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Ministry of Higher Education
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University of Karbala
College of Education for pure Sciences
Department of Chemistry

Preparation and Study of New Co-polymer As A Drug Delivery

A Thesis
Submitted to the Council of College of Education for Pure Sciences
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By

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Dedication

Specially dedicated

To my lovely parents

To my brothers

To my sisters

To my friends

Zahra Mushtaq

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All praise to ALLAH for giving me the inner strength and good health for completing the dissertation.The author is truly indebted to his supervisors Assist. Prof. Dr. **Mohammad Nadhum AL-Baiati** for putting this research plan and for his patience guidance and generous for sharing of knowledge and ideas and continuous supervision throughout the course of this project

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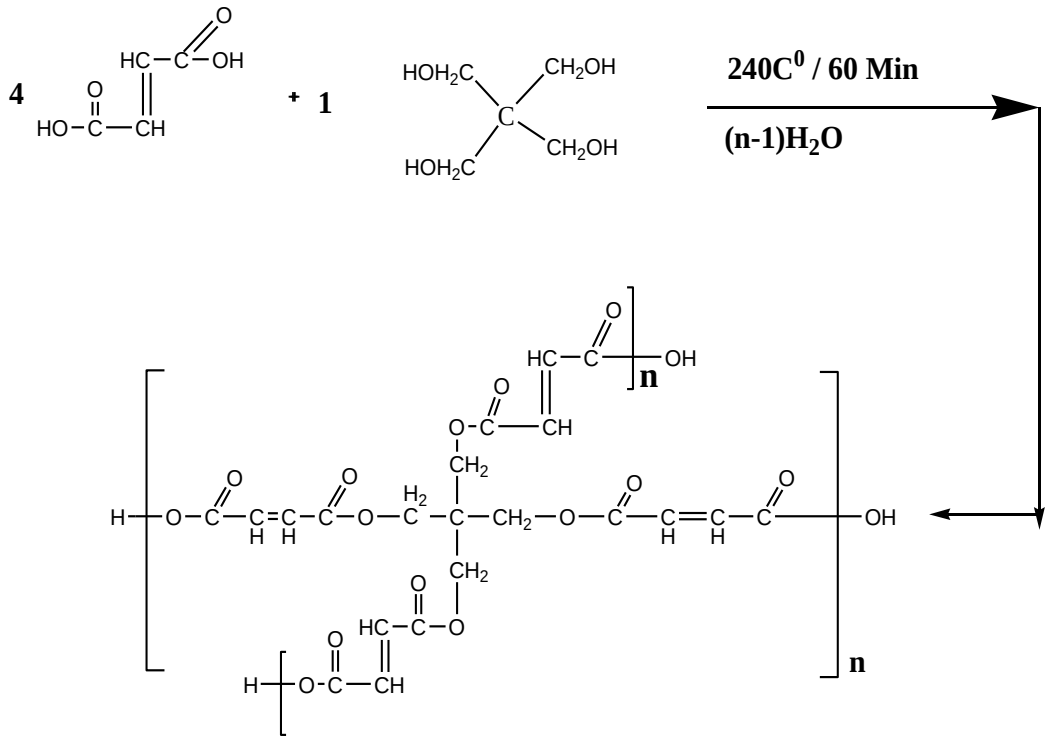
Abstract

In this work, a new co- polymers was synthesized from the reaction of pentarythritol with fumaric acid to form the linear co- polymer at 240 C^{o}, as in the following scheme. The product co-polymer was identified by FT-IR and ^{1}HNMR spectroscopy. Three different moles of acrylic acid monomer (0.5, 1.0 and 1.5 mole), were added to obtain three new co- polymers



(The linear co-polymer)

The swelling ratio was measured for all the hydrogel samples, in three different media (pH=2.2), (pH=7.0) and (pH=8.0) at constant temperature 310K, as function of time. Albumin was loaded into polymeric matrix by immersing the hydrogel in buffer solution (pH=2.2) and (pH=8.0) was allowed to load at temperature 310K, the concentration of albumin

released was measured on UV-Vis spectrophotometer. The drug release studies from the albumin loaded hydrogel was studied in two different media (pH=2.2), (pH=8.0), at temperature 310K as function of time. Where observed when increased drug concentration leads to increase in the release process.

The results obtained showed that the protein loading and release process in the basic medium were higher than in the acidic medium, indicating that the combined co-polymer is selective in the medium.

List of Contents

List of Tables

	List of Abbreviations	
Symbol	**Description**	
IPN	Interpenetrating polymeric net work	
T4	Tetra iodo thyronine	
KDa	Kilo Dalton	
Pm	Pico meter	
ADV	Acoustic droplet vaporization	
PEG	Poly ethylene glycol	
Deb	Deborah number	
S_w	Swelling inter face number	
FT-IR	Fourier Transform Infrared	
UV-Vis	Ultraviolet-visible	
^{1}HNMR	Proton nuclear magnetic resonance	
DMSO	Dimethyl sulfoxide	
$\overline{Mn}$	Average number of Molecular Weight	
MEKP	Methyl ethyl ketone peroxide	
ASTM	American Section of the International Association for Testing Materials	

CHAPTER ONE

Introduction

1. INTRODUCTION

1.1 Hydrogels

Polymer the word 'polymer' is the Greek word,(poly) means many and (mer) means unit or parts, a polymer is a large molecule that comprises repeating structural units joined by the covalent bonds.Classification of polymers based on some special consideration, and based on source under, natural polymers, semi-synthetic and synthetic polymers, based on the structure, linear polymer, branch chain and crosslinked. And also based on molecular forces ,elastomers, fibers, thermoplastic and thermosetting; also classification based on the basis of types of monomers, homopolymer and hetropolymer (Copolymer)[1]. Copolymer can be classified in the following types .Random copolymer, block and graft copolymer .

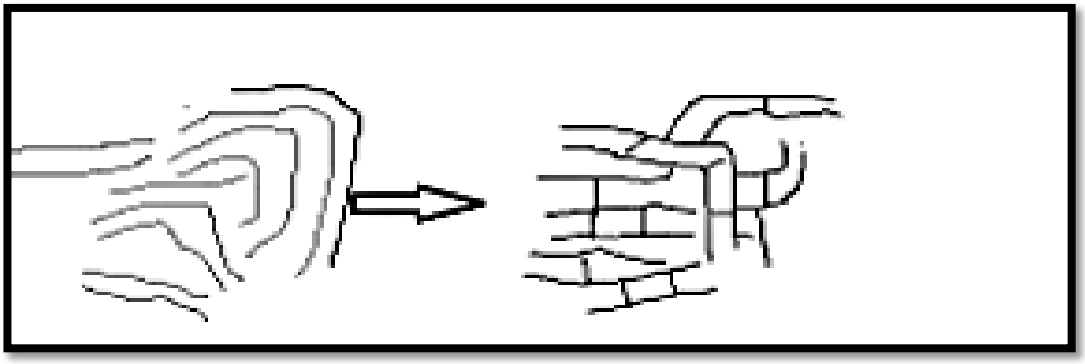
Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of absorbing amounts of water or biological fluids. Due to their high water content, porosity and soft large consistency, they closely simulate natural living tissue, more than any other class of synthetic biomaterials. Hydrogels may be chemically stable or they may degrade and eventually disintegrate and dissolve [2]. They are prepared from materials such as gelatin, polysaccharides, cross-linked polyacrylamide polymers, polyelectrolyte complexes, and polymers or copolymers derived from methacrylate esters. They are insoluble in water and are available in dry or hydrated sheets or as a hydrated gel in drug delivery systems designed for single use [1]. Furthermore, hydrogels can be formulated in a variety of physical forms, including slabs،micro particles, nano particles, coatings, and films. As a result, hydrogels are commonly used in clinical practice and medicine with a wide range of applications, including

Tissue Engineering and Regenerative Medicine; Diagnostics, Cellular immobilization, Separation of biomolecules or cells, and barrier materials to regulate biological adhesions [3]. These unique physical properties of hydrogels have stimulated particular interest in their use in drug delivery applications. Their highly porous structure can easily be tuned by controlling the density of cross-links in the gel matrix and the affinity of the hydrogels for the aqueous the environment in which they are swollen [3]. Their porosity also permits loading of drugs into the gel matrix and subsequent drug release at a rate dependent on the diffusion coefficient of a small molecule or a macromolecule through the gel network [3]. Since the polymer cannot dissolve due to the covalent cross-links, water uptakes far in excess of those achievable with hydrophilic linear polymers can be obtained [4]. Indeed, the benefits of hydrogels for drug delivery may be largely pharmacokinetic – specifically that a depot formulation is created from which drugs elute slowly, maintaining a high local concentration of drug in the surrounding tissues over an extended period of time, although can also be used for systemic delivery [3]. Hydrogels are also generally highly biocompatible , which may be attributed to the high water content of hydrogel .Biodegradability or dissolution in case of hydrogels may be brought about by enzymatic, hydrolytic, or environmental (e.g. pH, temperature, or electric field) pathways; however, degradation is not always desirable depending on the time frame and location of the drug delivery device[3]. Hydrogels are relatively deformable and can conform to the shape of the surface onto which they are applied. In the latter context, the muco-adhesive or bio-adhesive properties of some hydrogel scan be advantageous by keeping them immobilized at the site of application or in applying them on surfaces that are not horizontal. However the amount and homogeneity of drug loading into hydrogels may be limited, particularly in the case of hydrophobic drugs. The high water content and large pore sizes of most hydrogels often result in relatively rapid drug release, over a period of few

hours to a few days. Ease of application can also be problematic; although some hydrogels are sufficiently deformable to be injectable, many are not, necessitating surgical implantation [3].

1.2 Hydrogels and Cross-linking

The term "hydrogel" represents water insoluble polymeric network that has capacity to absorb large amount of water [5,6]. A hydrogel is a macromolecular polymer gel constructed of a network of cross-linked polymer chains. They are synthesized from hydrophilic monomers by either chain or step growth, along with a functional cross linker to promote network formation. Synthetic or natural polymers, homopolymer or copolymer, are used to make three dimensional networks by molecular entanglements or by chemical crosslinking [7].



(Figure1.1): Cross-linking in polymer

The property of hydrogels to swell under biological conditions makes them an ideal class of materials for biomedical applications, such as drug delivery and tissue engineering [8,9]. Cross linking either physically or chemically gives hydrogel a 3D network structure, making it insoluble. This insoluble cross-linked structure allows effective immobilization and release of active agents and biomolecules. Hydrogels appear similar to natural soft tissues because of their high water content.

1.3 Classification of hydrogel products.

The hydrogels can be broadly classified on different bases as detailed below:

1) Classification based on source; Hydrogels can be classified into two groups based on their natural or synthetic origins [10] .

2) Classification according to polymeric composition; the method of preparation leads to formations of some important classes of hydrogels; Can be exemplified by the following [11]:

(a) Homo polymeric hydrogels are referred to polymer network derived from a single species of monomer, which is a basic structural unit comprising of any polymer network. Homo-polymers may have cross-linked skeletal structure depending on the nature of the monomer and this polymerization technique.

(b) Co-polymeric hydrogels are comprised of two or more different monomer species with at least one hydrophilic component, arranged in a random, block or alternating configuration a length chain of the polymer network .

(c) Multi-polymer interpenetrating polymeric network (IPN), an important class of hydrogels, is made of two independent cross-linked synthetic and/or natural polymer components, contained in a network form. In semi-IPN hydrogel, one component is a cross-linked polymer and other component is a non-cross linked .

3) Classification based on configuration; The classification of hydrogels depends on their physical structure and chemical composition can be classified as follows [12]:

(a) Amorphous (non-crystalline)

(b) Semi crystalline; A complex mixture of amorphous and crystalline phases

(c) Crystalline.

4) Classification based on type of cross-linking; Hydrogels can be divided into two categories based on the chemical or physical nature of the cross-link junctions [13].

(a) Chemically cross-linked networks have permanent junctions.

(b) While physical networks have transient junctions that arise from either polymer chain entanglements or physical interactions such as ionic interactions, hydrogen bonds, or hydrophobic interactions.

5) Classification based on physical appearance; Hydrogels appearance as matrix, film, or microsphere depends on the technique of polymerization involved in the preparation process [14] .

6) Classification according to network electrical charge; Hydrogels may be categorized into four groups on the basis of presence or absence of electrical charge located on the cross-linked chains [15]:

(a) Non-ionic (neutral)

(b) Ionic (including anionic or cationic).

(c) Amphoteric electrolyte (ampholytic) containing both acidic and basic groups .

(d) Zwitter-ionic (polybetaines) containing both anionic and cationic groups in each structural repeating unit .

7)Classification according to mechanism controlling the drug release; they are classified into[17]:

a. Diffusion controlled release systems.

b. Swelling controlled release systems.

c. Chemically controlled release systems.

d. Environment responsive systems.

1.4 Properties of hydrogel

1.4.1 Swelling properties

All polymer chains in hydrogels are cross linked to each other either physically or chemically and thus, considered as one molecule regardless of its size. For this reason, there is no concept of molecular weight of hydrogels and therefore, sometimes called infinitely large molecules or super macro-

molecules [16] . One of the variables that effects capacity of water absorption is the degree and type of cross linking agent used. A small change in environmental condition may trigger fast and reversible changes in hydrogel [17].

The alteration in environmental parameters like pH, temperature, electric signal, presence of enzyme or other ionic species may lead to a change in physical texture of the hydrogel [18]. These changes may occur at macroscopic level as precipitate formation, changes in size and water content of hydrogels [19]. The difference in concentration of mobile ions in the hydrogel interior relative to external solution (osmotic pressure), changes in solvent pH, drives the volume change. Hydrogels with acidic or basic functional groups respond to the fluctuations in the external environmental pH. Degree of ionization of the functional groups dictates its swelling profile and hence the volume changes [20].

1.4.2 Mechanical properties

Mechanical properties of hydrogels are very important from the pharmaceutical and biomedical point of view. The evaluation of mechanical property is essential in various biomedical applications viz. ligament and tendon repair, wound dressing material, matrix for drug delivery, tissue engineering and as cartilage replacement material. The mechanical properties of hydrogels should be such that it can maintain its physical texture during the delivery of therapeutic moieties for the predetermined period of time [21]. By changing the degree of crosslinking the desired mechanical property of the hydrogel could be achieved. Increasing in the degree of crosslinking, a stronger hydrogel can be obtained through the higher degree of crosslinking decreases the elongation% of the hydrogels creates a more brittle structure [22]. Hence there is an optimum degree of crosslinking to achieve a relatively strong and yet elastic hydrogel copolymerization with co-monomer, may result into

hydrogen bonding within the hydrogel which has also been utilized by many researchers to achieve desired mechanical properties [23].

Crosslinking is not a property of hydrogels, while it is more of a cause of all the other properties of the material itself. The crosslinking degree can be correlated to basically every characteristic of a hydrogel. The nature of the crosslinking can vary a lot. Indeed, the hydrogels network can be obtained in many different ways. The processes can be divided into two big categories; the first of all, the so called physical crosslinking that occurs, for example thanks to hydrophobic to interaction between chains ,ionic interactions between a poly-anion and a poly-cation (complex coacervation)or ionic inter-actions between a polyanion and multivalent cations (iono-tropic hydrogel).

The second category comprises the chemical bound gels. The crosslinking can occur by ultraviolet irradiation, heating or chemical crosslinking via cross linker with a huge ensemble of reactions, such as Michaels reaction, Michaelis-Arbuzov reaction, nucleophile addition and so on. By controlling the degree of crosslinking is possible to tune the property of the material and optimize it form any different applications getting theoretically, in this way, a wide spectrum applications, in this starting from the same original polymer [24-26] .

1.4.3 Biocompatible properties

It is important for the hydrogels to be biocompatible and nontoxic in order to make it applicable in biomedical field. Most polymers used for this purpose must pass cytotoxicity and in-vivo toxicity tests [27]. Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application. Biocompatibility studies consist of two parameters namely biosafety and bio functionality [28]:

(a)Biosafety i.e., appropriate host response not only systemic but also local (i.e. surrounding tissue), the absence of cytotoxicity, mutagenesis, and/or carcinogenesis and

(b)Bio functionality i.e., the ability of material to perform the specific task for which it is intended

This definition is particularly relevant in tissue engineering since the nature of tissue construct is to continuously interact with body through the healing and cellular regeneration process as well as, during scaffold degradation [29].

Furthermore,initiators, organic solvents, stabilizers, emulsifiers, unreacted monomers and cross linkers used in polymerization and hydrogel synthesis may be toxic to host cells if they seep out to tissues or encapsulated cells [30]. To remove hazardous chemicals from preformed gels, various purification processes should be followed such as solvent washing or dialysis [26].

1.4.3.1 Evaluation of biocompatibility

1) In vitro cell culture tests are often used to screen the tissue compatibility of implantable devices. The cell culture methods are also known as cytotoxicity tests. Three primary cell culture assays are used to evaluate biocompatibility of the hydrogels [31].

a) Elution (extract dilution).

b) Direct contact.

c) Agar diffusion.

These assays are described in the US Pharmacopeia and in standards published by the International Standards Organization.

2) In vivo assessment of tissue compatibility of a hydrogel is the knowledge of chemical composition of the biomaterial and the conditions of tissue exposure (including nature, degree, frequency and duration of exposure). Principles generally applied to the biological evaluation of hydrogels are described as follows [32] :

The material(s) of manufacture; Intended additives, process contaminants, and residues; Leachable substances; Degradation products; other components and their interactions in the final product determine the properties and characteristics of the final product. Most of the problems associated with hydrogel regarding toxicity, are the unreacted monomers, oligomers and initiators that leach out during application. Modifying the kinetics of polymerization and extensive washing of the resulting hydrogel can reduce the toxicity. The formation of hydrogels without any initiators and using alternate path like radiation may eliminate the problem of the residual initiator.

1.5 **Different kinds of stimuli-responsive hydrogels**

Peppas[33] defined the hydrogels, “hydrogels are hydrophilic, three-dimension networks, which are able to imbibe large amounts of water or biological fluids, and thus resemble, to a large extent, a biological tissue". They are insoluble in any solvent due to the polymer chains being cross-linked by either covalent bonds or physical interactions such as entanglements and crystallites. Due to the properties of hydrogels, such as high content of water, soft and rubbery consistence, as well as low interfacial tension with water or biological fluids, they are expected to be potential alternatives for natural tissues [34]. According to different applications, the hydrogel can be prepared to respond to various stimuli in the body such as pH, ionic strength and temperature [35].

1.5.1 Thermo responsive Hydrogel

The equilibrium between the hydrophobic and hydrophilic segments is the key to control the properties of a synthetic thermo responsive hydrogel. In detail, the temperature has a remarkable effect on the hydrophobic interactions between hydrophobic polymer segments and the hydrophilic interactions between hydrophilic polymer segments and water molecules. Thus, a small

temperature change can interrupt the original equilibrium and induce sol-gel transition [36].

1.5.2 pH-responsive hydrogel

Variations in pH are known to occur at several body sites, such as the gastro intestinal tract, vagina, and blood vessels; and these can provide a suitable base for pH- responsive drug release. In addition, local pH charges in response to specific substrates can be generated and used for modulating drug release [37, 38].

The pH –responsive drug delivery systems have been targeted for per oral controlled drug delivery, taste-masking of bitter drugs, and intravascular drug release during elevated blood pH in certain cardiovascular defects [39]. pH-responsive hydrogels are a class of bio-materials that exhibit desirable physical and chemical properties at specific pH ranges. Acidic or basic groups are bonded to the polymer chains. The acidic groups deprotonate at high pH, while the basic groups protonate at low pH. The association, dissociation, and binding of various ions to polymer chains cause hydrogel swelling in an aqueous solution [40]. In general, the size of gel will respond to environment pH as well as salt concentration. Thus, an equilibrium model was established by Moore's group to predict the swelling/de swelling behavior of hydrogels in different pH solutions [41].

The validation of the model was conducted by comparing the simulations with experimental results. This model was then utilized to investigate the effects of different hydrogels and solution conditions on the degree and rate of swelling/de swelling of those hydrogels. It was found that the higher the concentration and buffer diffusivity are, the faster the kinetic [42].

AII these parameters can be used to tune the performance of hydrogel micro actuators suggesting that the mechanical properties of the hydrogel can be varied considerably by varying the pH of solutions [43].

1.5.3 Light – and chemical-Responsive Hydrogels

Light-responsive hydrogels are promising functional materials for potential application in the areas of drug/ gene delivery, micro lenses, sensors, etc. [44, 45]. Due to the fact that the activation process via light can be remote and noninvasive [46]

1.6 Hydrogels based on natural materials

1.6.1 Hydrogel based on polypeptide

Albumin formed from Latin: albumin. "(egg)white, dried egg white") are a family of globular proteins, the most common of which are the serum albumins. All the proteins of the albumin in family are water –soluble, moderately soluble in concentrated salt solutions, and experience heat denaturation. Albumins are commonly found in blood plasma and differ from other blood proteins in they are not glycosylated [47].

