0.238	0.257
(Day)						
1	0.094	0.119	0.185	0.212	0.242	0.262
2	0.096	0.126	0.192	0.223	0.255	0.273
3	0.098	0.137	0.203	0.235	0.268	0.284
4	0.1	0.144	0.215	0.247	0.276	0.296
5	0.118	0.159	0.228	0.259	0.289	0.307
6	0.118	0.159	0.228	0.259	0.289	0.307

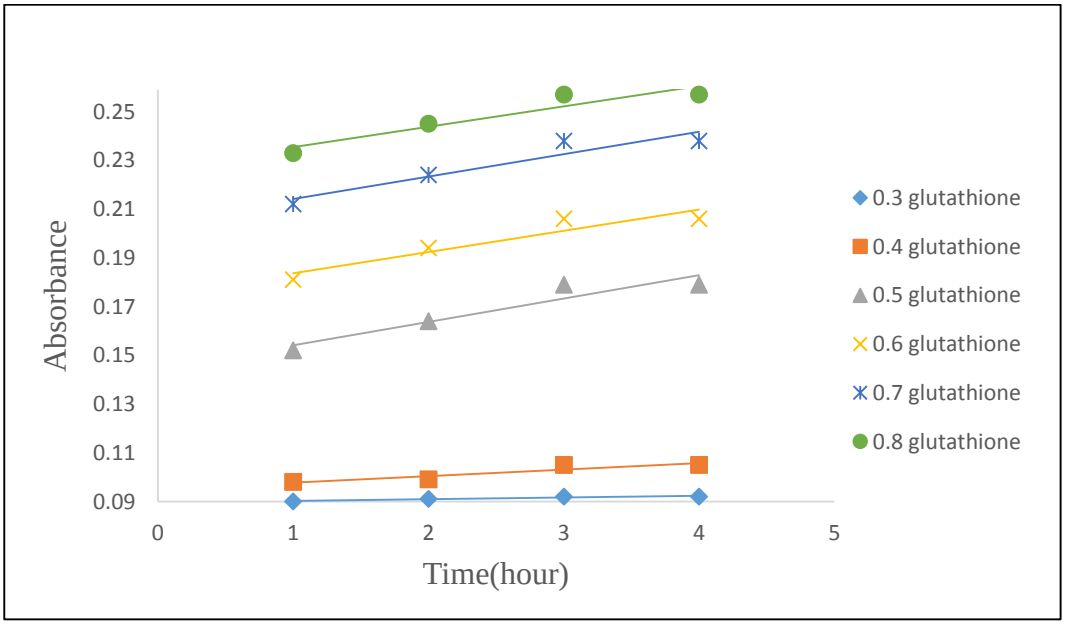


Figure (3-33): Release of Glutathione curves and time (hour), of the hydrogel nano co-polymer containing 0.15 mole of acrylic acid monomer in pH=2.2, Temp.=310K

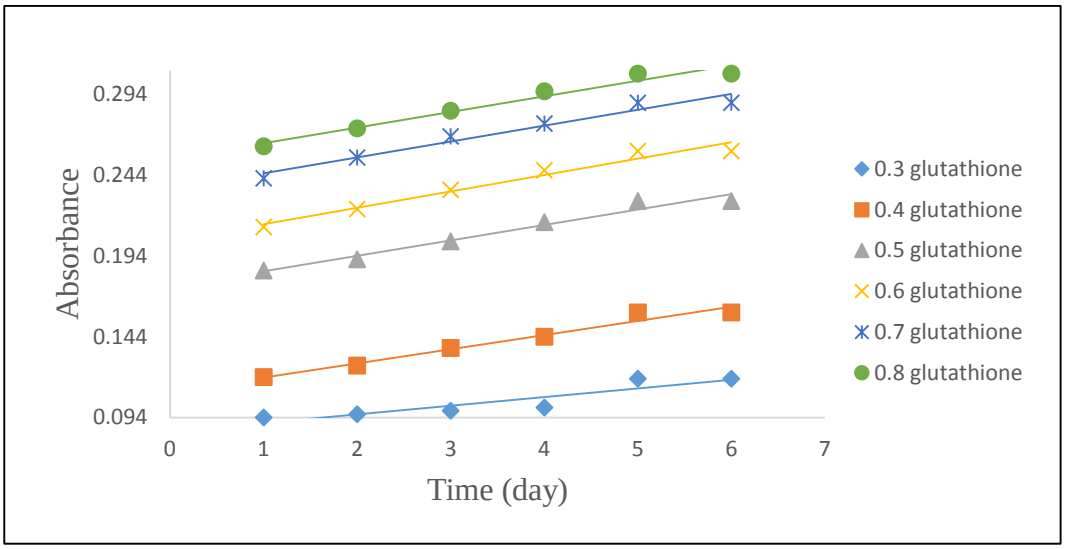


Figure (3-34): Release of Glutathione curves and time (day), of the hydrogel nano co-polymer containing 0.15 mole of acrylic acid monomer in pH=2.2, Temp.=310K

Table (3-11): Release of Glutathione per time (hour and day) of containing 0.25 mole of acrylic acid monomer in pH=2.2, Temp.=310K

Time (hour)	Absorbance					
	Concentration of glutathione					
	0.3	0.4	0. 5	0.6	0.7	0.8
1	0.091	0.099	0.161	0.19	0.221	0.242
2	0.092	0.104	0.173	0.204	0.234	0.254
3	0.093	0.118	0.189	0.217	0.247	0.267
4	0.093	0.118	0.189	0.217	0.247	0.267
(Day)						
1	0.095	0.123	0.194	0.223	0.252	0.273
2	0.097	0.134	0.203	0.234	0.264	0.285
3	0.099	0.146	0.215	0.246	0.276	0.296
4	0.115	0.157	0.226	0.255	0.287	0.307
5	0.129	0.169	0.239	0.269	0.299	0.318
6	0.129	0.169	0.239	0.269	0.299	0.318