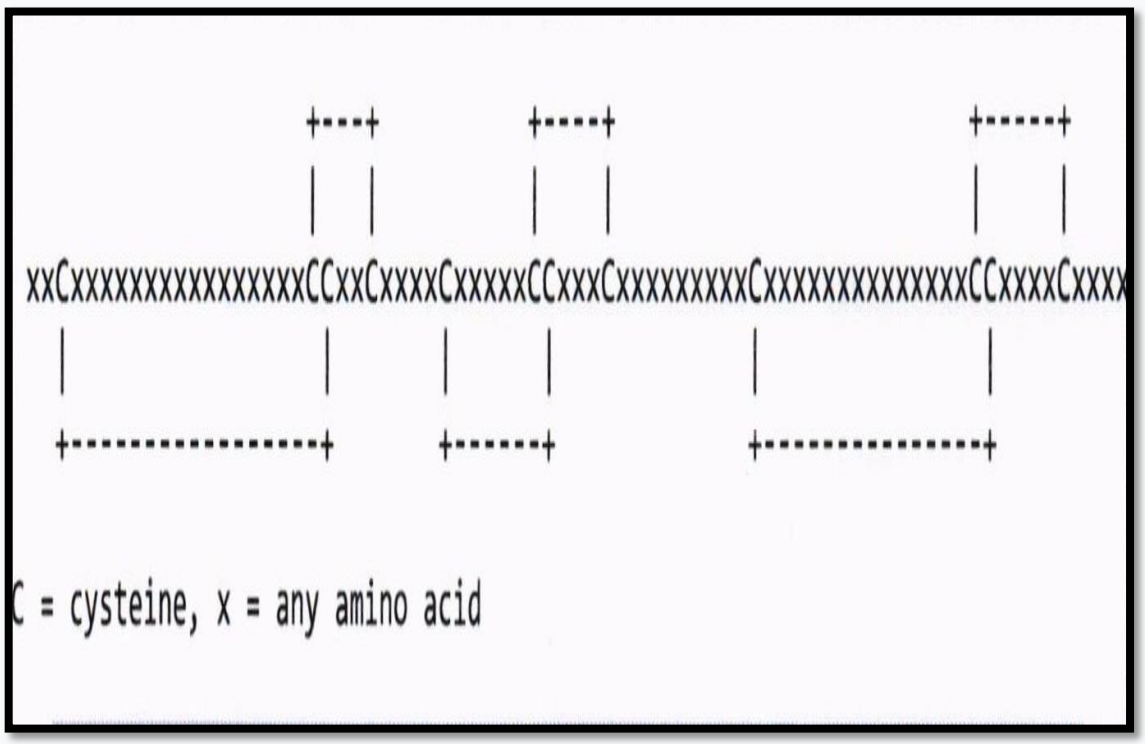
Substances containing albumins, such as egg white, are called albuminoids. A number of blood transport proteins are evolutionarily related, including serum albumin, alpha-fetoprotein, vitamin D-binding protein and a famine [48, 49]. Albumin binds to the cell surface receptor al bond in [50].

1.6.2 Function of albumin

Serum albumin is the main protein of human blood plasma, it binds water cations (such as Ca^{+2},$Na^{+}$and K^{+}), fatty acids, hormones, bilirubin, thyroxin(T4) and pharmaceuticals (including barbiturates):its main function is to regulate the oncotic pressure of blood. Alpha-fetoprotein (alpha-fetoglobulin), is a fetal plasma protein that binds various cations, fatty acids and bilirubin. Vitamin D-binding protein binds to vitamin D and its meta bolites, as well as to fatty acids, the isoelectric point of albumin is 4.9 [51]. .

1.6.3 Structure of albumin

The 3D structure of human serum albumin has been determined by X-ray crystallography to are solution of 2.5 angstroms (250pm). Albumin is a 65-70KDa protein. Albumin comprises three homo-logonsdomanis that assemble to form a heart-shaped protein. Each domain is a product of two sub domains that possess common structural motifs. The principal regions of ligand binding of human serum albumin are located in hydrophobic cavities in subdomains IIA and IIIA ,which exhibit similar chemistry structurally ,the serum albumins are similar ,each domain containing five or six internal disulfide bonds ,as shown schematically blow [52, 53].:



(Figure 1.2):Three-dimensional of human serum albumin

1.6.4 Serum albumin

Serum albumin is the most abundant blood plasma protein and is produced in the liver and forms a large proportion of all plasma protein [51].

The human version is human serum albumin, and it normally constitutes about 50% of human plasma protein. They also serve as carriers for molecules of low water solubility this way isolating their hydrophobic nature, including lipid-soluble hormones, bile salts, un conjugated bilirubin, free fatty acids (apo-protien), calcium, ions (transferrin), and some drugs like warfarin, phenobutazone, clofibrate & phenytoin. For this reason, it is sometimes referred as a molecular "taxi". Competition between drugs for albumin binding sites many cause drug inter action by increasing the free fraction of one of the drugs, thereby affecting potency [52, 53].

1.6.5 Serum albumin levels

Normal range of human serum albumin in adults (>3y.0) is 3.5- 5 g/dL. For children less than three years of age, the normal rang is broader, 2.9-5.5 g/dL. Low albumin (hypo-albuminemia) may be caused by liver disease, nephrotic syndrome, burns, protein-losing enteropathy, malabsorption, malnutrition, late pregnancy, artifact, genetic variations and malignancy. High albumin (hyper-albuminemia) is almost always caused by dehydration. ln some cases of retinol (Vitamin A) deficiency, the albumin level can be elevated to high-normal values(e.g 4.9 g/d L).This is because retinol causes cells to swell with water (this is also the reason too much Vitamin A is toxic). This swelling also likely occurs during treatment with 13-cis retinoic acid (isotretnoin), a pharmaceutical for treating severe acne, amongst other conditions. ln lab experiments it has been shown that all-trans retinoic acid down regulates human albumin production [54- 56] .

1.6.6 Medical uses of albumin

For patients with low blood volume, there is no evidence that albumin reduces mortality when compared with cheaper alternatives such as normal saline, or that albumin reduces mortality in patients with burns and low albumin levels. Therefore, the Cochrane Collaboration recommends that it not be used, except in clinical trials. In acoustic droplet vaporization (ADV), albumin is sometimes used as a surfactant. ADV has been proposed as a cancer treatment by means of occlusion therapy [57, 58] .

1.7 Synthetic Hydrogels

Synthetic polymer-based hydrogels, due to their widely variable and easily tuned properties, have been extensively studied. By varying the chemical composition and preparation methods the structure of the hydrogels can be controlled. Beneficial properties including porosity, swelling ability, stability, biocompatibility /biodegradability, and mechanical strength can all be tuned for specific application purposes [59].

Hydrogel are polymer networks having hydrophilic properties. While hydrogels are generally prepared based on hydrophilic monomers, hydrophobic monomers are sometimes used in hydrogel preparation to regulate the properties for specific applications; In general, hydrogels can be prepared from either synthetic polymers or natural polymers. The synthetic polymers are hydrophobic in nature and chemically stronger compared to natural polymers. Their mechanical strength results in slow degradation rate, but on the other hand, mechanical strength provides the durability as well. These two opposite properties should be balanced through optimize design. Also, it can be applied to preparation of hydrogels based on natural polymers provided that these polymers have suitable functional groups or have been functionalized with radically polymerizable groups. In the most succinct sense, a hydrogel is

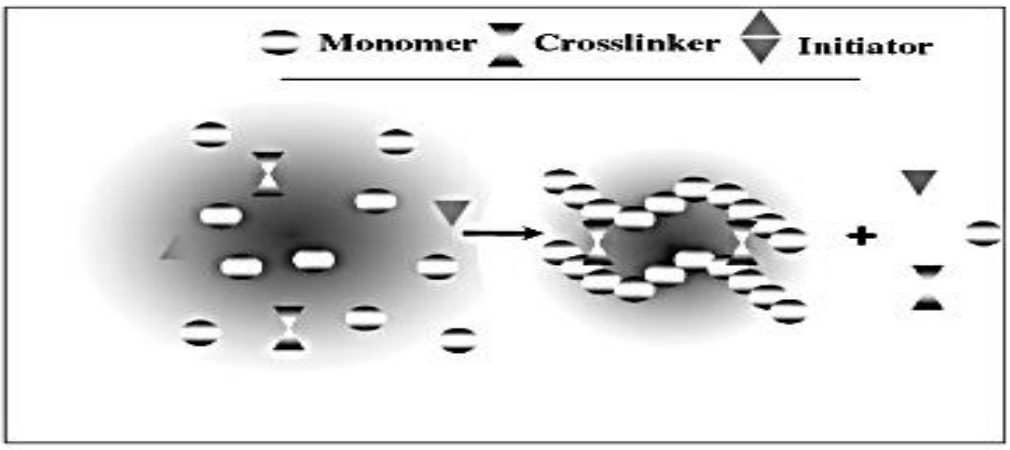
simply a hydrophilic polymeric network cross-linked in some fashion to produce an elastic structure. Thus, any technique which can be used to create a cross-linked polymer can be used to produce a hydrogel [60]. Copolymerization / cross-linking free-radical polymerizations are commonly used to produce hydrogel by reacting hydrophilic monomers with multifunctional cross-linkers. Water soluble linear polymers of both natural and synthetic origin are cross-linked to form hydrogels in a number of ways [59]:

1. Linking polymer chains via chemical reaction

2. Using ionizing radiation to generate main-chain free radicals which can recombine as cross-link junctions. 3.Physical interactions such as entanglements, electrostatics, and crystallite formation

. Any of the various polymerization techniques can be used to form gels, including bulk, solution, and suspension polymerization.

In general, the three integral parts of the hydrogel preparation are monomer, initiator and cross-linker. To control the heat of polymerization and the final hydrogel properties, diluents can be used, such as water or other aqueous solutions. Then, the hydrogel mass needs to be washed to remove impurities left from the preparation process. These include non-reacted monomer, initiators, cross-linkers, and unwanted products produced via side reactions (Figure1.3). Hydrogels are usually prepared from polar monomers, according to their starting materials; they can be divided into natural polymer hydrogels, synthetic polymer hydrogels, and combinations of the two classes. From a preparative point of view, they can be obtained by graft polymerization, cross-linking polymerization, networks formation of water soluble polymer, and radiation cross-linking, etc. [61]

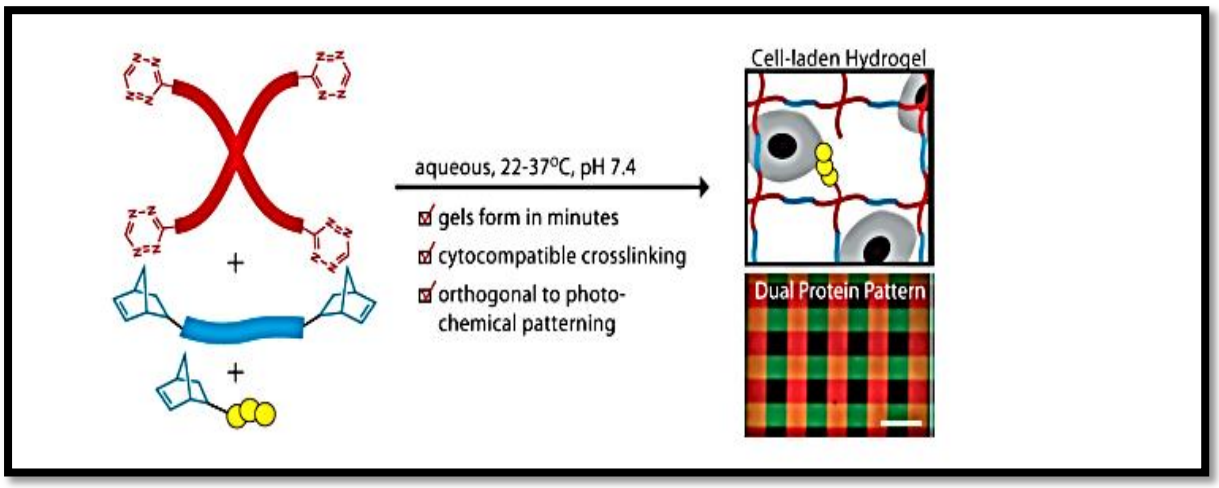


(Figure1.3):Schematic diagram of hydrogel preparation

1.8 Applications in biomedical field

1.8.1 Hydrogel for three-dimensional cell culture

Hydrogels, with high water content as well as tissue like mechanical properties, have been demonstrated to be capable of combining with cells to engineer various tissues in both vitro and vivo. A crucial requirement for the construction of three-dimensional regenerative tissue insufficient quantities is an artificially created environment that enables biological cells to grow or interact with their surroundings in all three dimensions. Anseth's group reported a new cross-linking chemistry by the tetrazine-norbornene click reaction for the formation of cell-laden hydrogels for 3D cell culture (Figure 1.4). A PEG functionalized with benzylaminotetrazine moiety was specifically chosen and used because in their previous work it was shown to have high reactivity toward norbornene. The bio-orthogonality, ideal reaction kinetics, and amenability to photochemical patterning made this hydrogel platform have potential applications in a variety of fundamental, as well as, translational tissue engineering applications [62-64].



(Figure1.4): Synthetically tractable click hydrogels for three-dimensional cell culture formed using tetrazine-norbornene chemistry.

1.8.2 Hydrogel for self-Healing

Self-healing is one of the most outstanding properties of natural materials such as skin, bones and wood. Thus, hydrogels that can self-heal open up another field for biomedical applications. Even though synthetic hydrogels are fabricated to mimic biological tissues, most of the time they still lack the ability to self-heal. This drawback will limit their utilization in many applications that require high stress. As a consequence, researchers dedicate a lot of effort to improving the mechanical properties of hydrogels; including the self-healing property the process of healing cracks in natural systems usually contains an energy dissipation mechanism. The self-healing can occur in the presence of sacrificial bonds, which can break and reform dynamically before or during the failure occurring. To prepare a self-healing hydrogel, both covalent and non-covalent interactions have been reported. Other than chemical cross-linkers, hydrophobic interactions can also play an important role as a cross-linker for self-healing hydrogels [65-70].

1.8.3 Hydrogel for drug delivery

To deliver drugs, porous structure of hydrogels can provide a matrix for drug loading and protect drugs from hostile environment at the same time. Moreover, this porosity can be controlled by varying the crosslinking density of the gel matrix. The release rate, another important parameter for drug carriers, mainly depends on the diffusion coefficient of this molecule through the gel network and can also be tuned according to specific requirements [71, 72].

Biocompatibility and biodegradability can be obtained by designing certain chemical and physical structures for hydrogels. All of those properties lend hydrogels great potential to be used for drug delivery. Nevertheless, the relatively rapid diffusion of drugs out of the gel matrix, as well as the duration of drug release ,is still limited .It can be improved by covalent crosslinking with other functional group, such as ethoxy silane, amine ,or carbohydrates, to prevent the dilution of the polymer in water. In addition, to load drug into a gel .Matrix, conjugating drugs to a hydrogel cross linked network is another way to deliver drugs [73, 74].

1.9 Drug delivery system

Treatment of diseases has always been a major issue for researchers as long as .Mankind has existed .As technology has advanced, proteins, peptides, and other materials have been identified as “drugs” which can be used to treat physiological life processes, pain, and discomfort [75]. Drugs can vary in their characteristics to the extent that drugs used to treat the same symptoms might differ in characteristics such as hydrophobicity, chemical composition, size and effectiveness [76]. Increasing understandings of cellular biology at the molecular level and breakthroughs in proteomics have led to the concept of gene delivery. Drugs have to reach the site of action following administration (oral, intravenous, etc.) in a specific manner and in specific quantity. This is the basis of the drug delivery field. Drug delivery aims at delivering the right drug at the

right place, at right concentration for the right period of time [77]. Sometimes direct delivery of such drugs is difficult, due to the treacherous route of delivery or discomfort caused to the patient. Of the many routes of drug administration, oral administration has been considered to be most convenient, and hence the majority of dosage forms are designed for oral delivery. Different types of hydrogels can be used for delivery of drugs to certain regions in the gastrointestinal tract ranging from the oral cavity to the colon, as shown in (Figure1.5) [78].

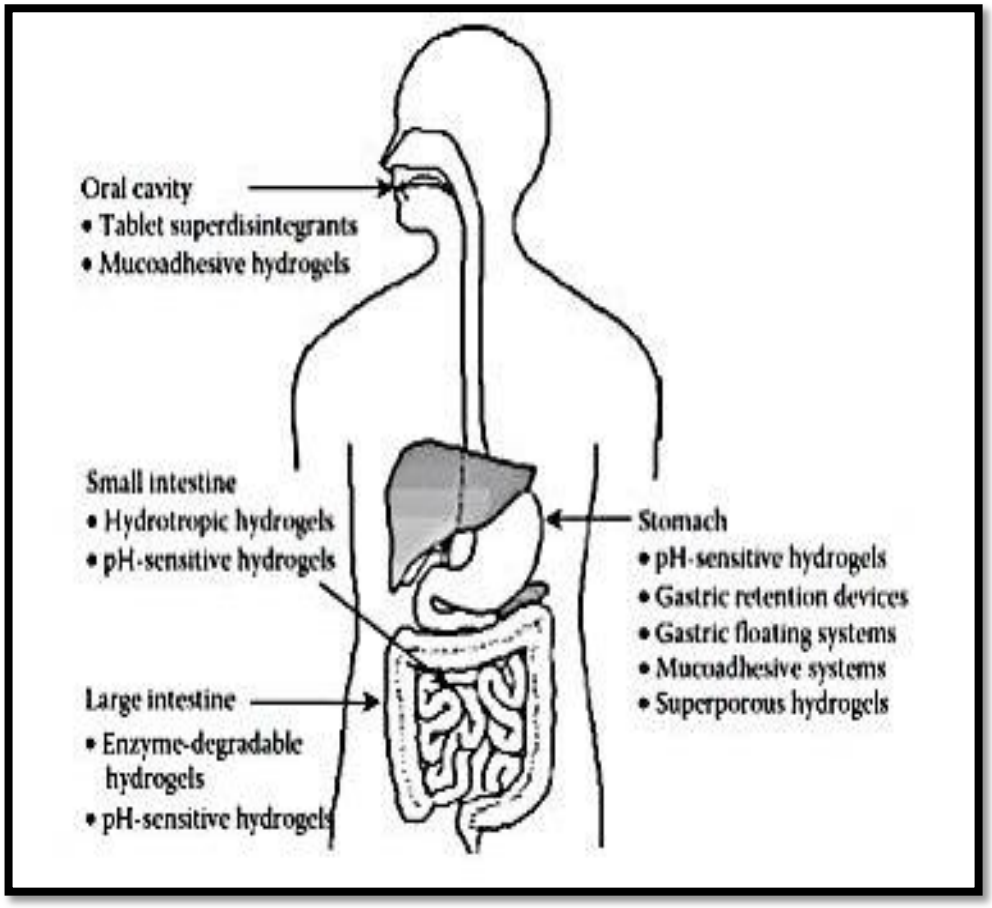


Figure (1.5): Various hydrogels and hydrogel formulations that can be used indifferent segments of the gastrointestinal tract for drug delivery.

The interest of hydrogels as platforms for drug delivery systems is rising continuously; their suitability for pharmaceutical applications being mainly

determined by their mechanical properties, drug loading and controlled drug release capability [79].

1.9.1 Hydrogel: swelling-controlled drug delivery systems

A hydrogel is considered to be a polymeric material that has the ability to absorb >20% of its weight of water and still maintain a distinct 3D structure. The hydrophobicity of the polymer imparts water-attracting properties to the system. Their characteristic water-insoluble behavior is attribute to the presence of chemical or physical cross-links, which provide a network structure and physical integrity to the system. Hydrogels are elastic in nature because of the presence of a memorized reference configuration to which they return even after being deformed for a long time. In a true sense, hydrogels consist of polymers combined with water to create a solid with certain water like properties, such as permeability for many water-soluble substances. Hydrogels are available in various structural and chemical forms, on which basis they have been broadly classified in the literature. Traditionally, controlled release polymeric systems have been classified into 'matrix' and 'reservoir' types. Matrix systems are most commonly employed because of their ease in development, cost-effectiveness and better performance. However, these systems tend to follow Higuchi's model .Wherein drug release is proportional to the square root of time (t½), This leads to non-uniform release rates, continuously decreasing in the beginning and more rapidly thereafter. The key benefit of hydrogels for controlled drug delivery lies in the near constant release rates [80, 81].