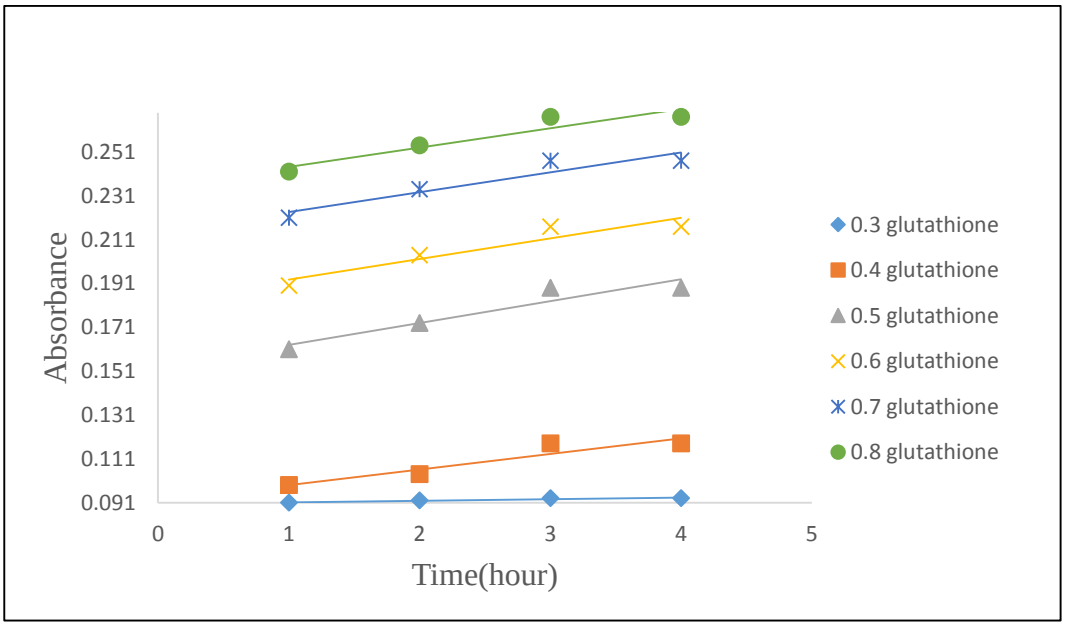


Figure (3-35): Release of Glutathione curves and time (hour), of the hydrogel nano co-polymer containing 0.25 mole of acrylic acid monomer in pH=2.2, Temp.=310K

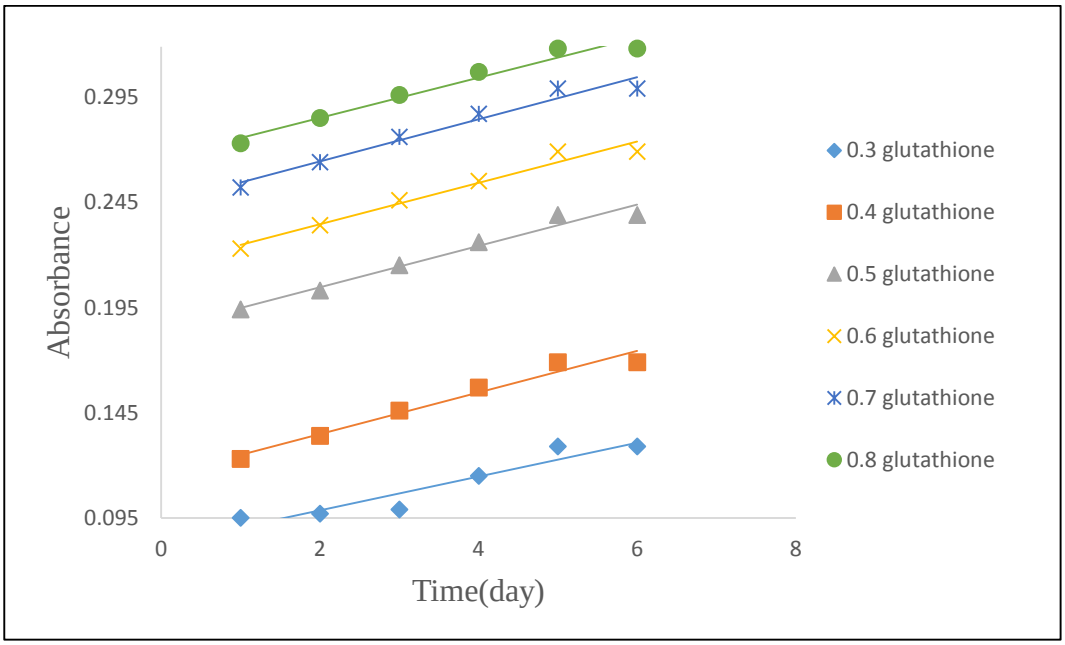


Figure (3-36): Release of Glutathione curves and time (day), of the hydrogel nano co-polymer containing 0.25 mole of acrylic acid monomer in pH=2.2, Temp.=310K

Table (3-12): Release of Glutathione per time (hour and day) of containing 0.35 mole of acrylic acid monomer in pH=2.2, Temp.=310K

Time (hour)	Absorbance					
	Concentration of glutathione					
	0.3	0.4	0. 5	0.6	0.7	0.8
1	0.093	0.112	0.182	0.212	0.241	0.262
2	0.094	0.124	0.195	0.226	0.256	0.275
3	0.095	0.138	0.208	0.239	0.269	0.287
4	0.095	0.138	0.208	0.239	0.269	0.287
(Day)						
1	0.097	0.143	0.213	0.242	0.273	0.291
2	0.099	0.155	0.224	0.255	0.284	0.302
3	0.115	0.166	0.236	0.267	0.295	0.313
4	0.127	0.177	0.248	0.278	0.307	0.324
5	0.139	0.189	0.259	0.289	0.319	0.336
6	0.139	0.189	0.259	0.289	0.319	0.336

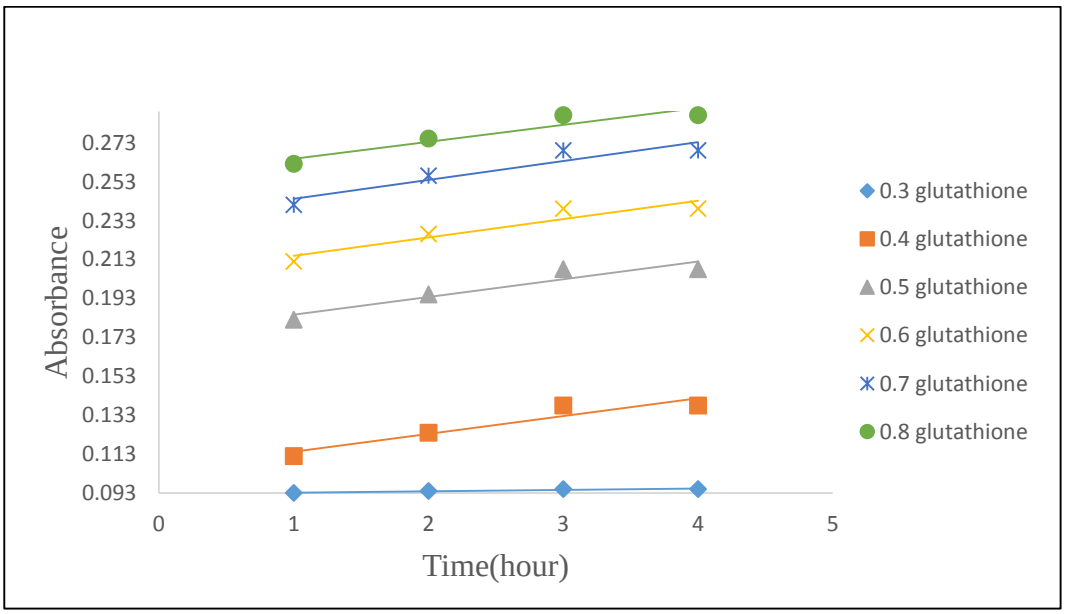


Figure (3-37): Release of Glutathione curves and time (hour), of the hydrogel nano co-polymer containing 0.35 mole of acrylic acid monomer in pH=2.2, Temp.=310K

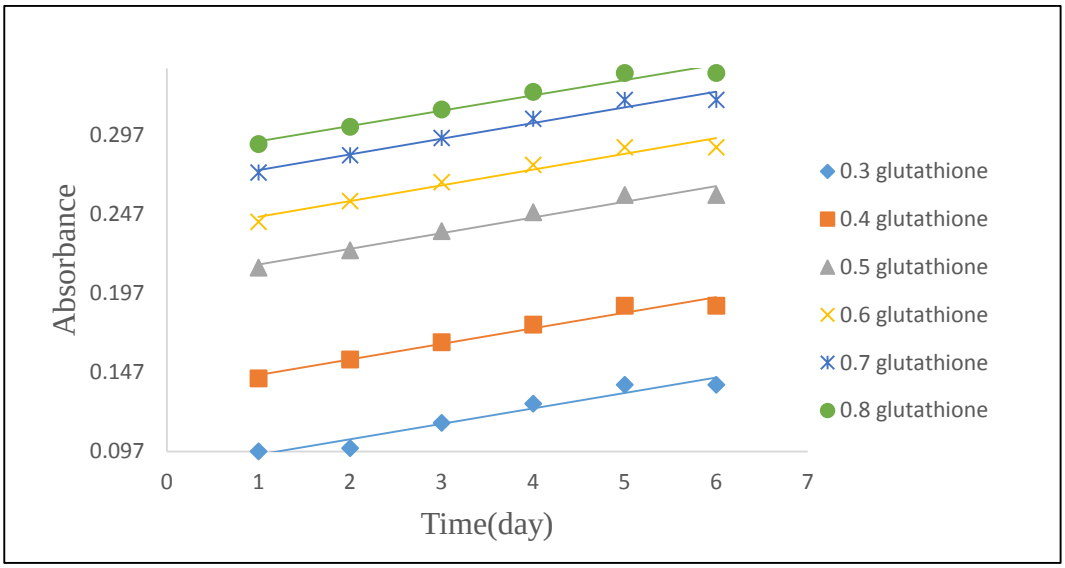


Figure (3-38): Release of Glutathione curves and time (day), of the hydrogel nano co-polymer containing 0.35 mole of acrylic acid monomer in pH=2.2, Temp.=310K

Table (3-13): Release of Glutathione per time (hour and day) of containing 0.15 mole of acrylic acid monomer in pH=8.0, Temp.=310K