1.9.2 Development of Hydrogel-based drug delivery system

Preparation of hydrogel-based drug product involves either cross-linking, of linear polymers or simultaneous polymerization of mono functional

monomers and cross-linking with poly functional monomers [82]. Further, the mechanical strength of poorly cross-linked hydrogels can be adequately enhanced by various methods [83]. Polymers from natural, synthetic or semi-synthetic sources can be used for synthesizing hydrogels. Usually, polymers containing hydroxyl, amine, amide ,ether, carboxylate and sulfonate as functional groups in their side chains are used A detailed list of various monomers and cross-linkers is available in the literature [84]. A stepwise methodology common to the preparation of hydrogel-based drug delivery systems is shown in (Figure1.6)[85]. The design of hydrogel-based dosage forms depends on the route of administration. The synthesis of hydrogels usually involves cross-linking of polymers within a mould to impart the desired shape suitable for administration into the body. Different shapes of hydrogels developed for various routes of administration include: Peroral route – spherical beads [86], cylinders [87] and discs [88]; implants-drum-shaped [89]; disc-shaped and cylindrical preparation [90].

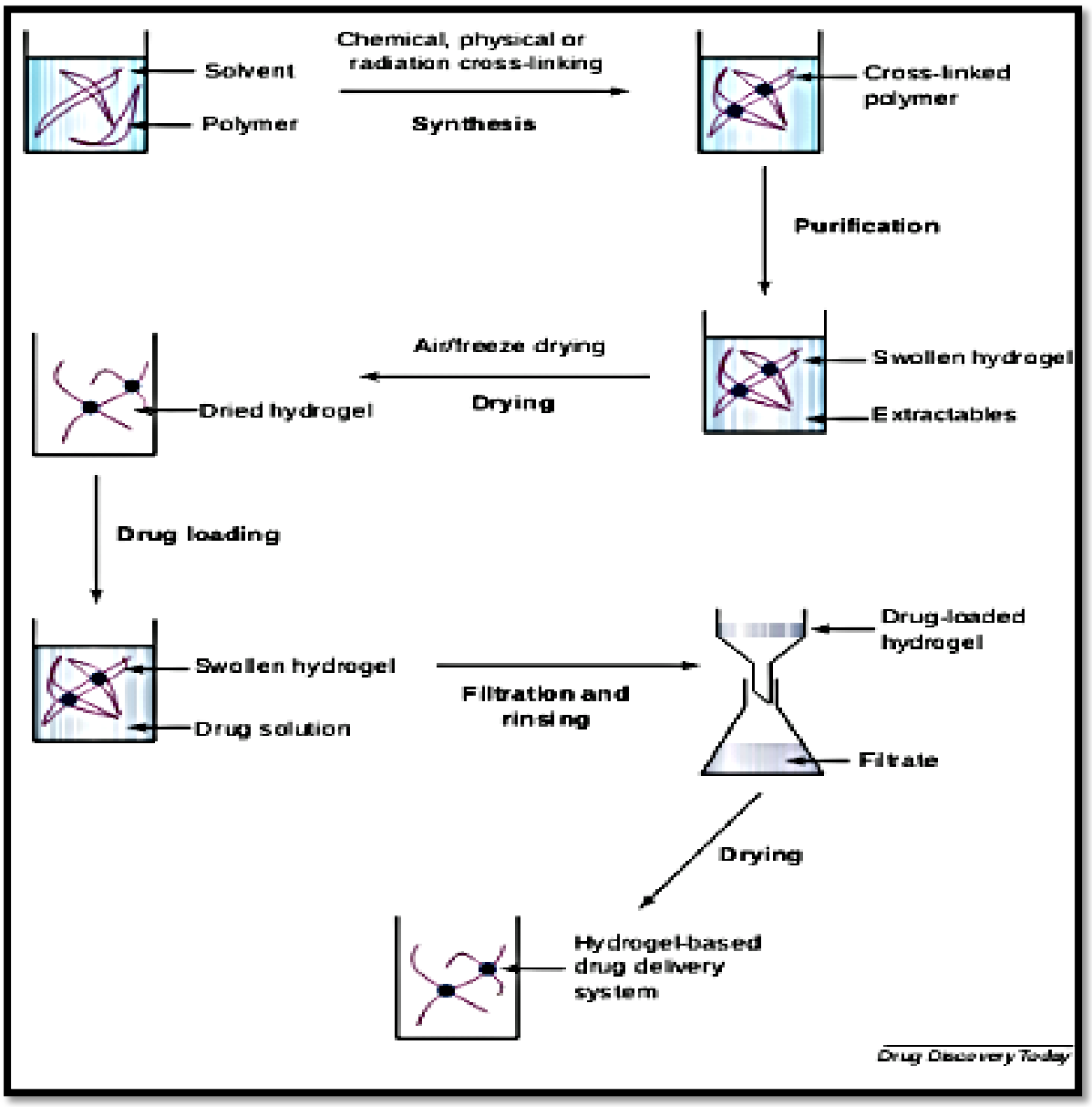


Figure (1.6): Schematic representation of the steps involved in preparation of a hydrogel based drug delivery system.

1.10 Drug-release mechanism

Most of the hydrogels are glassy in their dehydrated state, and drug release generally involves simultaneous absorption of water and desorption of drug via a swelling -controlled mechanism[91]. The rate-controlling factor mediating drug delivery is the resistance of the polymer to an increase in volume and change in shape[92]. A glassy hydrogel, on coming into contact with water or any other thermodynamically compatible medium, allows solvent

penetration into free spaces on the surface between the macromolecular chains. When enough water has entered the matrix, the glass transition temperature of the polymer drops to the experimental temperature. The presence of solvent in a glassy polymer causes the development of stresses that are accommodated by an increase in the radius of gyration and end-to- end distance of polymer molecules, which is seen macroscopically as swelling. The movement of solvent molecules into the dry (glassy) polymer matrix takes place with a well-defined velocity front and a simul-taneous increase in the thickness of the swollen (rubbery) region with time in the opposite direction. Such swelling and diffusion do not generally follow a Fickian diffusion mechanism. The existence of a slow macromolecular relax-ational process in the swollen region is believed to be responsible for the observed non-Fickian behavior[93]. Various approaches used for predicting these mechanisms are: fitting of release data with a power function of time, determination of various dimensionless parameters, such as Deborah number (Deb.) and swelling interface number (S_w)[94]: and moving boundary analysis of drug release from swellable polymers with constant or concentration-dependent diffusion coefficients, using microscopic imaging under polarized light[95]. Drug –loaded hydrogels may act as reservoirs that release the drug; immediately or in a sustained way; by mechanisms such as diffusion or erosion. They can be also used as targeting agents for site-specific delivery; using two main approaches: (a) systems that modify their structure; swelling or eroding; in response to changes in the characteristics of the physiological medium (smart hydrogels) and (b) devices in which the drug is covalently bonded to the polymer via a labile covalent bond that can broke at specific biological conditions [96, 97].

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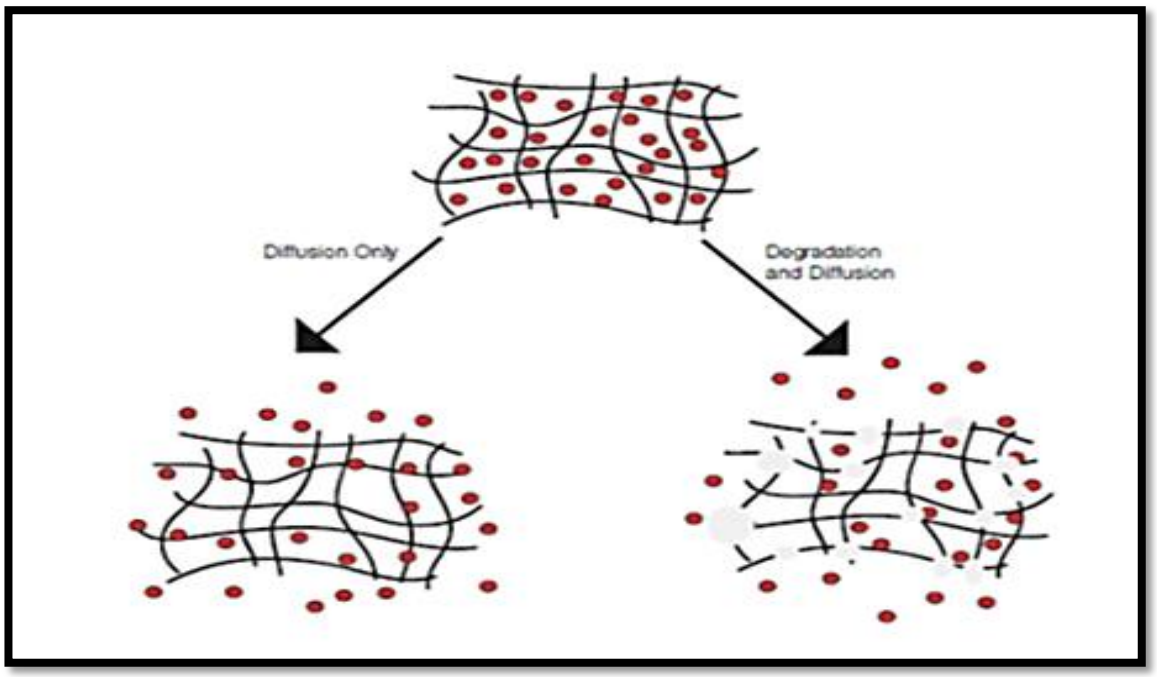

Figure (1.7): Mechanisms of drug release

1.11 Drug release pattern

The pH-responsive drug release can be designed in a monophasic or pulsatile pattern. Peroral controlled delivery requires uniform drug release with an increase in pH gradient in different segments of gastrointestinal lumen. Albumin cross-linked modified resin hydrogels were studied for their swelling behavior at different pH values. Swelling of the hydrogel was found to increase markedly above pH 7.0, thus correlating with the maximal transit time of the drug delivery system through the intestines. Hydrogels are not homogeneous in their structure. The presence of more than two phases (swollen and collapsed) has been reported in hydrogels consisting of copolymers of randomly distributed positively and negatively charged groups. In these hydrogels, polymer segments interact with each other through attractive or repulsive electrostatic forces and hydrogen bonding. Combination of these forces seems to result in the existence of several phases, each characterized by a distinct degree of swelling, with abrupt changes. Hence, such a system can be used for multi-phased drug delivery [98, 99].

1.12 The aim of work

The aim of this work prepare a new three types of modified co-polymers ,studying the swelling of these co-polymers, at constant temperature 310 K, and in three different medium pH (pH 2.2,pH 7.0 and pH 8.0), and the study of the ability of these co-polymers to loaded drug(albumin) in the acidic and basic medium at constant temperature 310K and released the drug (albumin) also in the acidic and basic medium also at constant temperature 310K(temperature of the human body) .And so to calculate the effective co-polymers prepared in the drug (albumin) transfer.

CHAPTER TWO

Experimental

2. Experimental

2.1 Chemicals

Table (2-1): Shows all chemicals were used produced by companies: (B.D.H), (SIGMN), (C.D.H) and (MERCK)

Table (2-1): Chemical material, purity and companies supply

No.	Chemical Material	Company	Purity %
1	Acrylic acid monomer	B.D.H	99.0
2	Hydro chloric acid	C.D.H	99.0
3	Fumaric acid	SIGMN	99.0
4	Albumin	SIGMN	90.0
5	Pentaerythritol	SIGMN	99.0
6	Hydroquinone	SIGMN	90.0
7	Potassium Chloride	MERCK	90.0
8	O-Xylene	B.D.H	98.0
9	Borax	B. D .H	99.0
10	Cobalt Octoate / 6 %	B.D.H	96.8
11	Methylethylketone Peroxide	B.D.H	98.0
12	Sodium bicarbonate	SIGMN	99.8

2.2 Instrument Analysis and Equipments:

The instruments and equipments used in this study are listed below:

1- FT-IR-spectrophotometer, (FT-IR) Shimadzu Perkin- Elmer 1725X / College of Sciences / Karbala University (Iraq).

2- UV-Vis Spectrophotometer, UV-Vis1800 PC Shimadzu / College of Education for pure Science / Karbala University (Iraq).

3- ^{1}HNMR Spectroscopy, Bruker spectrometer, 400 MHz, Switzerland, France with DMSO d_6, University of Osmania / Hyderabad (India).

2.3 Preparation of modified co-polymer

In a 250 ml three-necked round bottom flask, (4.0 mole, 464 gm) of Fumaric acid, and (1.0 mole, 136 gm) of Pentaerythritol, were mixed together. This flask was equipped with a thermometer and a mechanical stirrer. The mixture warmed carefully with an electric heating mantel to 180C° until a clear liquor is formed and then about 15 ml of Xylene was added carefully to the reaction flask, in the form of batch (two drops in each batch), withdrawal of water formed in the esterfication process, and the flask was gently heated. Heating was stopped after 60 min. at240C°, until no more water came off. The flask was allowed to cool to 50C°, and ($1.36x10^{-3}$ mole, 0.147 gm) of Hydroquinone was added to the reaction flask, with stirred by mechanical stirrer. The negative test of $NaHCO_3$ solution proves that the prepared modified polyester resin doesn't contain unreacted acid , and at $55C^{o}$, (0.5, 1.0 and 1.5 mole) about (36,72 and 108 gm), respectively of Acrylic acid monomer, was added to the modified polyester resin and stirred by mechanical stirrer until a pourable syrup was formed.

The viscosity and density of the prepared resin were calculated using Brookfild digital viscometer instrument and Hydrometer instrument respectively. The average number of molecular weight ($\overline{Mn}$) was determined using end group analysis method [100] .The procedure of this method as follows:

About 1 gm of resin sample are weighted accurately into a beaker, 10 ml of xylene solvent were added to the resin sample. The resin was allowed to dissolve in the solvent, with careful warming in a water bath and then addition two drops of phenolphthalein as indicator. The solution was titrated with 1N of sodium hydroxide solution until a faint pink color. The volume of sodium hydroxide solution used was noted.

The average number molecular weight ($\overline{Mn}$) of the resin is then calculated as follows:

$$\overline{Mn} = r \cdot q \cdot w / g \quad \ldots..(1)$$

Where: r : The number of reactive groups per molecule .

q : The equivalent weight of the reagent .

w : The weight of resin sample .

g : The number of grams of reagent.

Acid value:

The acid value of a resin is defined as the number of mg of sodium hydroxide required to neutralize 1 gm of resin. This value was determined using the same procedure of end group analysis and the acid value of the resin is then calculated as follows[100]:

$$\text{Acid value} = \frac{\text{volume of sodium hydroxide}}{\text{Weight of sample}} \times 56 \quad \ldots..(2)$$

2.4 Preparation of polymeric samples

The samples of polymeric were prepared by adding different number of moles of the acrylic acid monomer (0.5,1.0 and 1.5mole) to the modified resin prepared in step above with continuous stirrer, and using Methylethylketone peroxide (MEKP), as a hardener (initiator cross-linking process), and cobalt octet 6% (as accelerator). Three different co-resins were formed different between them from where number of moles of the acrylic acid monomer adds to it. After the preparation of the samples of polymeric molded in matrixes glasses, where hardened resins and measurements (110x50x30)cm and cutting as a disc in dimensions (thickness=3mm & diameter=1cm) according to ASTM: D-2849, and the weighted of the dry discs was exactly 0.4 gm of all samples were used in the swelling study.

2.5 Swelling Measurement

Dried hydrogel discs were used to determine the swelling ratio. The swelling ratio was determined by immersing the xerogel discs (0.4 gm) in 50 ml of different pH (pH=2.2, pH=7.0 and pH=8.0) and was allowed to soak for 5 hours and 5 days in constant temperature (310K).

After each 1 hr. and 24 hr., hydrogel discs were removed from the water, blotted with filter paper to remove surface water, weighted and the swelling ratio was calculated using the equation [101]

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

The method of prepared buffer solutions was [102]:

1- pH = 2.2

This solution was prepared by mixing 50 ml of 0.2 M of KCl and 7.8 ml of 0.2 M of HCl.

2- pH = 8.0

This solution was prepared by mixing 100 ml of 0.025 M of Borax and 41 ml of 0.1 M of HCl.

2.6 Preparation of standard calibration curve [97, 99]

A standard calibration curve for albumin was determined by preparation solutions different concentrations from albumin in the range of (0.025- 0.225 %). The solutions were prepared, using deionized water as solvent. The absorbance of the resulting solutions was measured at λ_{max} 398.0 nm using deionized water as a blank on Shimadzu UV - 1800PC spectrophotometer. Figure (2-1) showed the linear relationship between the concentration of the albumin and the absorbance.

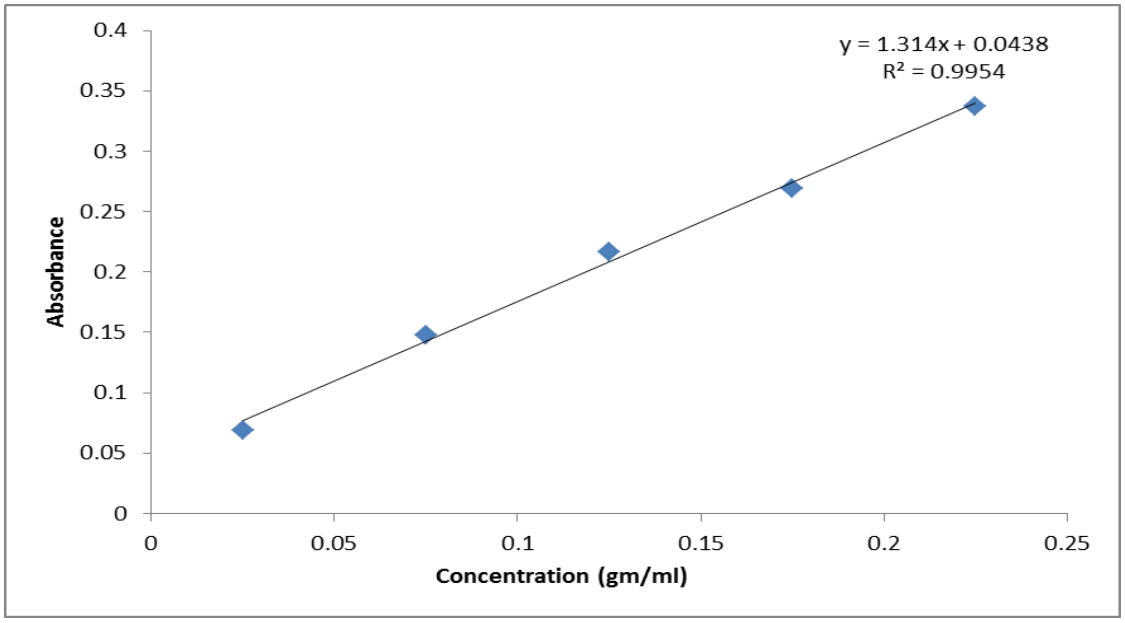

Figure (2-1): Calibration curve of the albumin (the absorbance in 1.0 cm cell) at λ_{max} 398.0 nm

2.7 Drug (albumin) loaded [103].

The albumin is a family of globular proteins water-soluble, and moderately soluble in concentrated salt solutions, experience heat denaturation, and because the prepared gels swell extensively in water. The albumin was loaded through immersing the xerogel discs in buffer solution pH (pH=2.2 and pH=8.0) containing different weights of albumin and was allowed to load for each hour and day at constant temperature (310K). After every 1hr and 24hr, they were removed from the water, blotted with filter paper to remove surface water, weighted and the albumin content ratio was calculated by using equation (1), and the same time absorbance the albumin concentration in buffer solutions was evaluated using UV- Spectrophotometer at λ_{max} 398.0 nm. The measurement was continued until a constant of disc content was repeated for each sample.

2.8 Drug (albumin) Release [104].

A loaded hydrogel disc was used in order to determine the amount of albumin released from the hydrogel network. After reaching the equilibrium state of the disc from through a constant of disc content in a buffer solution marinated in it. The loaded hydrogel disc was immersed in buffer solution at pH(pH=2.2 and pH=8.0)respectively at temperature (310K). The amount of albumin release was evaluated using UV-spectrophotometer at λ_{max} 398.0 nm each hour and day. The measurement of release continued until a stability absorbance was repeated for each sample.

CHAPTER THREE

Results & Discussion

3. RESULTS AND DISCUSSION

3.1 Preparation of modified resin

The modified resin was synthesized by the reaction of four moles of Fumaric acid with one mole of (pentarythritol) which had tetra hydroxyl, at 240 C^{o} for 60 Min. Figure (3-1) represents the equation of preparation the modified resin.

The negative test of $NaHCO_3$ solution proves that the prepared modified resins don't contain any un-reacted acid. Table (3-1) represents the physical properties of modified resin.