Time (hour)	Absorbance					
	Concentration of glutathione					
	0.3	0.4	0. 5	0.6	0.7	0.8
1	0.095	0.13	0.201	0.231	0.262	0.281
2	0.096	0.144	0.213	0.243	0.273	0.293
3	0.097	0.156	0.225	0.255	0.285	0.305
4	0.098	0.166	0.237	0.268	0.298	0.317
(Day)						
1	0.103	0.172	0.241	0.272	0.302	0.32
2	0.112	0.183	0.252	0.283	0.313	0.332
3	0.125	0.194	0.264	0.294	0.324	0.343
4	0.134	0.205	0.275	0.305	0.335	0.354
5	0.146	0.216	0.286	0.316	0.346	0.365
6	0.157	0.227	0.297	0.327	0.357	0.376
7	0.168	0.238	0.308	0.338	0.368	0.387
8	0.179	0.249	0.319	0.349	0.379	0.398
9	0.179	0.249	0.319	0.349	0.379	0.398

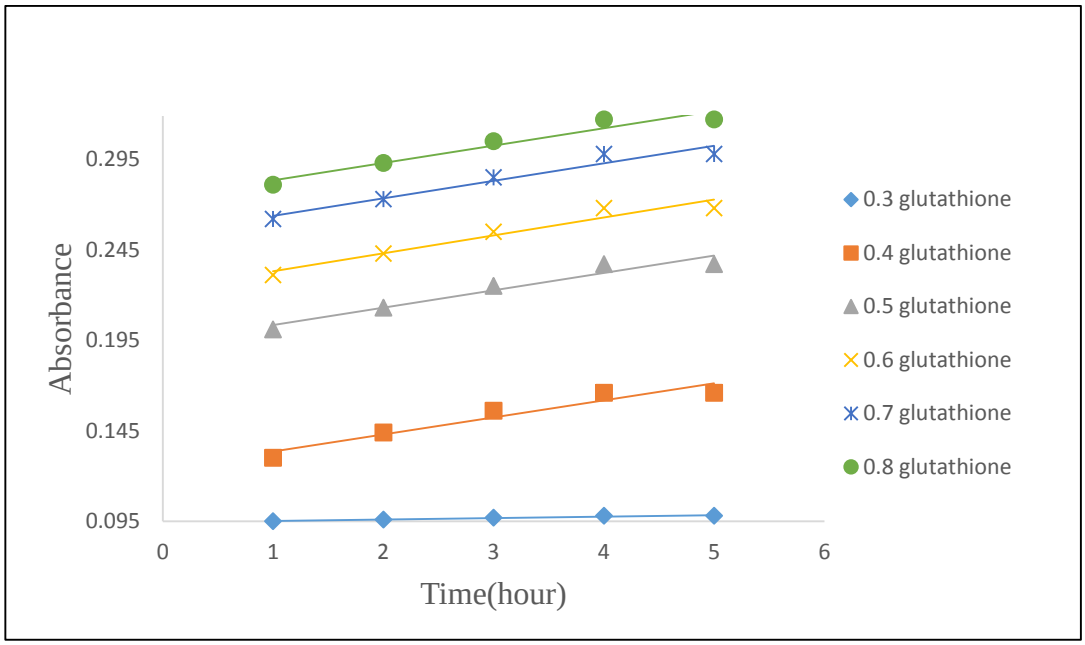


Figure (3-39): Release of Glutathione curves and time (hour), of the hydrogel nano co-polymer containing 0.15 mole of acrylic acid monomer in pH=8.0, Temp.=310K

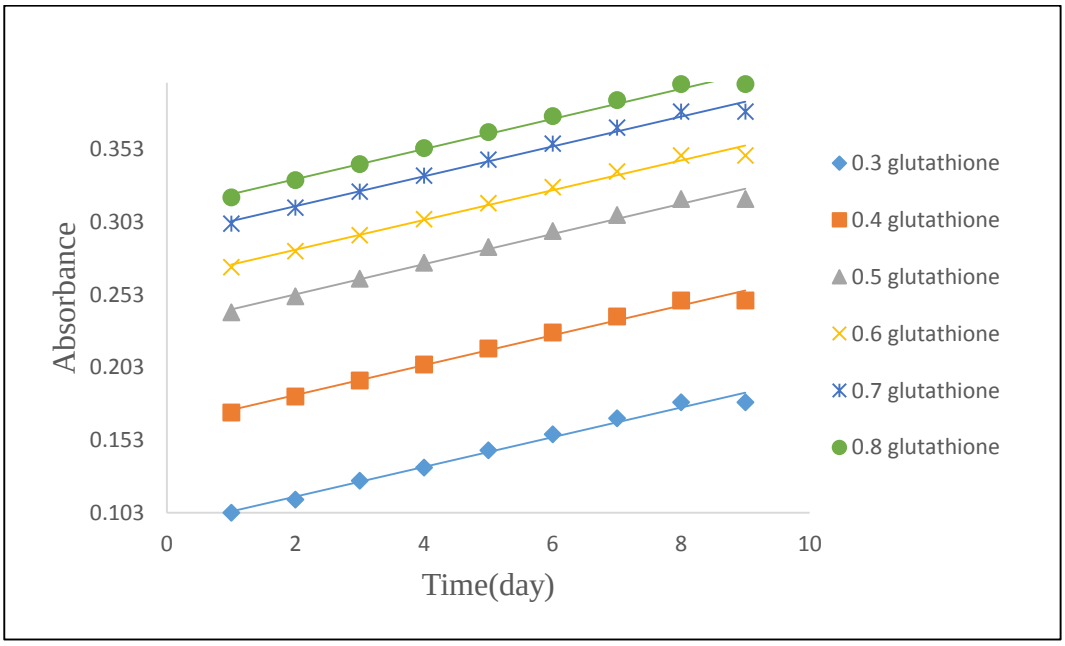


Figure (3-40): Release of Glutathione curves and time (day), of the hydrogel nano co-polymer containing 0.15 mole of acrylic acid monomer in pH=8.0, Temp.=310K