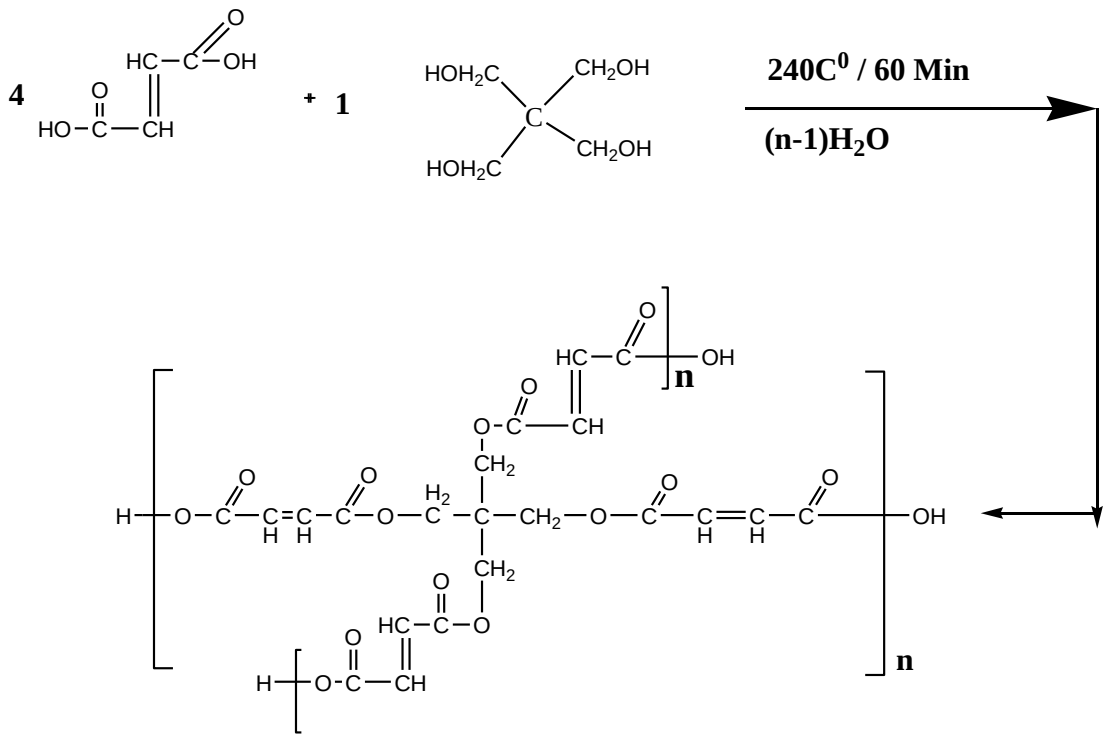

Figure (3-1): Preparation of the modified resin

Table (3-1): Physical properties of the modified resin after addition of acrylic acid monomer

Physical properties	Value
Molecular Weight ($\overline{Mn}$)	Around 1840 gm/mole
Solid content	57 %
Viscosity	21 poise
Gel time	12-16 min at $25C^0$
Acid Value	26
Density	1.3 (gm/cm^3)

This modified resin was diagnosed by FT-IR spectrophotometer and ^{1}HNMR spectrophotometer[105]; Figure(3-2), shows the appearance of a strong broad band at about 3338cm^{-1} for stretching carboxylic acid (-OH) with stretching (H-bond),it also shows a weak band at about 3100 cm^{-1} due to the =C-H olefin. The spectrum also showed a weak band at about 2887 cm^{-1} due to C-H aliphatic, and the spectrum also shows a strong band at about 1716cm^{-1} assigned to a stretching band C=O for ester group .It also shows a bands at about 1014 cm^{-1} assigned to C-O absorption band.

Figure(3-3) shows the spectrum of ^{1}HNMR [106]; which explain the singlet signal, at 13.24 ppm characteristic of proton in carboxylic acid group, furthermore the signals at 6.27-6. 46 ppm for two protons of methylene fumaric in the structure of polymer, the multiples at 4.24- 4.50 ppm of methyl protons, but the signal in 3.44- 3.62 ppm due to the proton of aliphatic alcohol, so this spectrum was confirmed the structure of our target polymer.

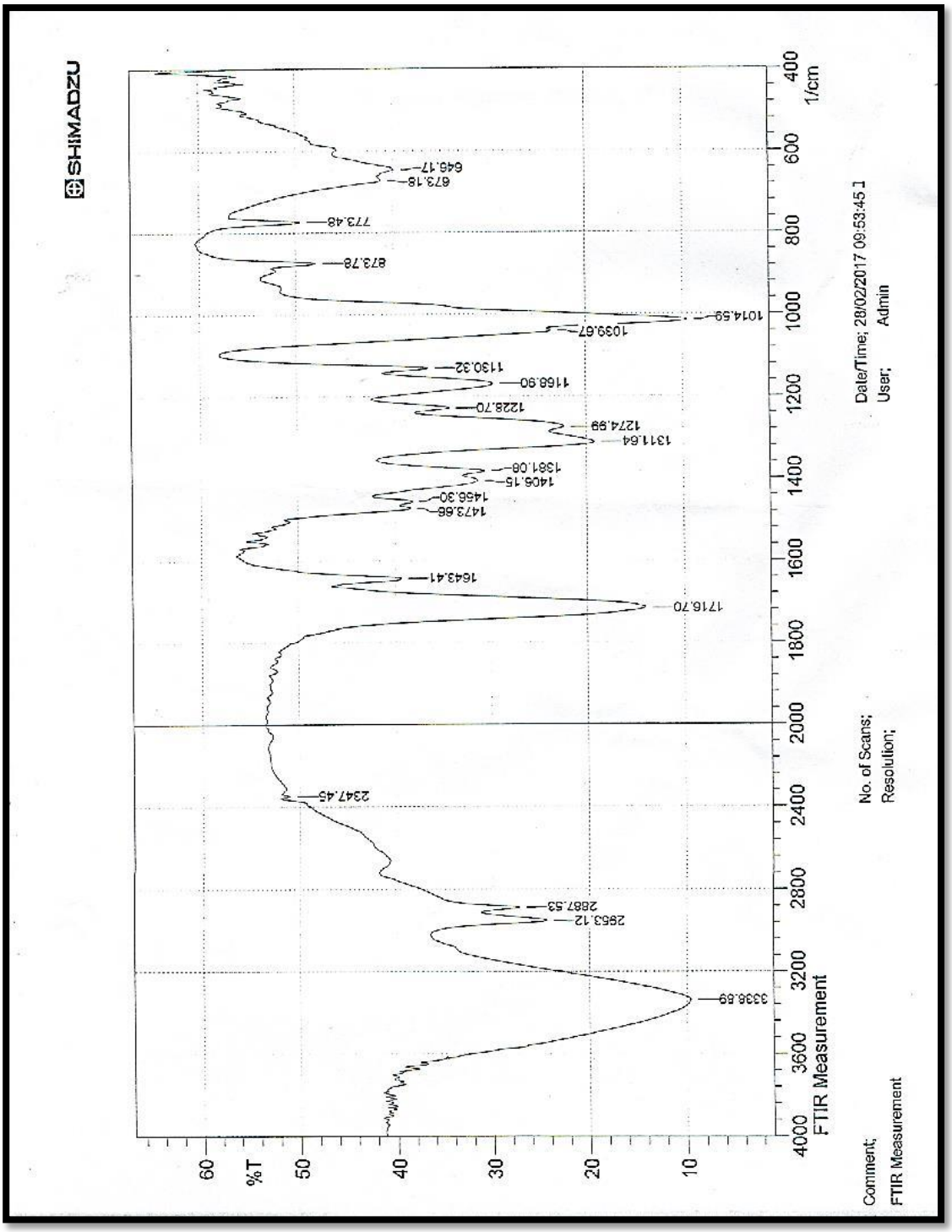

Figure (3-2): The FT-IR spectrum of the modified resin

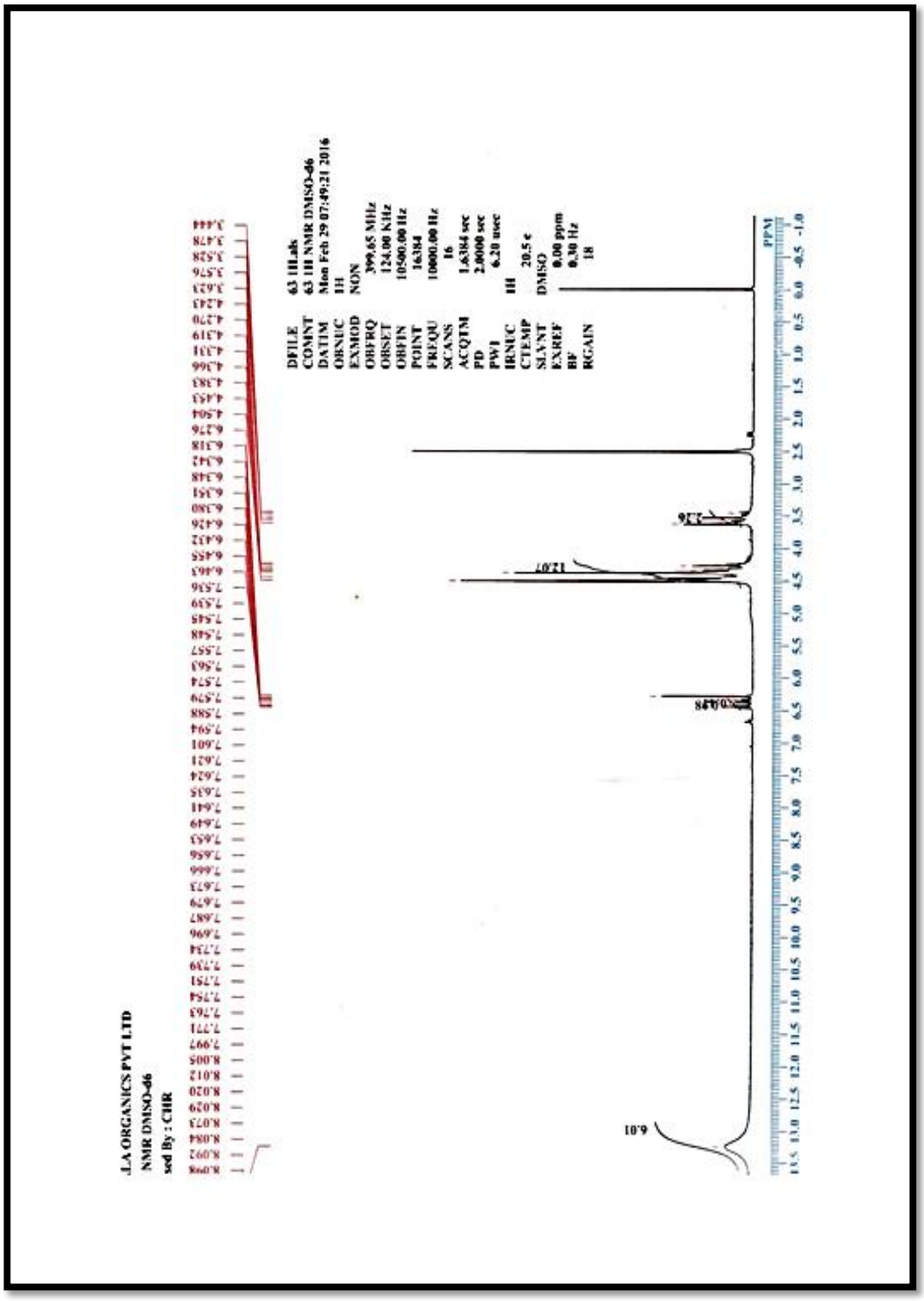

Figure (3-3): [1]HMNR spectrum of the modified resin

3.2 Swelling

A chemically cross-linked polymer is increasing its volume, Figure (3-4), numerous fold by absorbing great amount of solvent [107] .

The degree to which the volume increases depends on the degree to which the polymer "likes" the solvent and the degree of cross-linking. Solvents swell cross-linked polymer networks to a degree determined by both the solvent−polymer interactions and the polymer network structure [108].

According to the Flory−Rehner theory[109], the swellings degree is a balance between the entropy of the polymer and liquid mixing, the entropy change caused by reduction in the number chain of polymer conformations upon swelling, and the heat of mixing of the polymer and liquid.

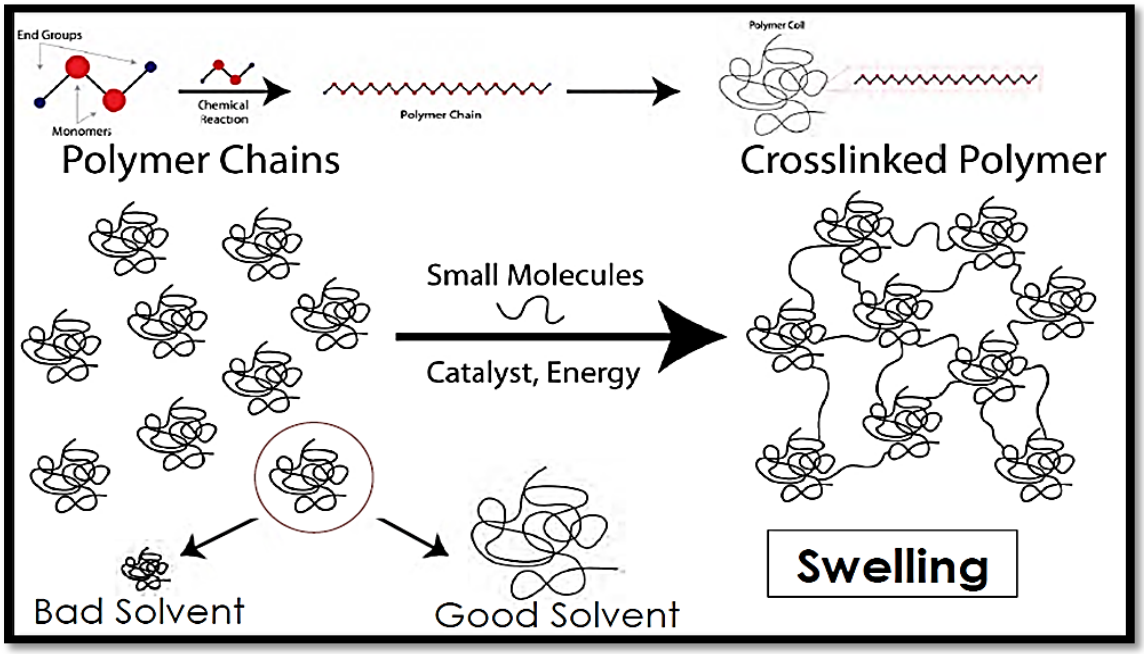

Figure (3-4): Represent of the swelling of the polymers

There are two types of swelling, limited swelling, when they are limited solubility of the polymer in solvents. When a solvent enters it, it does not dissolve it but instead swells it [110]. The chains are in an entangled and relaxed conformation between two network junctions. However, when the solvent enters the polymer, the liquid molecules move the network junctions away from each other (as the polymer swells in the solvent). As the network junctions move away, the polymeric chains do not separate completely from each other; figure (3-5) [111].

Thus, two phases are formed; one is separated from the solute in the swelling polymer and the other from the pure solute [112], and unlimited swelling. It is that process which leads to spontaneous dissolution .The liquids that possess a high to a certain polymer and known as good solvents to penetrate through the chain to give this type of swelling that led lastly to polymeric dissolution [113]. Several factors are controlled of polymers swelling, including the nature of the solvent, molecular weight of the polymer, the structural reformation, the number of links, the degree of the surrounding medium heat [114] .

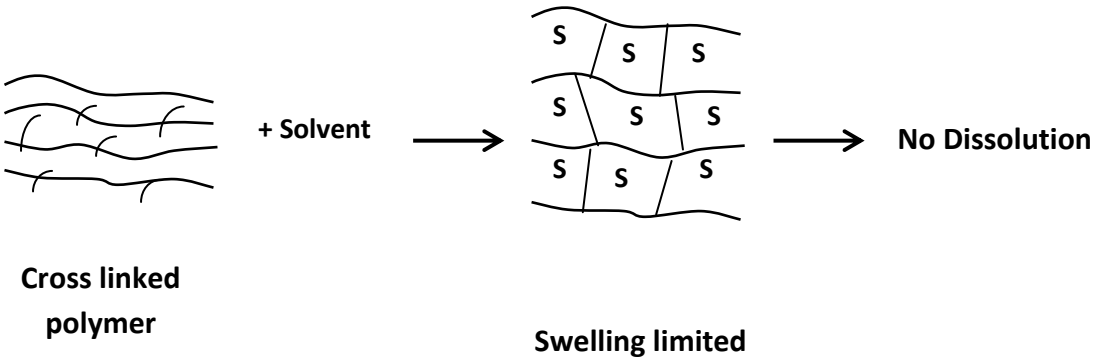

Figure (3-5): Swelling limited for certain polymers

3.2.1 Effect of Cross-linking on swelling

The cross-linking of linear polymers with a double bond monomer provides one or more points of connection between linear polymer chains to produce the polymer network. Thus, the cross-linking density of the polymeric network is equal to the number of chemical bonds between linear polymer chains in the polymer network [115]. The degree of elasticity of polymeric chains is significantly affected by the amount and the type of cross-link in the polymer network. Polymeric networks with large cross-linking with certain monomers have very little elasticity and are selective compared with the polymers that little cross-linking [116]. On the other hand, the polymeric chains with little cross-linking are characterized by less selective and therefore more flexible. The degree of cross-linking is very important in determining the behavior of swelling and expanding the polymer network [117]. Thus, when increasing the concentration of cross-linking in polymer chains, this leads to a decrease in swelling, ie, a decrease in a ability of water absorption, The reason is the decrease in available free space between polymer chains, This is due to the increased density of the polymeric network resulting from the increase of cross-linked in the polymer network, which weakens its ability to absorb water and swelling [118].

In this work, three moles of acrylic acid monomer (0.5, 1.0 and 1.5 mole) were added respectively to form three polymers that vary in their degree of cross-linking, thus increasing the cross-linking density by increasing the number of added monomers. But because of containment acrylic acid on a free hydroxyl group, it a hydrophilic site to bind water molecules, thus increasing swelling [116].

3.2.2 **Swelling in the buffer solution**

The swelling curves of modified resin showed a plot of buffer solution content for different compositions against swelling time (hour and day). The initial swelling rate was medium, the maximum being reached within the first few hours of the swelling. The shape of the swelling curves indicated that water–soluble molecules were being released from the xerogel (dried) upon swelling. The thicker discs required a longer time to attain maximum equilibrium [119].

The increase of buffer solution content (%) with increasing time is an indication that, polymeric network's ability to absorb solution significantly hampered due to the presence of cross linking in the hydrogel which depends largely on the surrounding medium acidic, where in the medium of a high pH becomes acidic ionic aggregates more gradually [120].

It has been observed that the time required for the swelling of the hydrogel decreases with the increase in the density of the cross linking network's and also has noted that the speed of the swelling of hydrogel increase dramatically in the solution with a high pH compared with the solution with a low pH; For this reason, we found that the solution be further swelled when the pH=8 and that because of increased hydrophilicity and the resulting increase hydrophilic groups so the hydrogel become because of his ability to absorb solution in large quantities and gives swelled bigger, this corresponds with the findings of earlier research [121] .

In this work the thickness of the dry discs was exactly 3.0 mm and the diameter of the dry discs was exactly 10.0 mm and the weighted of the

xerogel(dry) discs was exactly 0.4 gm of all samples were used in the swelling study.

A plot of solvent content versus time showed the curves of modified resin for three different numbers of moles from acrylic acid compositions ranging from 0.5, 1.0 and 1.5 mole, against swelling time (1,2,3,4 and 5 hours and 1,2,3,4 and 5 days) at constant temperature (310 K) , as shown in Tables (3-2) to (3-4) and Figures (3-6) to (3- 11) respectively.