Table (3-14): Release of Glutathione per time (hour and day) of containing 0.25 mole of acrylic acid monomer in pH=8.0, Temp.=310K

Time (hour)	Absorbance					
	Concentration of glutathione					
	0.3	0.4	0. 5	0.6	0.7	0.8
1	0.097	0.151	0.22	0.25	0.282	0.301
2	0.098	0.163	0.232	0.261	0.293	0.312
3	0.099	0.175	0.243	0.272	0.304	0.324
4	0.103	0.187	0.255	0.284	0.316	0.336
(Day)						
1	0.112	0.192	0.26	0.291	0.321	0.341
2	0.123	0.203	0.272	0.303	0.332	0.353
3	0.134	0.214	0.283	0.314	0.343	0.364
4	0.145	0.225	0.294	0.325	0.354	0.375
5	0.156	0.236	0.305	0.336	0.365	0.386
6	0.167	0.247	0.316	0.347	0.376	0.397
7	0.178	0.258	0.327	0.358	0.387	0.408
8	0.189	0.269	0.339	0.369	0.399	0.419
9	0.189	0.269	0.339	0.369	0.399	0.419

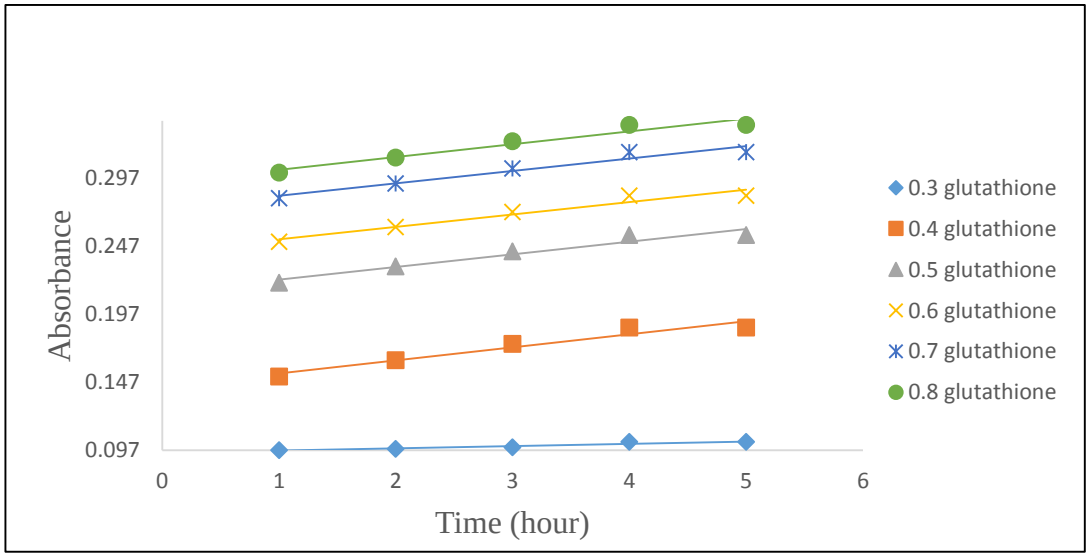


Figure (3-41): Release of Glutathione curves and time (hour), of the hydrogel nano co-polymer containing 0.25 mole of acrylic acid monomer in pH=8.0, Temp.=310K

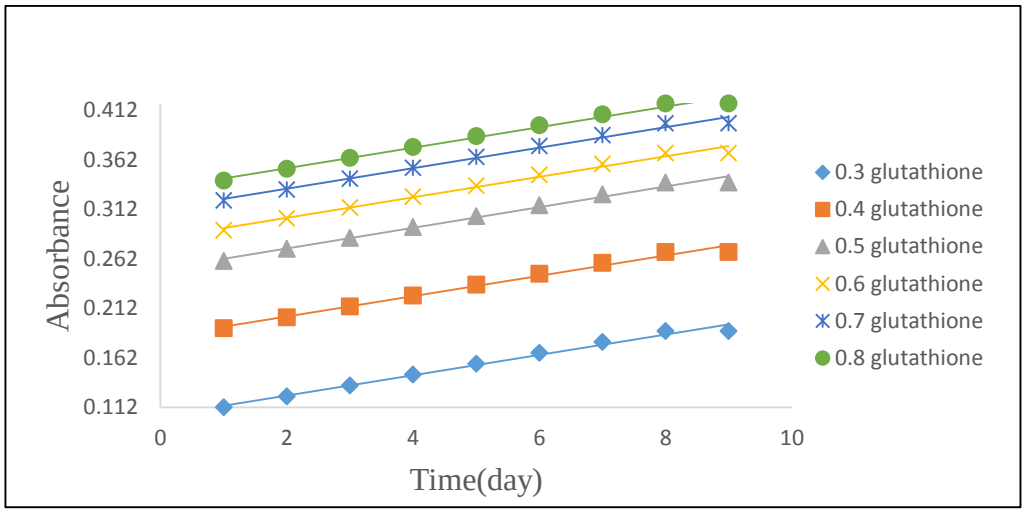


Figure (3-42): Release of Glutathione curves and time (day), of the hydrogel nano co-polymer containing 0.25 mole of acrylic acid monomer in pH=8.0, Temp.=310K

Table (3-15): Release of Glutathione per time (hour and day) of containing 0.35 mole of acrylic acid monomer in pH=8.0, Temp.=310K