Table (3-2): Swelling Ratio (%) of modified resin with different number of moles of acrylic acid monomer per time(hour and day) at pH= 2.2, Temp.=310 K

Time (hour)	**Swelling Ratio (%)**		
	No. moles of acrylic acid monomer		
	0.5 mole	**1.0 mole**	**1.5 mole**
1	4.0077	4.1227	4.2375
2	4.0307	4.1457	4.2604
3	4.0537	4.1689	4.2833
4	4.0767	4.1916	4.3062
5	4.0997	4.2146	4.3291
(day)			
1	5.0107	5.1233	5.2357
2	5.0332	5.1459	5.2582
3	5.0558	5.1683	5.2806
4	5.0783	5.1908	5.3030
5	5.1008	5.2133	5.3254

Table (3-3): Swelling Ratio (%) of modified resin with different number of moles of with acrylic acid monomer per time (hour and day) at pH=7.0, Temp.=310 K

Time (hour)	Swelling Ratio (%)		
	No .of moles of acrylic acid monomer		
	0.5 mole	1mole	1.5 mole
1	6.0150	6.2353	6.4546
2	6.0592	6.2793	6.4984
3	6.1032	6.3232	6.5421
4	6.1473	6.3670	6.5857
5	6.1914	6.4109	6.6293
(day)			
1	7.0199	7.1926	7.4074
2	7.0632	7.2357	7.4503
3	7.1064	7.2786	7.4931
4	7.1495	7.3216	7.5358
5	7.1710	7.3645	7.5786

Table (3-4): Swelling Ratio (%) of modified resin with different number of moles of acrylic acid monomer per time(hour and day) at pH =8.0, Temp.=310K

Time (hour)	Swelling Ratio(%)		
	No. moles of acrylic acid monomer		
	0.5 mole	1.0 mole	1.5 moles
1	8.0882	8.1937	8.2989
2	8.1093	8.2148	8.3199
3	8.1305	8.2358	8.3409
4	8.1515	8.2569	8.3619
5	8.1726	8.2779	8.3829
(day)			
1	9.0909	9.1941	9.2971
2	9.1116	9.2147	9.3177
3	9.1322	9.2353	9.3382
4	9.1529	9.2559	9.3587
5	9.1735	9.2765	9.3792

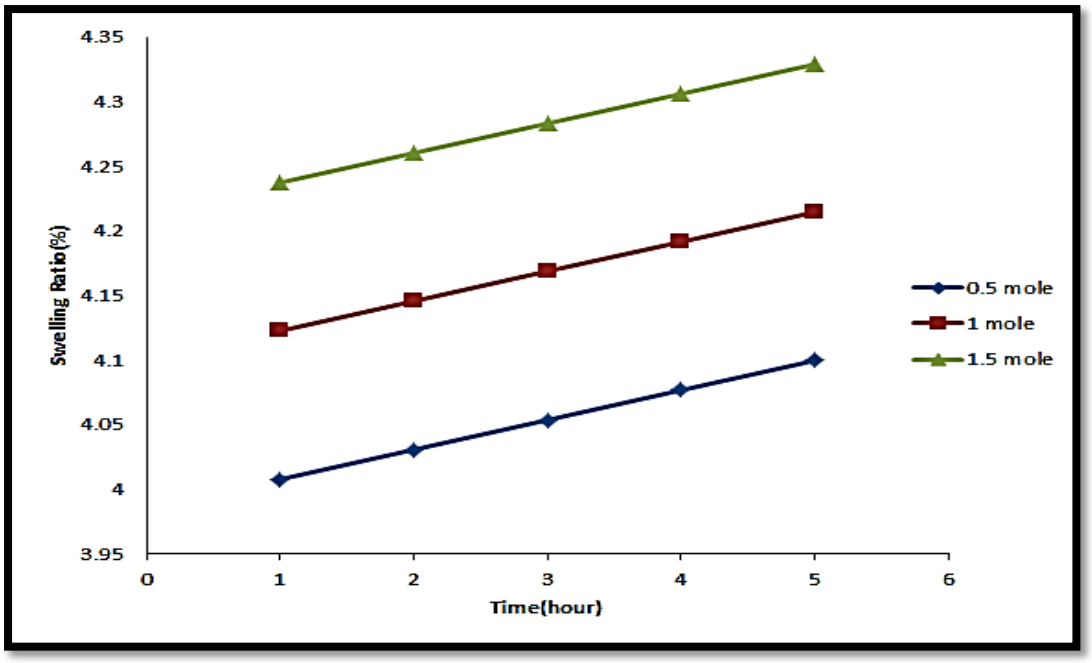

Figure (3-6): Swelling Ratio (%) curves and time(hour), of modified resin containing different number of moles of acrylic acid monomer at pH=2.2, Temp.=310K

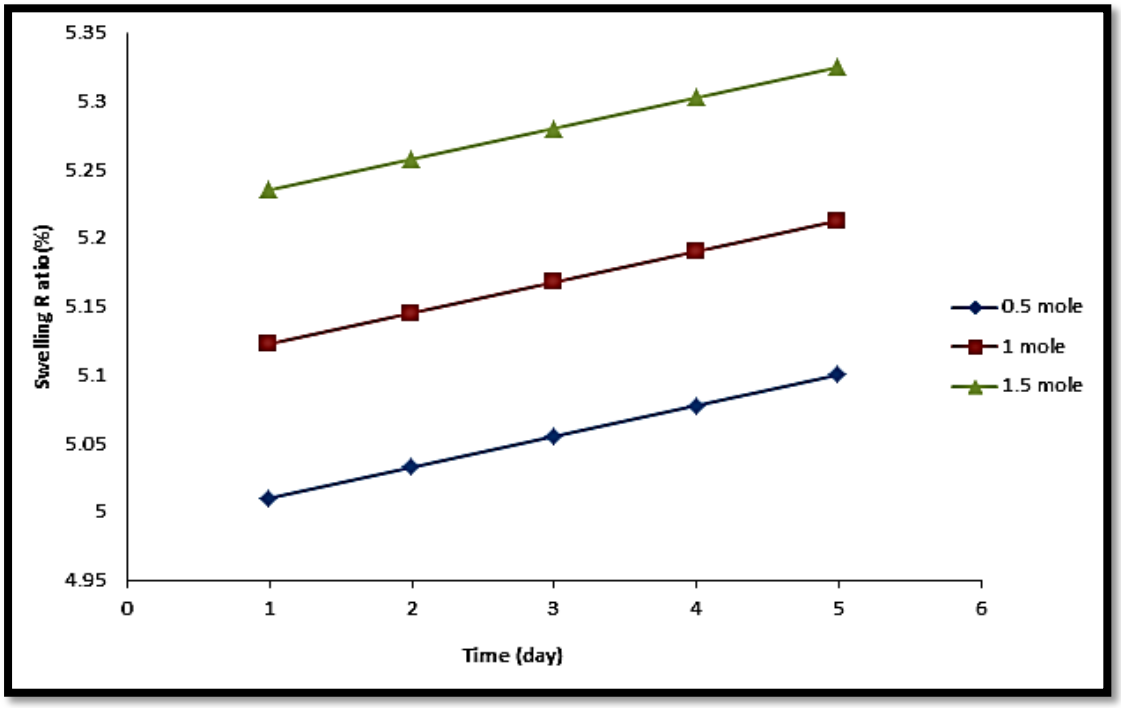

Figure (3-7): Swelling Ratio (%) curves and time (day),of modified resin containing different number of moles of acrylic acid monomer at PH=2.2, Temp.=310K

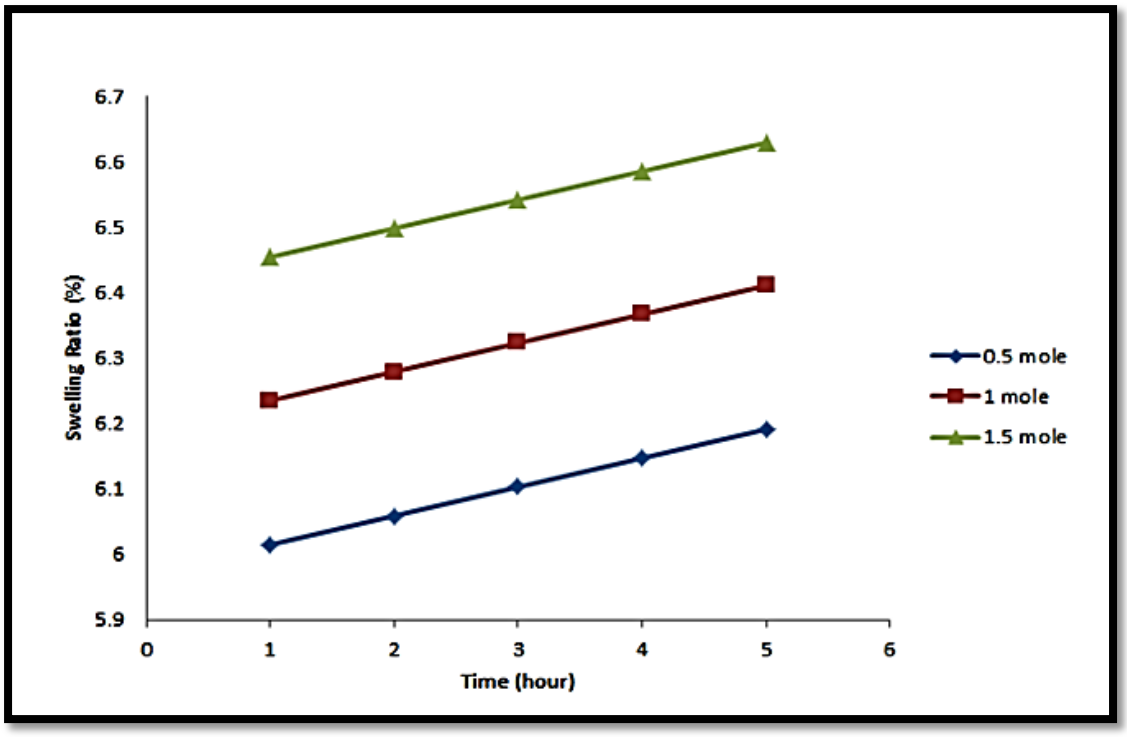

Figure (3-8): Swelling Ratio (%) curves and time(hour), of modified resin containing different number of moles of acrylic acid monomer at PH=7.0,Temp.=310K

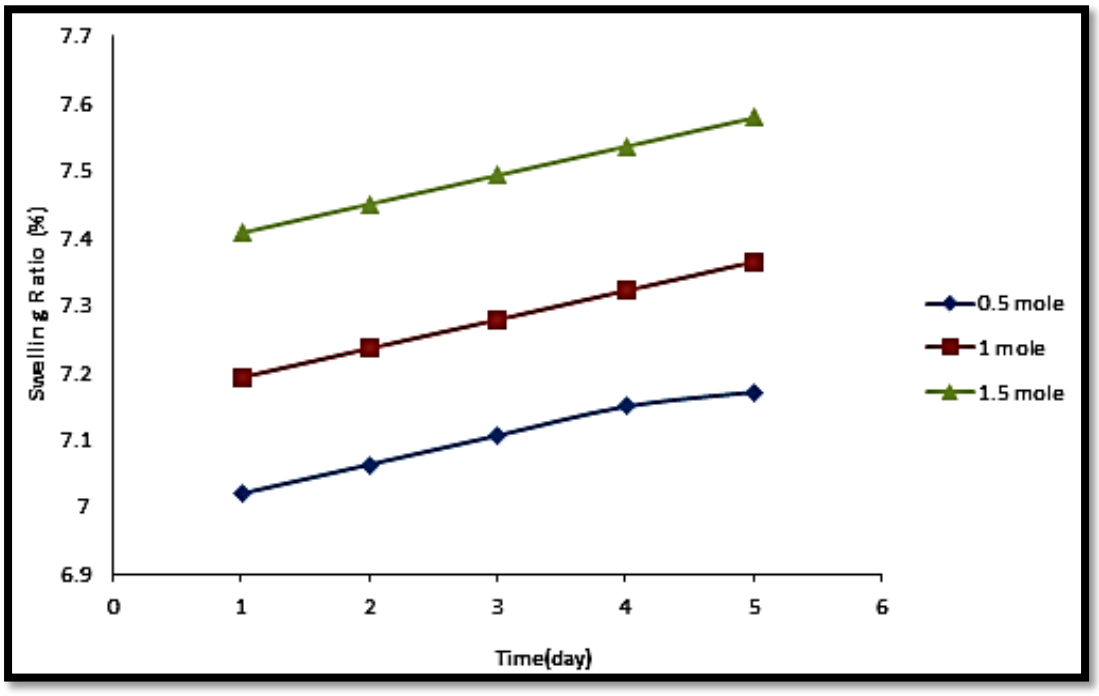

Figure (3-9): Swelling Ratio (%) curves and time(day), of modified resin containing different number of moles of acrylic acid monomer at pH=7.0, Temp.=310K

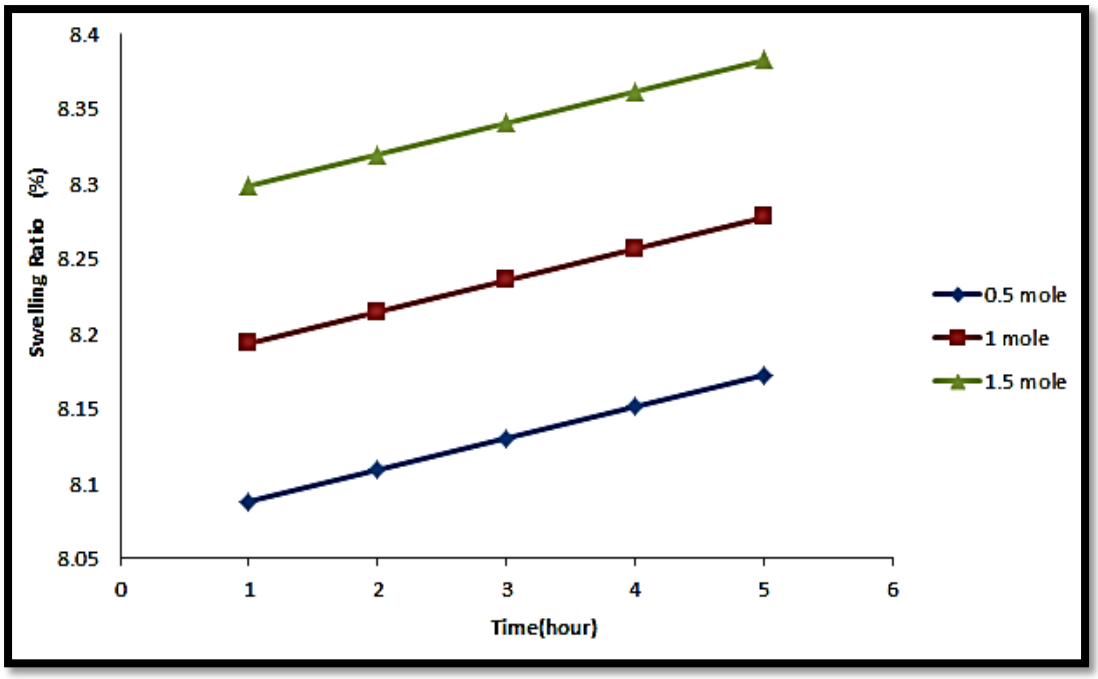

Figure (3-10): Swelling Ratio (%) curves and time(hour), of modified resin containing different number of moles of acrylic acid monomer at pH=8.0, Temp.=310K

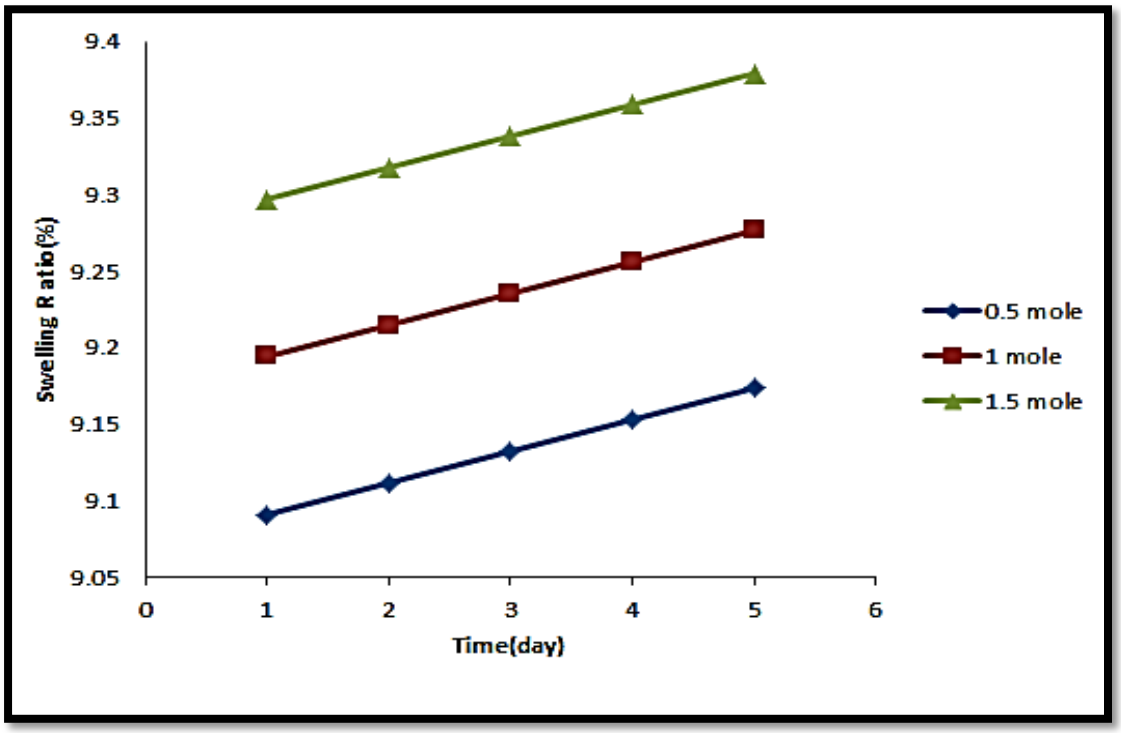

Figure (3-11): Swelling Ratio (%) curves and time(day)of modified resin containing different number of moles of acrylic acid monomer at pH=8.0, Temp. =310K

3.3 Loaded the protein

A plot of albumin content (%) versus time showed the curves of modified resin for three different numbers of moles from acrylic acid compositions ranging from 0.5, 1.0 and 1.5 mole, against loaded time (hour and day) at constant temperature (310 K) .As shown in Tables (3-5) to (3-7) and Figures (3-12) to (3-23) respectively for pH= 8.0 ,and as shown in Tables (3-8) to (3-10) and Figures (3-24) to (3-35) respectively for pH=2.2, by using UV-Spectrophotometer and measuring the absorbance of the solutions. It is possible to observe that the protein loading in the base medium reaches the equilibrium state after five hours of immersion of the sample in the base solution, but after 24 hours we notice an increase in protein loading until it reaches the equilibrium state after five days of immersion in the solution, But in the acid medium, the protein load reaches the equilibrium state after a three hours in a maximum, but after 24 hours the load increases until it reaches equilibrium after a maximum of three days. From this we conclude that loading in the basic medium is more efficient than loading in the acid medium.

Table (3-5): Albumin content (%) and absorption of solution (Abs.) per time (hour and day) of modified resin containing 0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Time (hour)	**Concentration of albumin**									
	0.025		**0.075**		**0.125**		**0.175**		**0.225**	
	%	**Abs.**	**%**	**Abs.**	**%**	**Abs.**	**%**	**Abs.**	**%**	**Abs.**
1	9.77	0.444	11.99	0.488	13.98	0.528	15.97	0.569	17.42	0.601
2	11.78	0.425	13.90	0.466	15.88	0.509	17.98	0.548	19.63	0.580
3	13.46	0.408	15.56	0.449	17.71	0.488	19.98	0.529	21.80	0.561
4	15.29	0.388	17.27	0.429	19.31	0.460	21.55	0.509	23.88	0.541
5	15.29	0.388	17.27	0.429	19.31	0.460	21.55	0.509	23.88	0.541
(day)										
1	16.46	0.361	19.63	0.409	22.57	0.455	25.46	0.488	26.38	0.480
2	18.35	0.340	21.55	0.388	24.51	0.430	27.26	0.468	28.56	0.460
3	20.67	0.321	23.72	0.369	26.52	0.411	29.13	0.449	30.50	0.440
4	22.24	0.309	25.62	0.348	28.56	0.391	31.11	0.429	32.83	0.420
5	22.24	0.309	25.62	0.348	28.56	0.391	31.11	0.429	32.83	0.420

Table (3-6): Albumin content (%) and absorption of solution (Abs.) per time (hour and day) of modified resin containing 1.0 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Time	**Concentration of albumin**									
(hour)	**0.025**		**0.075**		**0.125**		**0.175**		**0.225**	
	%	**Abs.**	**%**	**Abs.**	**%**	**Abs.**	**%**	**Abs.**	**%**	**Abs.**
1	10.43	0.431	13.02	0.477	15.68	0.518	17.98	0.559	19.45	0.592
2	12.82	0.411	15.16	0.458	17.61	0.499	19.98	0.538	21.55	0.571
3	14.68	0.391	17.24	0.439	19.63	0.478	21.91	0.519	23.72	0.550
4	16.58	0.379	19.21	0.419	21.55	0.458	23.55	0.499	25.91	0.531
5	16.58	0.379	19.21	0.419	21.55	0.458	23.55	0.499	25.91	0.531
(day)										
1	17.24	0.355	20.79	0.399	23.88	0.438	26.82	0.477	28.56	0.470
2	19.09	0.339	22.70	0.377	25.91	0.419	28.85	0.459	30.91	0.450
3	21.04	0.319	24.51	0.356	27.99	0.399	30.76	0.439	32.83	0.430
4	23.02	0.299	26.09	0.339	29.57	0.377	32.22	0.418	34.90	0.410
5	23.02	0.299	26.09	0.339	29.57	0.377	32.22	0.418	34.90	0.410

Table (3-7): Albumin content (%) and absorption of solution (Abs.) per time (hour and day) of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Time	**Concentration of albumin**									
(hour)	**0.025**		**0.075**		**0.125**		**0.175**		**0.225**	
	%	**Abs.**	**%**	**Abs.**	**%**	**Abs.**	**%**	**Abs.**	**%**	**Abs.**
1	12.40	0.411	15.00	0.457	17.04	0.499	19.45	0.536	21.61	0.571
2	14.48	0.395	17.13	0.438	19.27	0.477	21.38	0.519	23.56	0.551
3	16.27	0.373	19.09	0.419	21.10	0.459	23.43	0.499	25.76	0.531
4	18.22	0.355	21.03	0.399	23.06	0.439	25.46	0.479	27.85	0.512
5	18.22	0.355	21.03	0.399	23.06	0.439	25.46	0.479	27.85	0.512
(day)										
1	19.09	0.329	22.07	0.369	24.84	0.409	27.71	0.449	30.95	0.453
2	21.04	0.309	24.04	0.349	26.67	0.388	29.54	0.429	32.95	0.434
3	23.06	0.288	26.12	0.329	28.56	0.369	31.48	0.409	34.99	0.416
4	25.16	0.266	28.15	0.309	30.53	0.349	33.33	0.389	36.95	0.397
5	25.16	0.266	28.15	0.309	30.53	0.349	33.33	0.389	36.95	0.397

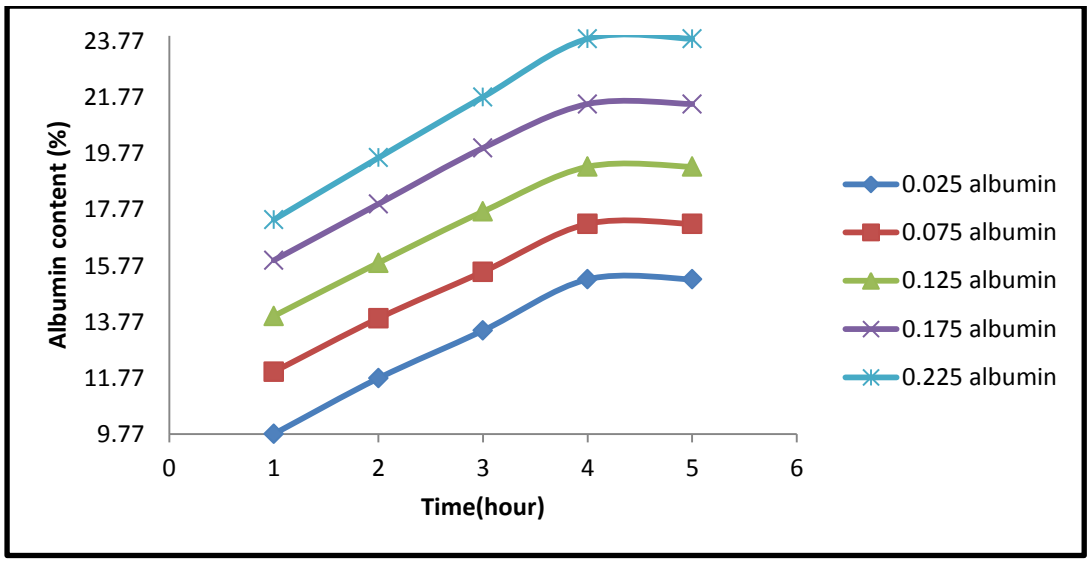

Figure (3-12): Albumin content (%) curves and time (hour), of modified resin containing0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

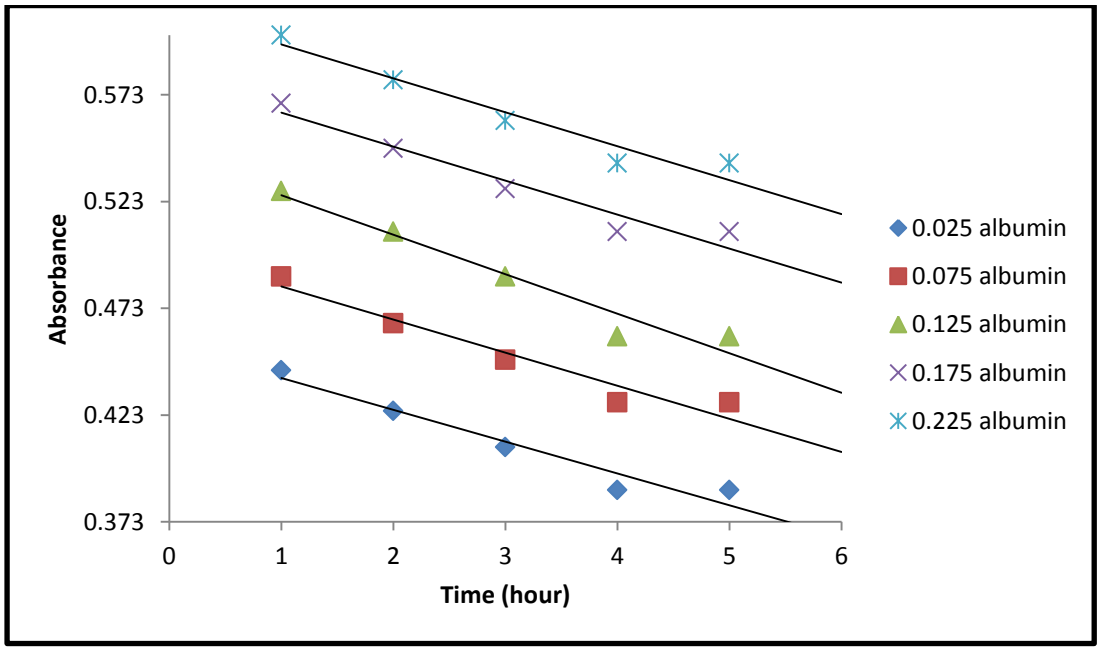

Figure (3-13): Absorbance (Abs.) curves and time (hour), of modified resin containing 0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

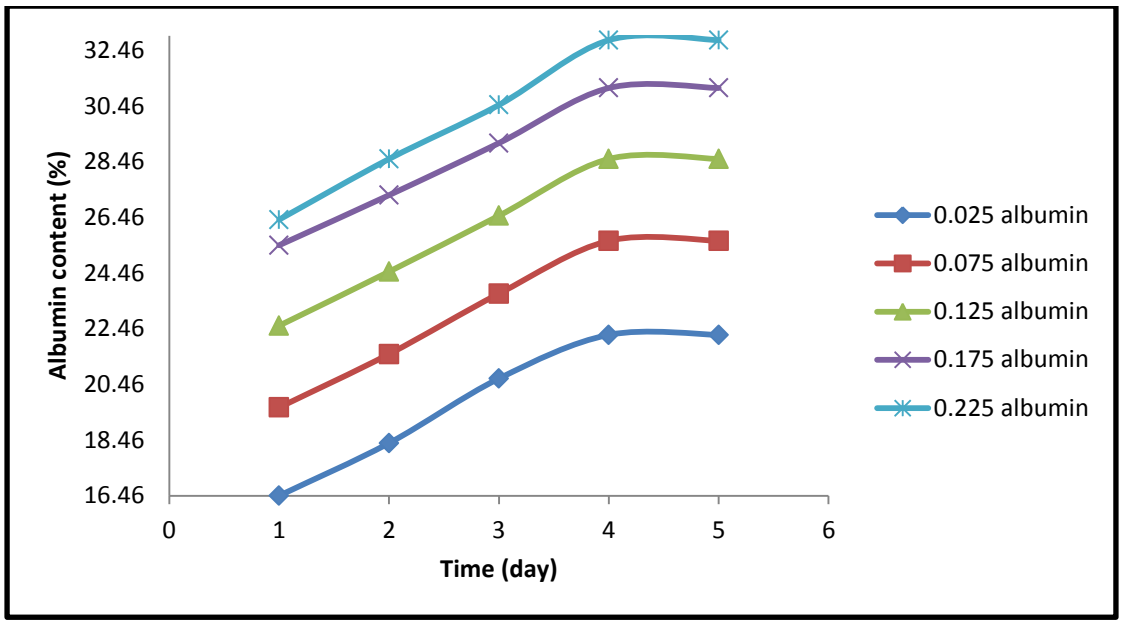

Figure (3-14): Albumin content (%) curves and time (day), of modified resin containing 0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

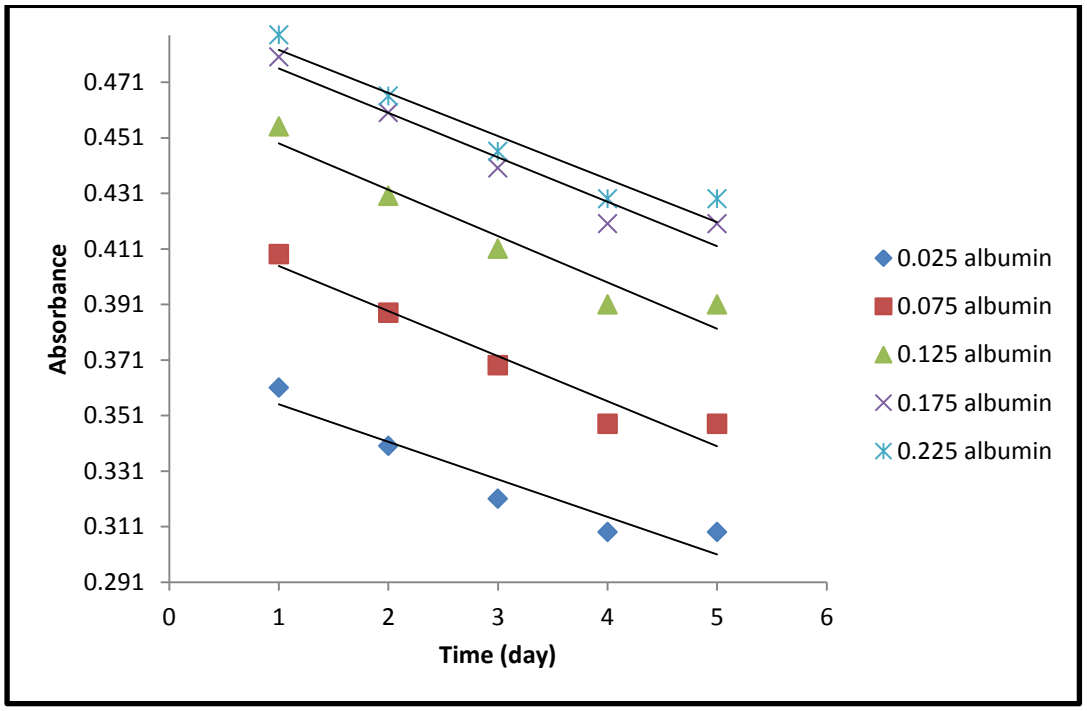

Figure (3-15): Absorbance (Abs.) curves and time (day), of modified resin containing 0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

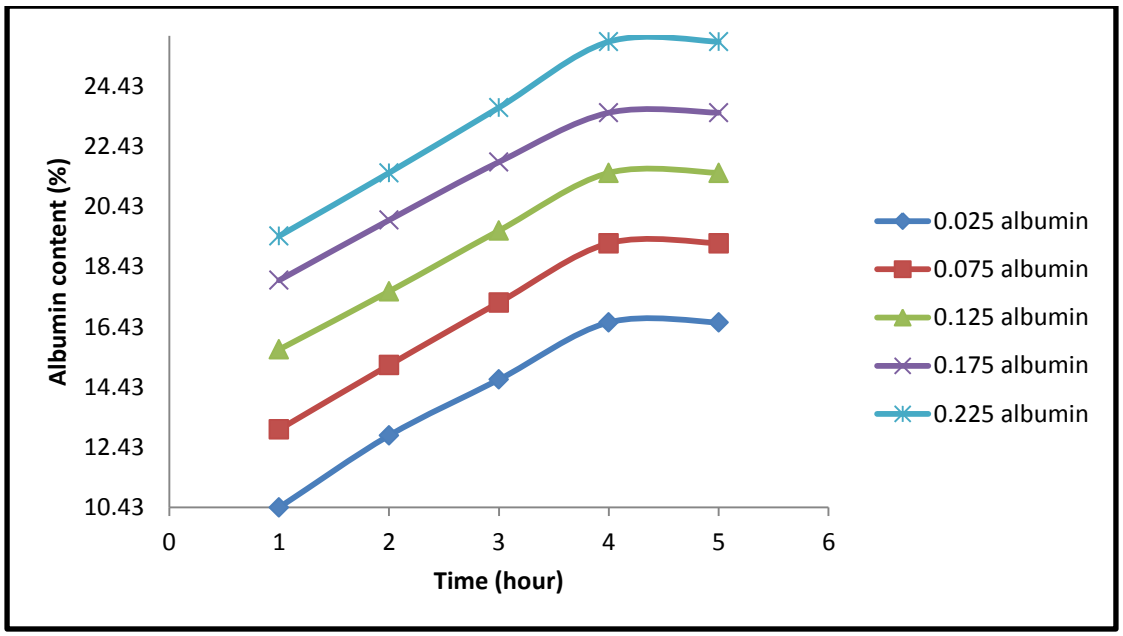

Figure (3- 16): Albumin content (%) curves and time (hour), of modified resin containing 1.0 mole of acrylic acid monomer at pH=8.0, Temp.=310K

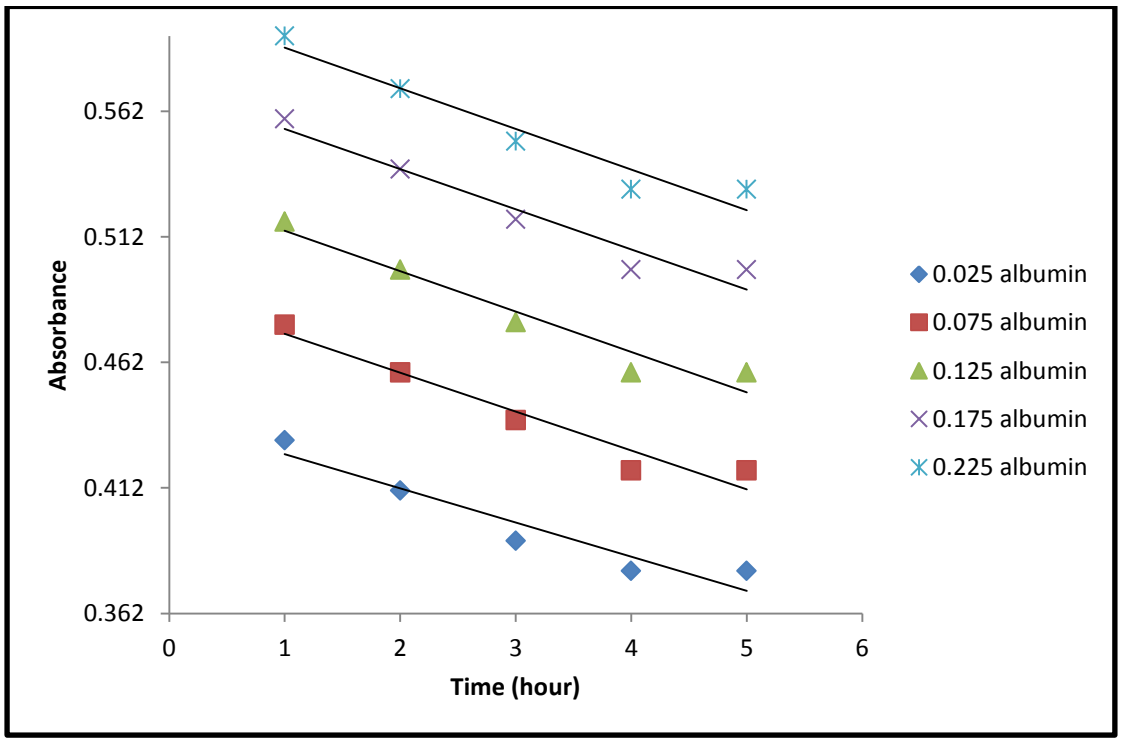

Figure (3- 17): Absorbance (Abs.) curves and time (hour), of modified resin containing 1.0 mole of acrylic acid monomer at pH=8.0, Temp.=310K

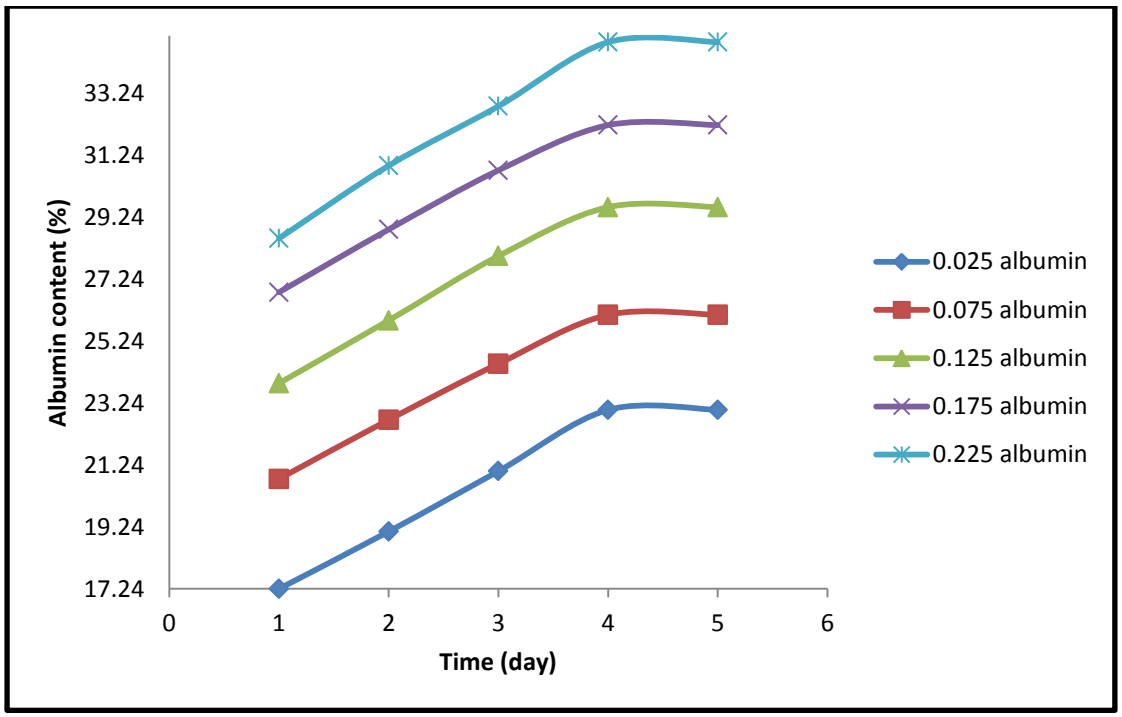

Figure (3-18): Albumin content (%) curves and time (day), of modified resin containing 1.0 mole of acrylic acid monomer at pH=8.0, Temp.=310K

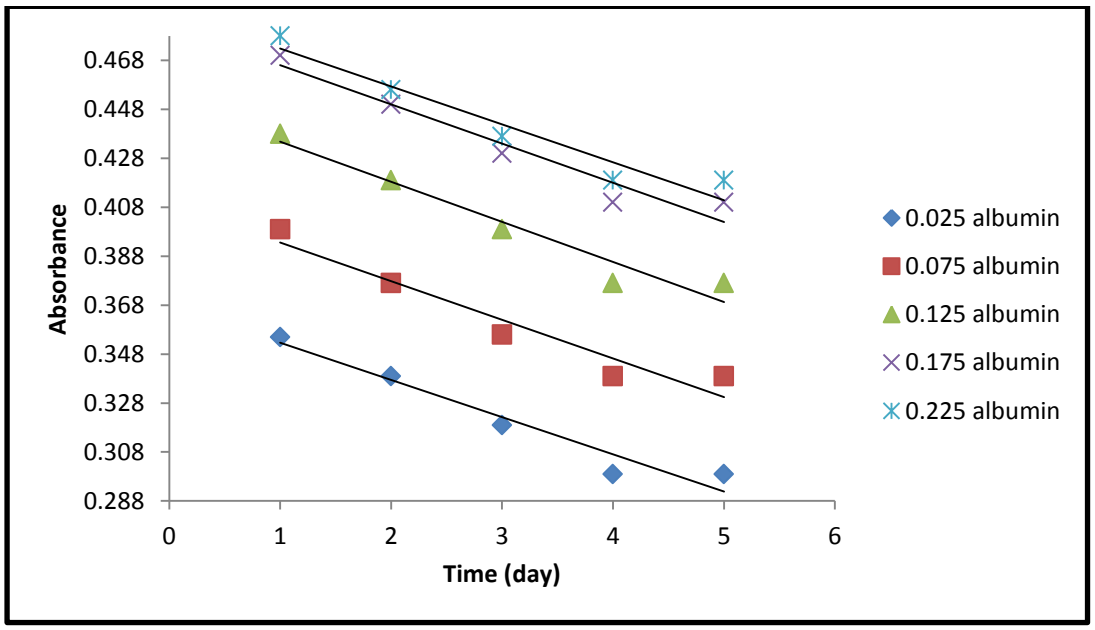

Figure (3- 19): Absorbance (Abs.) curves and time (day), of modified resin containing 1.0 mole of acrylic acid monomer at pH=8.0, Temp.=310K