Time (hour)	Absorbance					
	Concentration of glutathione					
	0.3	0.4	0. 5	0.6	0.7	0.8
1	0.1	0.182	0.251	0.281	0.311	0.331
2	0.112	0.193	0.263	0.294	0.324	0.343
3	0.124	0.204	0.274	0.305	0.335	0.354
4	0.136	0.215	0.286	0.317	0.347	0.366
(Day)						
1	0.141	0.222	0.291	0.321	0.352	0.371
2	0.152	0.233	0.302	0.332	0.363	0.382
3	0.163	0.244	0.313	0.343	0.374	0.393
4	0.174	0.255	0.324	0.354	0.385	0.404
5	0.185	0.266	0.335	0.365	0.396	0.415
6	0.196	0.277	0.346	0.376	0.407	0.426
7	0.207	0.288	0.358	0.388	0.418	0.437
8	0.219	0.299	0.369	0.399	0.429	0.449
9	0.219	0.299	0.369	0.399	0.429	0.449

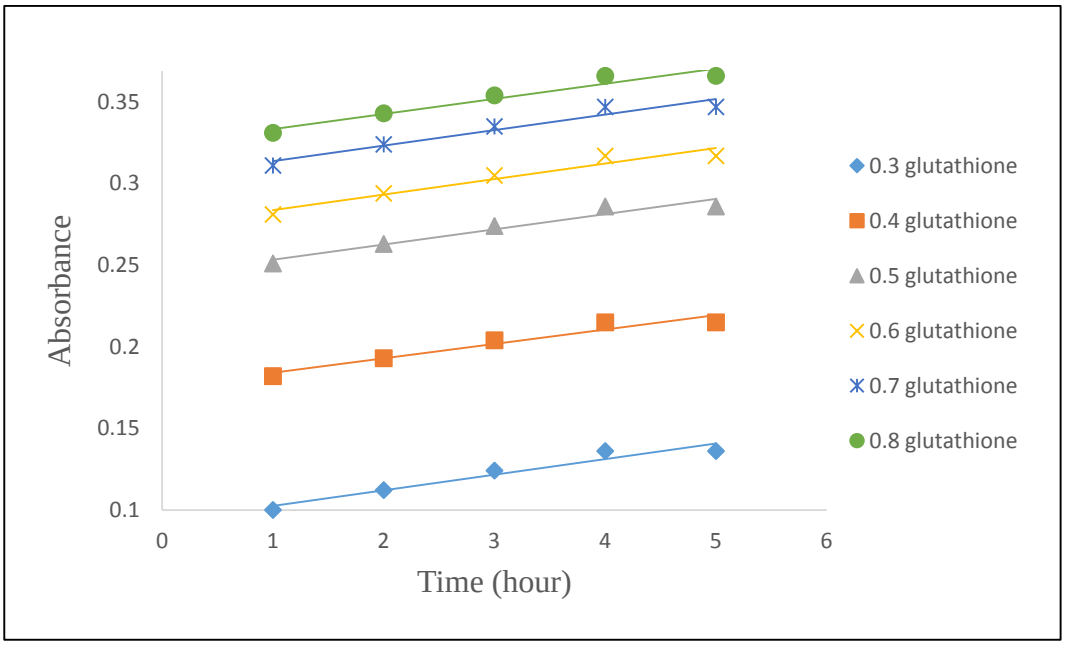


Figure (3-43): Release of Glutathione curves and time (hour), of the hydrogel nano co-polymer containing 0.35 mole of acrylic acid monomer in pH=8.0, Temp.=310K

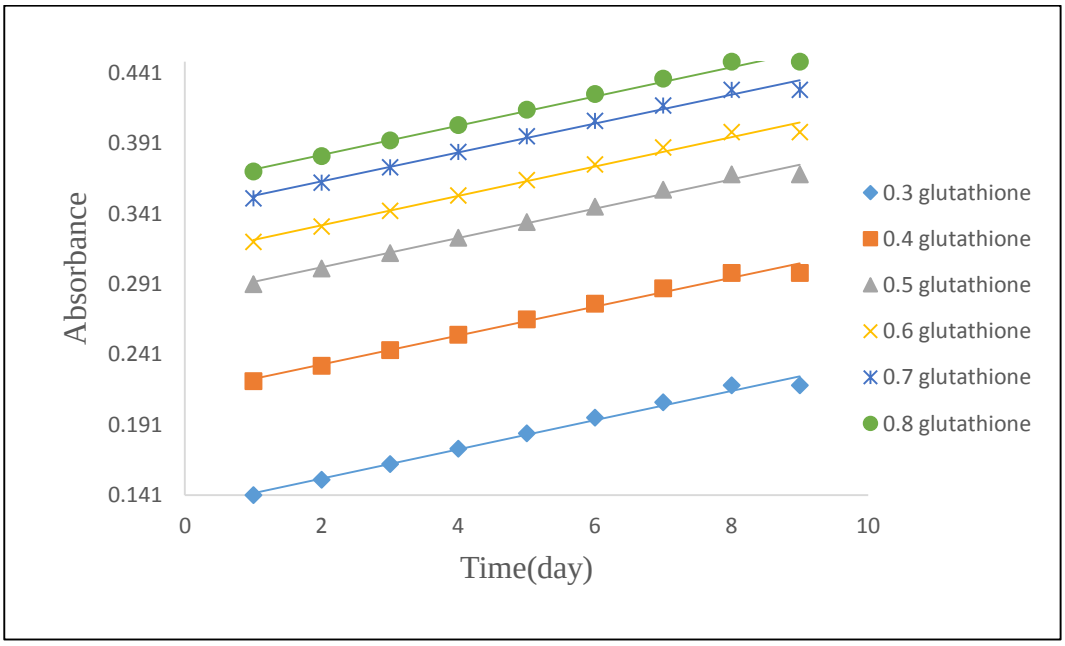


Figure (3-44): Release of Glutathione curves and time (day), of the hydrogel nano co-polymer containing 0.35 mole of acrylic acid monomer in pH=8.0, Temp.=310K

CHAPTER FOUR

Conclusion & Future Works

Conclusion & Future Work

1. Conclusion

Preparation of a novel nano co-polymer by reacting 1.5 mole of phthalic anhydride with 1 mole of glycerol under specific conditions, and characterizing this prepared nano co-polymer to know its structure, particle size, surface shape, etc. using FT-IR, ^{1}HMNR, DSC, AFM, XRD, and TEM techniques, Three different moles of acrylic acid monomer are added to the prepared co-polymer in order to prepare a new modified nano co-polymer.