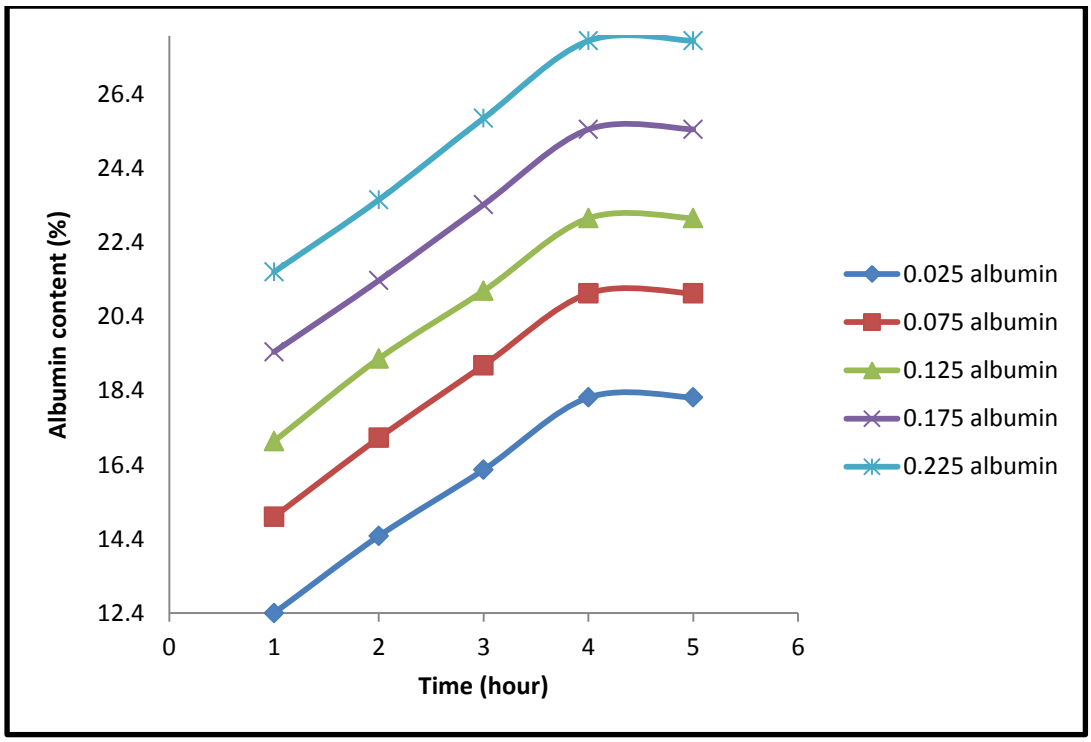

Figure (3-20): Albumin content (%) curves and time (hour), of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

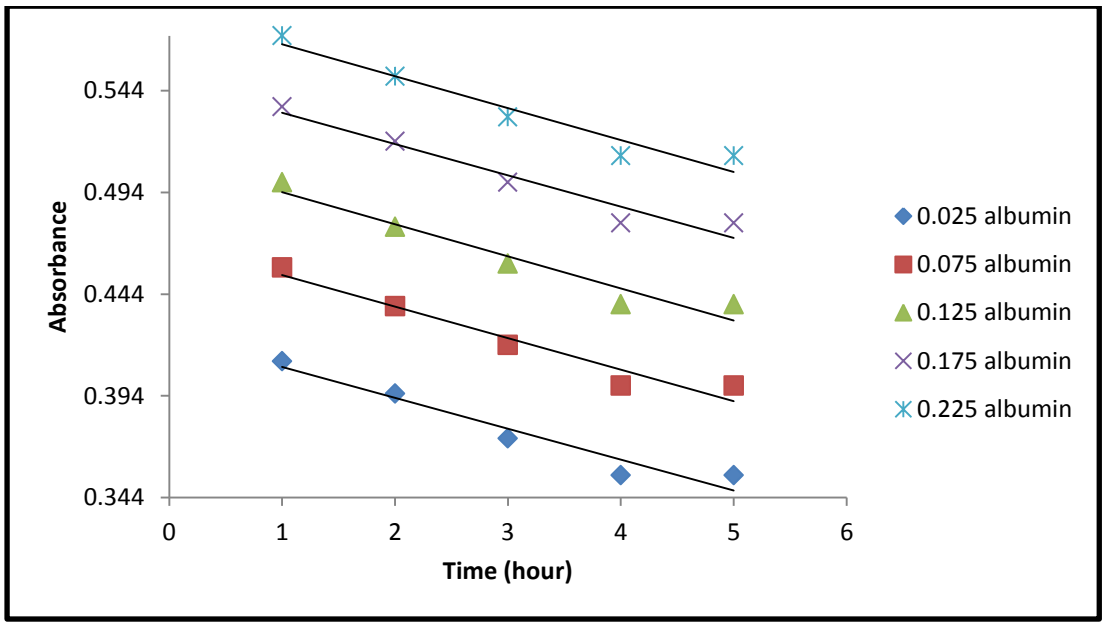

Figure (3-21): Absorbance (Abs.) curves and time (hour), of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

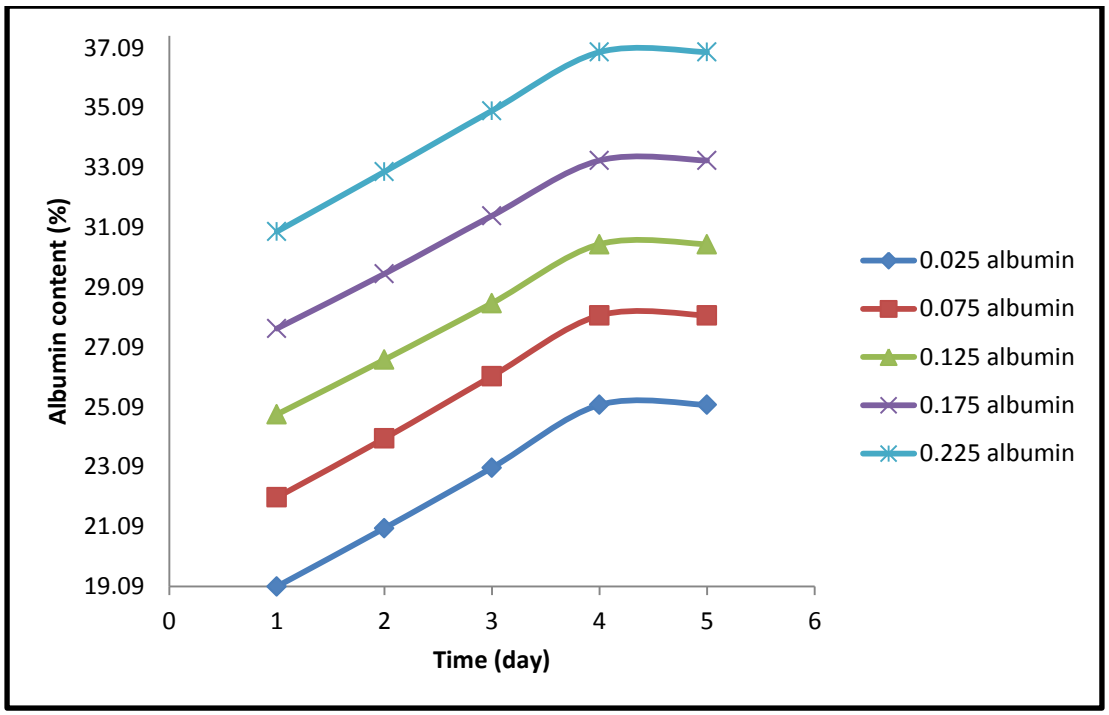

Figure (3-22): Albumin content (%) curves and time (day), of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

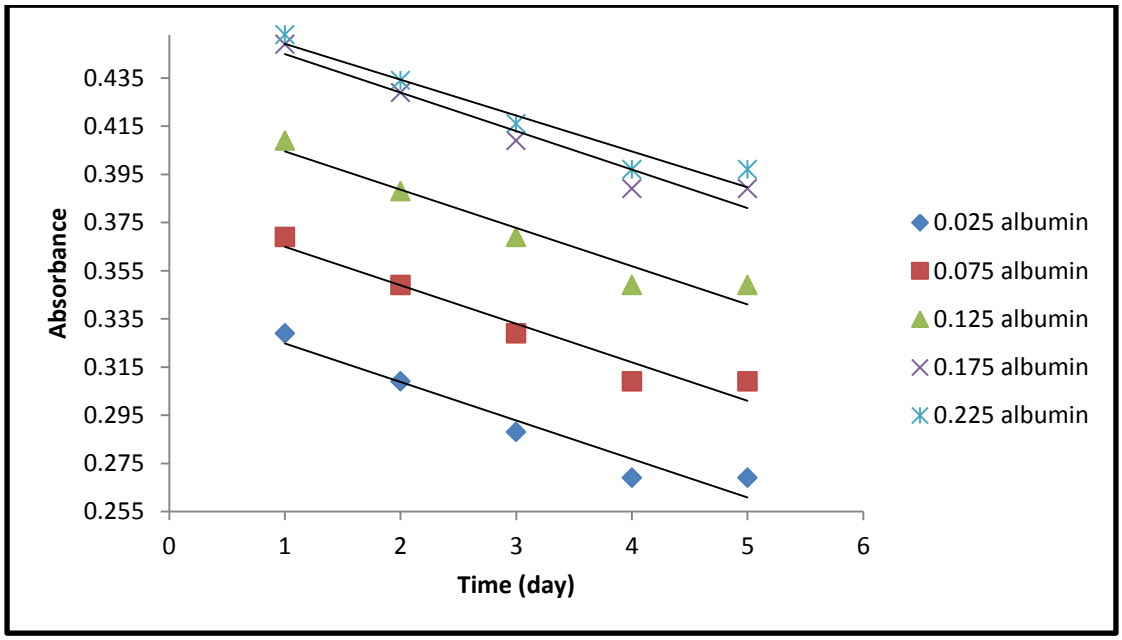

Figure (3-23): Absorbance (Abs.) curves and time (day), of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Table (3-8): Albumin content (%) and absorption of solution (Abs.) per time (hour and day) of modified resin containing 0.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

Time	**Concentration of albumin**									
(hour)	**0.025**		**0.075**		**0.125**		**0.175**		**0.225**	
	%	**Abs.**	**%**	**Abs.**	**%**	**Abs.**	**%**	**Abs.**	**%**	**Abs.**
1	5.10	0.500	7.06	0.549	9.20	0.589	11.45	0.629	13.66	0.660
2	7.41	0.488	9.32	0.528	11.50	0.569	13.05	0.609	15.29	0.641
3	7.41	0.488	9.32	0.528	11.50	0.569	13.05	0.609	15.29	0.641
(day)										
1	8.05	0.459	10.11	0.506	12.47	0.549	14.73	0.588	18.62	0.592
2	10.21	0.439	12.09	0.489	14.35	0.529	16.22	0.569	20.87	0.572
3	10.21	0.439	12.09	0.489	14.35	0.529	16.22	0.569	20.87	0.572

Table (3-9): Albumin content (%) and absorption of solution (Abs.) per time(hour and day) of modified resin containing 1.0 mole of acrylic acid monomer at pH=2.2, Temp.=310K

Time	**Concentration of albumin**									
(hour)	**0.025**		**0.075**		**0.125**		**0.175**		**0.225**	
	%	**Abs.**	**%**	**Abs.**	**%**	**Abs.**	**%**	**Abs.**	**%**	**Abs.**
1	6.01	0.493	8.20	0.538	10.21	0.578	12.61	0.619	14.27	0.652
2	8.15	0.479	10.21	0.517	12.40	0.559	14.66	0.599	16.92	0.630
3	8.15	0.479	10.21	0.517	12.40	0.559	14.66	0.599	16.92	0.630
(day)										
1	9.07	0.441	11.54	0.488	13.51	0.529	15.68	0.569	19.27	0.573
2	11.09	0.425	13.46	0.468	15.68	0.509	17.55	0.549	21.55	0.556
3	11.09	0.425	13.46	0.468	15.68	0.509	17.55	0.549	21.55	0.556

Table (3-10): Albumin content (%) and absorption of solution (Abs.) per time(hour and day) of modified resin containing 1.5mole of acrylic acid monomer at pH=2.2, Temp.=310K

Time (hour)	Concentration of albumin									
	0.025		0.075		0.125		0.175		0.225	
	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.
1	8.15	0.471	10.21	0.519	12.1 8	0.559	14.27	0.599	16.65	0.631
2	10.21	0.455	12.18	0.499	14.07	0.539	16.02	0.579	18.73	0.612
3	10.21	0.455	12.18	0.499	14.07	0.539	16.02	0.579	18.73	0.612
(day)										
1	11.09	0.426	13.66	0.469	15.97	0.509	17.95	0.544	21.80	0.550
2	13.02	0.409	15.88	0.449	17.91	0.488	19.77	0.523	23.88	0.530
3	13.02	0.409	15.88	0.449	17.91	0.488	19.77	0.523	23.88	0.530

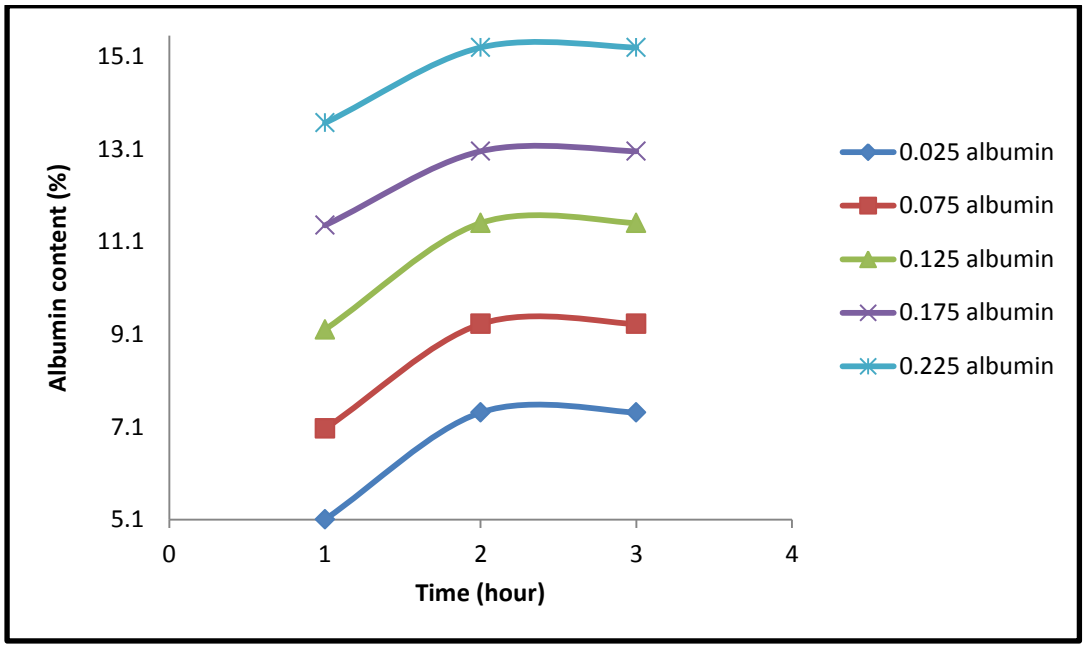

Figure (3-24): Albumin content (%) curves and time (hour), of modified resin containing 0.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

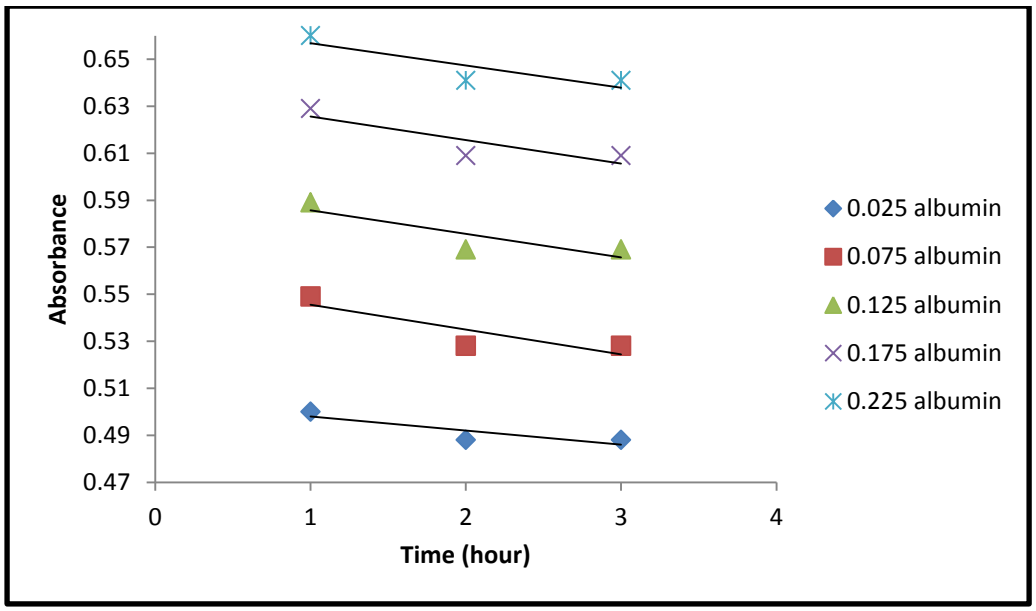

Figure (3-25): Absorbance (Abs.) curves and time (hour), of modified resin containing 0.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

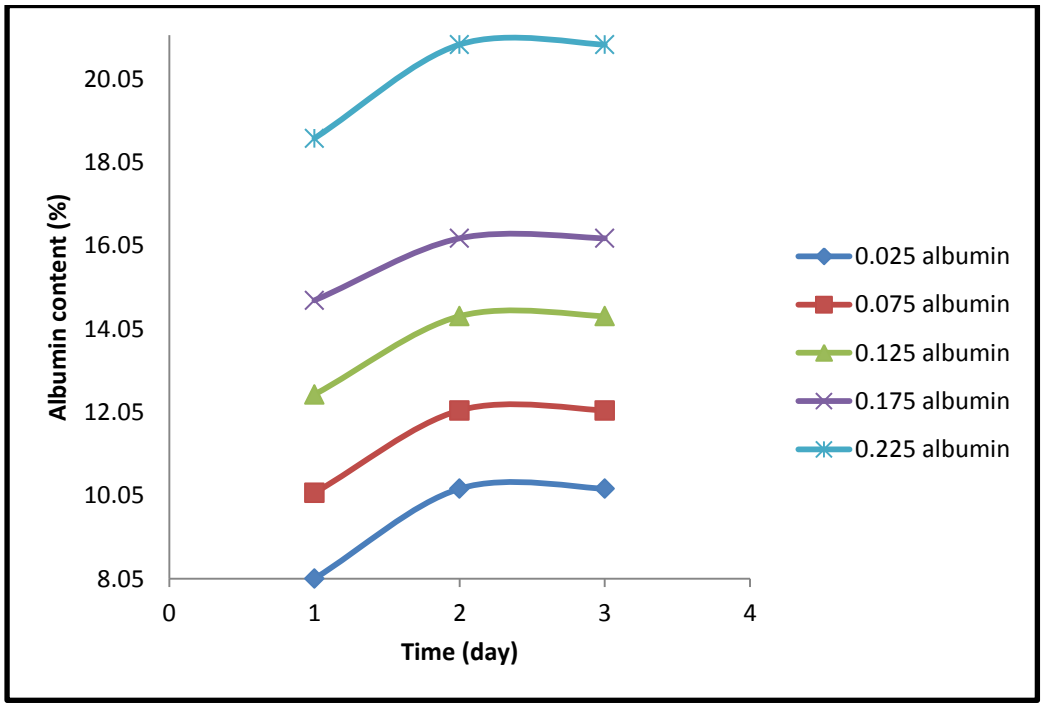

Figure (3-26): Albumin content (%) curves and time (day), of modified resin containing 0.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