Upon loading and releasing glutathione protein (daily and hourly) into this specific polymeric matrix prior and at pH (pH=2.2 and pH=0.8) at a constant temperature (body temperature). Our results (tables and figures) reveal that by increasing the concentration of the drug content an increase in the releasing and loading process of the protein observed in different media. Our results show that the loading and releasing process of protein in the basic medium is faster than in acidic medium.

So, we can conclude that the prepared novel nano co-polymer is sensitive to the surrounding medium.

2. Future work

We can suggest the following:

1- Utilize novel proteins to load onto discs of the polymer

2- Utilize new concentrations of drugs.

3 - Utilize of new monomers in the polymer network building.

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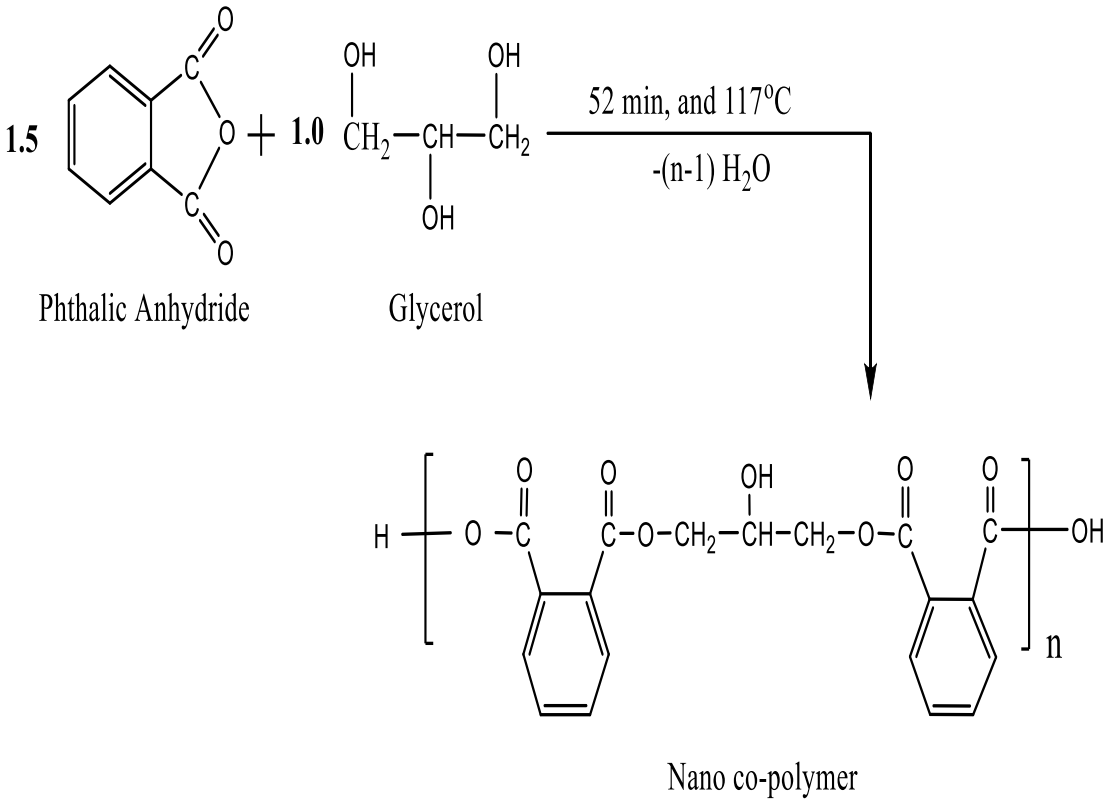
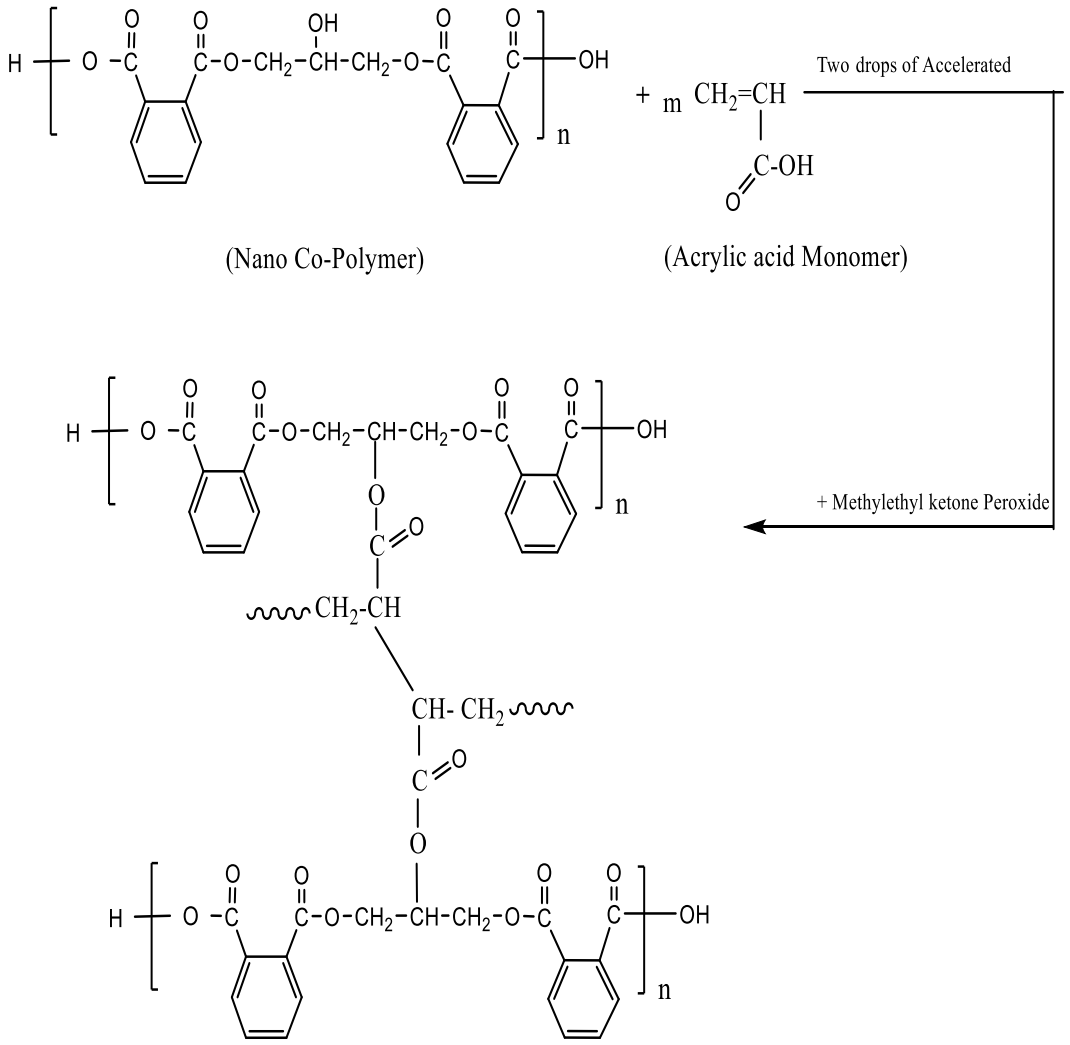
الخلاصة

في العمل الحالي، تم إنتاج بوليمر مشترك نانو جديد عن طريق تفاعل ١,٥ مول من أنهيدريد الفثاليك مع مول واحد من الجلسرين في ظروف محددة، كما هو موضح في التفاعل التالي ؛ تم البوليمر النانوي المشترك المحضر عبر التقنيات التالية (FT-IR ، ^{1}HMNR ، DSC ، AFM ، XRD ،و TEM).



(بوليمر نانوي مشترك خطي)

بعدها تمت إضافة ثلاثة مولات غير متماثلة من مونومر حمض الأكريليك (٠,١٥، ٠,٢٥، ٠,٣٥ مول) من أجل تحضير ثلاثة نانو بوليمر مشترك جديد، كما هو موضح في التفاعل التالي:



(Nano Co-Polymer) (Acrylic acid Monomer)

(Cross-Linked Graft Nano Co-Polymer)

تم تحميل بروتين الجلوتاثيون في مصفوفة بوليمرية محددة عن طريق غمر الهيدروجيل البوليمر النانوي المشترك داخل محلول عازل (الرقم الهيدروجيني = ٢,٢) أيضًا (الرقم الهيدروجيني = ٨,٠) وعند درجة حرارة ثابتة (٣١٠ كلفن) ثم سمح بالتحميل. تم تقييم تركيز الجلوتاثيون المحمل المتحرر باستخدام مقياس الطيف الضوئي بالأشعة المرئية وفوق البنفسجية. تم فحص دراسات إطلاق الدواء من البوليمر النانوي المشترك المحمل بالجلوتاثيون في وسائط مختلفة في الرقم الهيدروجيني (٢,٢، ٨,٠) في درجة حرارة ثابتة (٣١٠ كلفن) كدالة للوقت. حيث لوحظ أنه عندما يزداد تركيز الدواء فإن عملية إطلاقه تزداد نتيجة لذلك.

أشارت النتائج المتحصل عليها إلى أن عملية تحميل البروتين وإطلاقه في الوسط الأساسي (الرقم الهيدروجيني = ٨,٠) كانت أكبر منها في الوسط الحمضي (الرقم الهيدروجيني = ٢,٢)، على سبيل المثال كان أقصى امتصاص لإطلاق الجلوتاثيون في الوقت (ساعة ويوم) تحتوي على ٠,١٥ مول من مونومر حمض الأكريليك في (الرقم الهيدروجيني = ٢,٢) يساوي ٠,٣٠٧ نانومتر، بينما أقصى امتصاص لإطلاق نفس العينة ولكن في (الرقم الهيدروجيني = ٨,٠) يساوي ٠,٣٩٨ نانومتر.

هذا يوضح فعالية البوليمر النانوي في إطلاق البروتين في الوسط الحمضي (الرقم الهيدروجيني = ٢,٢) أقل مما هو عليه في الوسط القاعدي (الرقم الهيدروجيني = ٨,٠)، مما يعني أن البوليمر النانوي المشترك انتقائي / حساس في متوسط.

جمهورية العراق
وزارة التعليم العالي و البحث العلمي
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قسم الكيمياء

دراسة قابلية بوليمر مشترك نانوي جديد على توصيل الدواء

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

من قبل

مها مهدي عبيد الجبوري

بكالوريوس كيمياء / جامعة كربلاء (2016)

إشراف

الأستاذ الدكتور
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