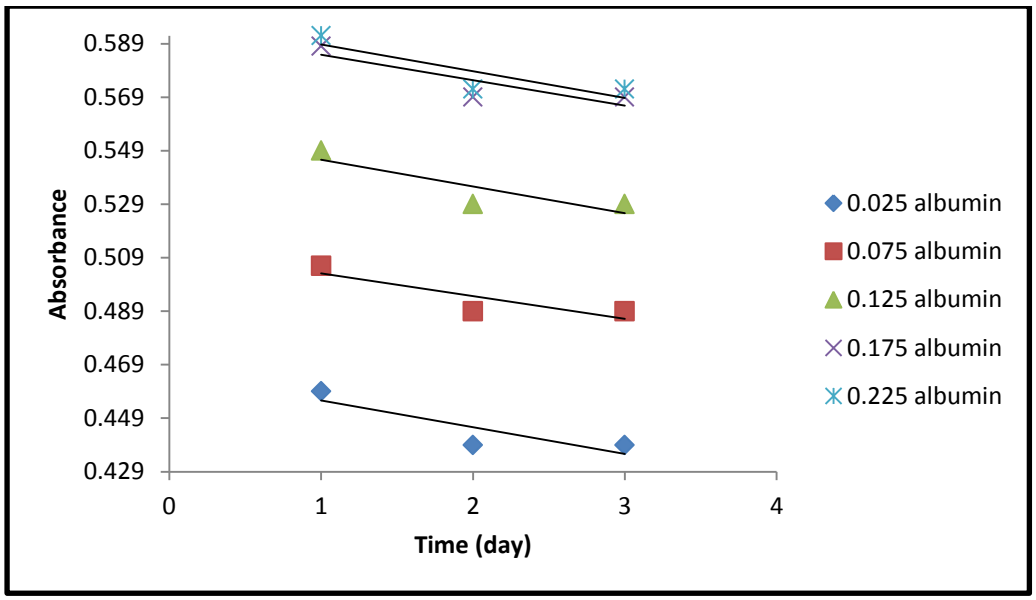

Figure (3-27): Absorbance (Abs.) curves and time (day), of modified resin containing 0.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

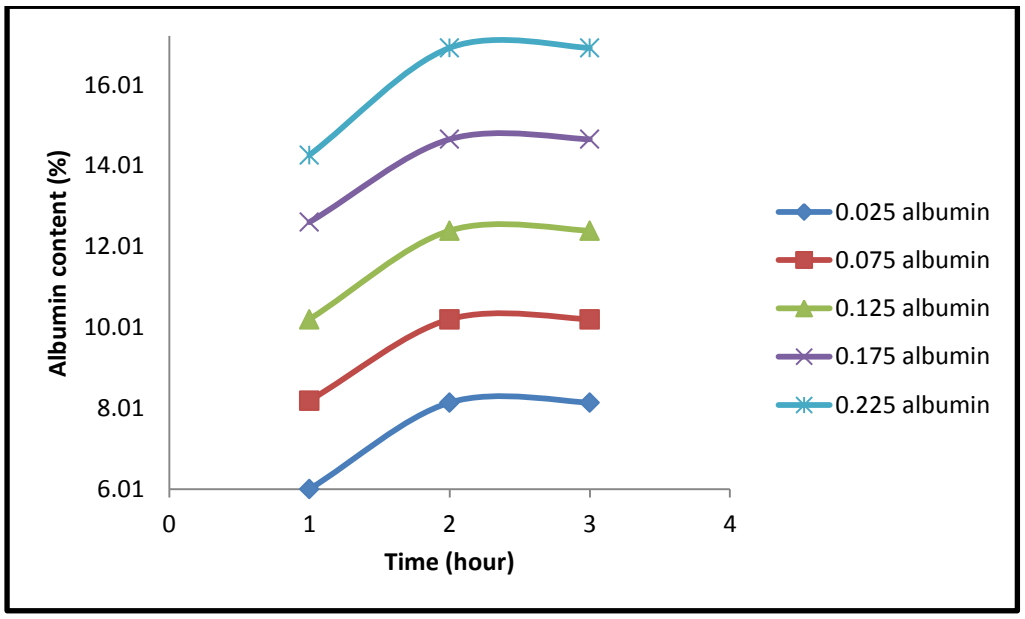

Figure (3-28): Albumin content (%) curves and time (hour), of modified resin containing 1.0 mole of acrylic acid monomer at pH=2.2, Temp.=310K

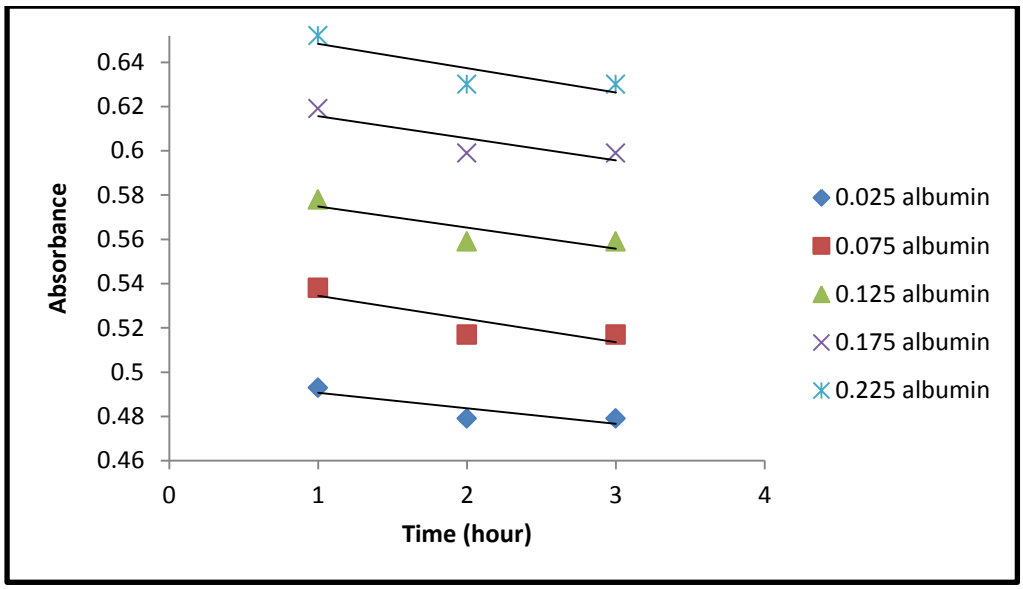

Figure (3-29): Absorbance (Abs.) curves and time (hour), of modified resin containing 1.0 mole of acrylic acid monomer at pH=2.2, Temp.=310K

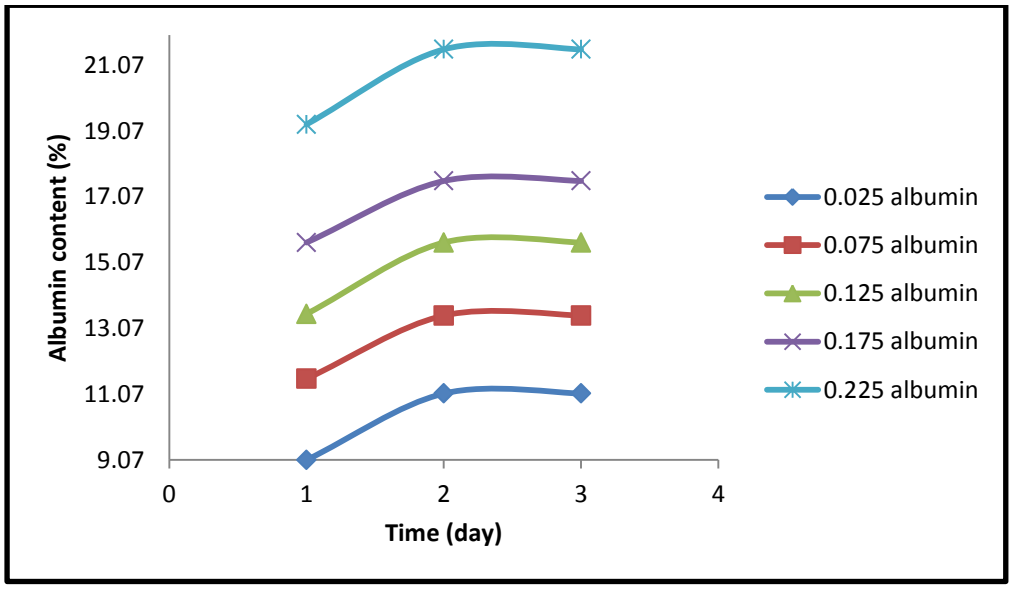

Figure (3-30): Albumin content (%) curves and time (day), of modified resin containing 1.0 mole of acrylic acid monomer at pH=2.2, Temp.=310K

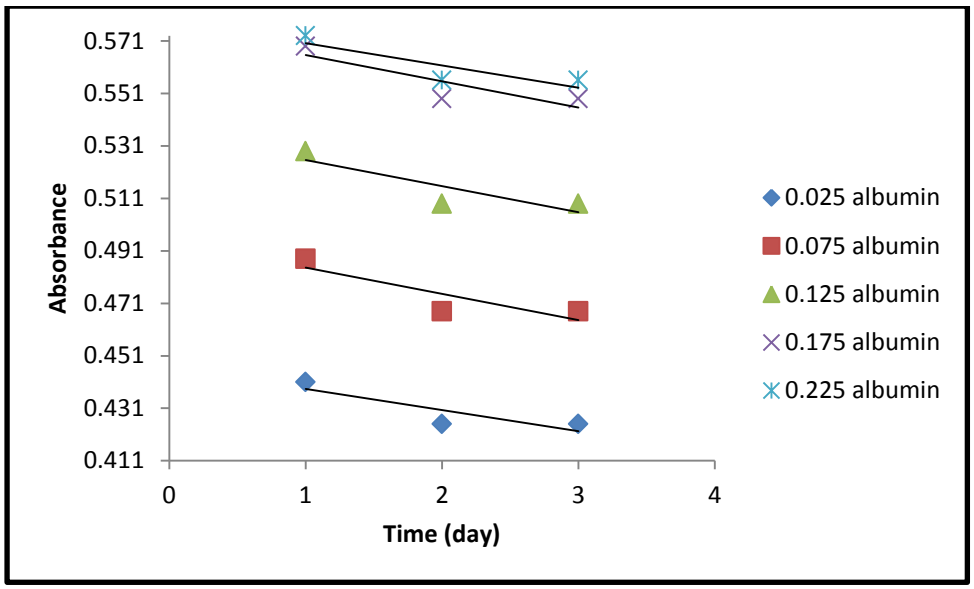

Figure (3-31): Absorbance (Abs.) curves and time (day), of modified resin containing 1.0 mole of acrylic acid monomer at pH=2.2, Temp.=310K

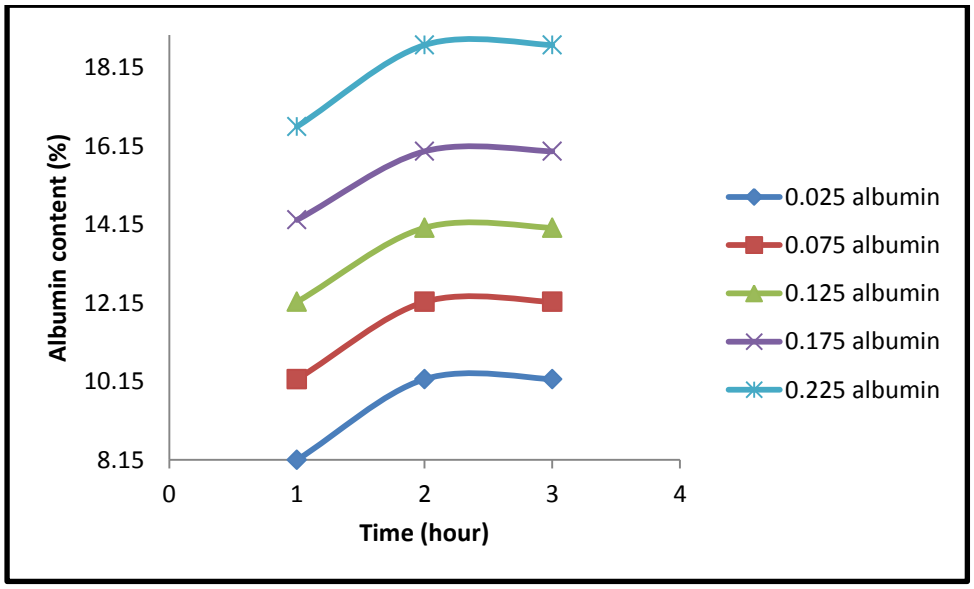

Figure (3-32): Albumin content (%) curves and time (hour), of modified resin containing 1.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

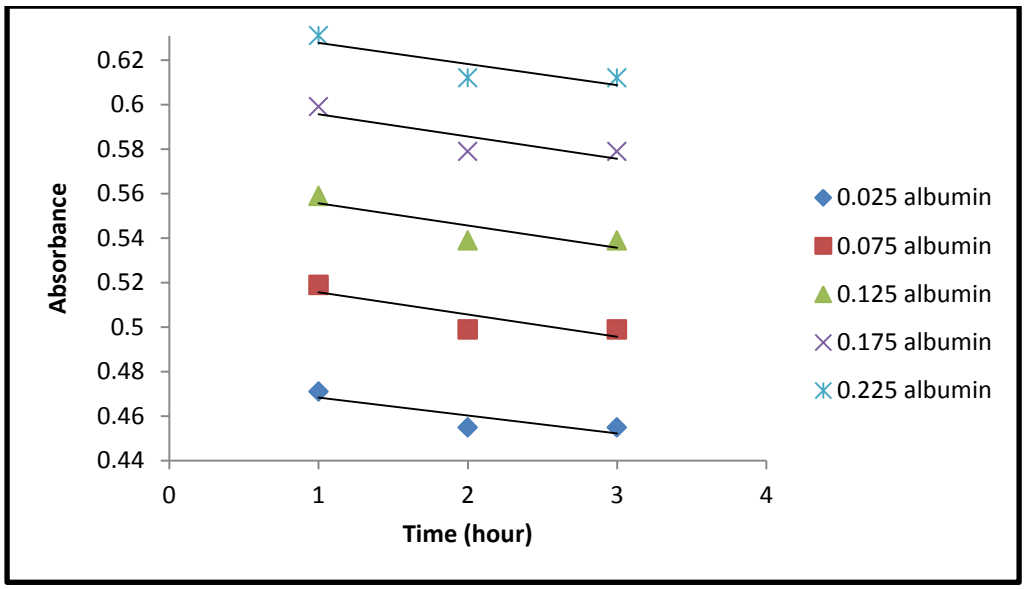

Figure (3-33): Absorbance (Abs.) curves and time (hour), of modified resin containing 1.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

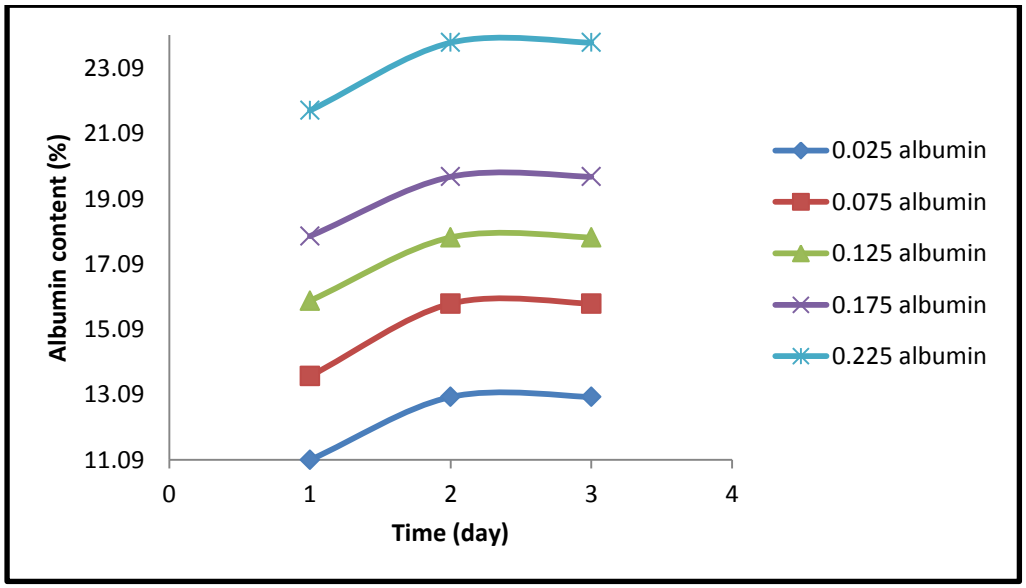

Figure (3-34): Albumin content (%) curves and time (day), of modified resin containing 1.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

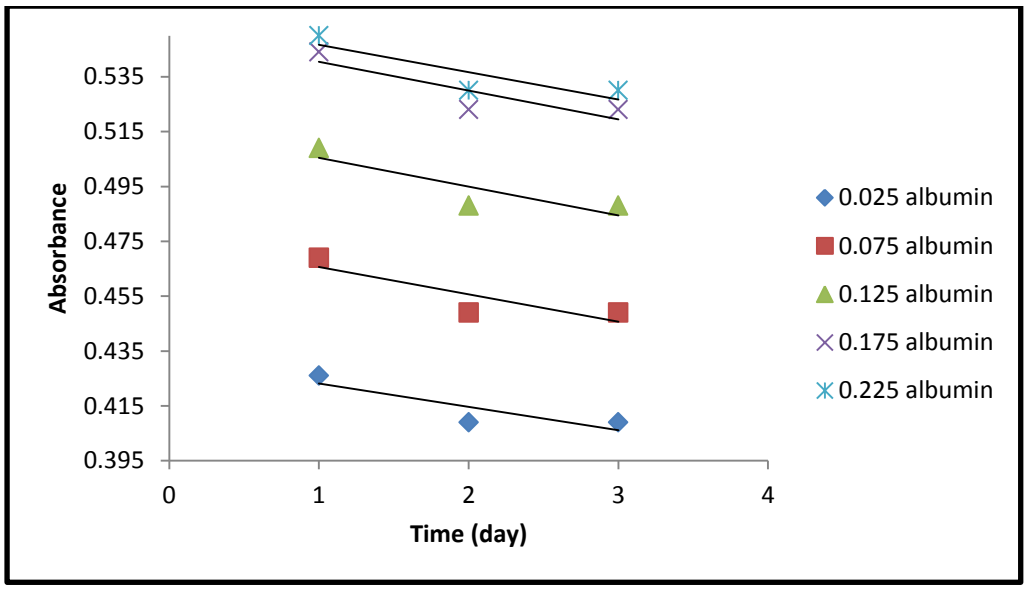

Figure (3-35): Absorbance (Abs.) curves and time (day), of modified resin containing 1.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

3.4 **Release of albumin**

Tables (3-11) to (3-13) and Figures (3-36) to (3-41), represent the release of albumin from the measured samples in the basic medium pH=8.0. Tables (3-14) to (3-16) and Figures (3-42) to (3- 47), represent albumin release from measured models in the acidic medium pH=2.2.

It can be clearly observed that the process of releasing the albumin protein in the basic medium (pH=8.0) is greater than the process of release in the acid medium (pH=2.2), which indicates the effectiveness of the co- polymer on the release of protein in the basic medium higher than in the acid medium. because of when pH increases the polymer swells due to the electrostatic repulsion of the negatively charged groups. the pH in which acids become ionized depends on the polymers pka(depends on the polymers composition and molecular weight).

Table (3-11): Release of albumin per time (hour and day) of modified resin containing 0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Time	**Absorbance**				
(hour)	**Concentration of albumin**				
	0.025	**0.075**	**0.125**	**0.175**	**0.225**
1	0.133	0.166	0.188	0.209	0.223
2	0.144	0.174	0.196	0.219	0.232
3	0.152	0.184	0.206	0.229	0.244
4	0.165	0.196	0.219	0.239	0.252
5	0.165	0.196	0.219	0.239	0.252
(day)					
1	0.173	0.207	0.228	0.248	0.275
2	0.183	0.218	0.238	0.259	0.282
3	0.193	0.225	0.246	0.265	0.293
4	0.209	0.239	0.259	0.279	0.302
5	0.209	0.239	0.259	0.279	0.302

Table (3-12): Release of albumin per time(hour and day) of modified resin containing 1.0 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Time	**Absorbance**				
(hour)	**Concentration of albumin**				
	0.025	**0.075**	**0.125**	**0.175**	**0.225**
1	0.149	0.175	0.195	0.218	0.233
2	0.157	0.183	0.205	0.227	0.243
3	0.163	0.193	0.214	0.237	0.252
4	0.177	0.206	0.227	0.249	0.262
5	0.177	0.206	0.227	0.249	0.262
(day)					
1	0.189	0.213	0.237	0.259	0.285
2	0.199	0.223	0.245	0.269	0.294
3	0.206	0.233	0.256	0.278	0.306
4	0.216	0.242	0.264	0.284	0.315
5	0.216	0.242	0.264	0.284	0.315

Table (3-13): Release of albumin per time(hour and day) of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Time	**Absorbance**				
(hour)	**Concentration of albumin**				
	0.025	**0.075**	**0.125**	**0.175**	**0.225**
1	0.159	0.185	0.205	0.228	0.242
2	0.168	0.194	0.213	0.237	0.251
3	0.177	0.201	0.224	0.247	0.263
4	0.189	0.214	0.236	0.259	0.272
5	0.189	0.214	0.236	0.259	0.272
(day)					
1	0.209	0.234	0.256	0.279	0.308
2	0.219	0.243	0.266	0.289	0.317
3	0.225	0.253	0.273	0.298	0.326
4	0.238	0.263	0.285	0.309	0.336
5	0.238	0.263	0.285	0.309	0.336

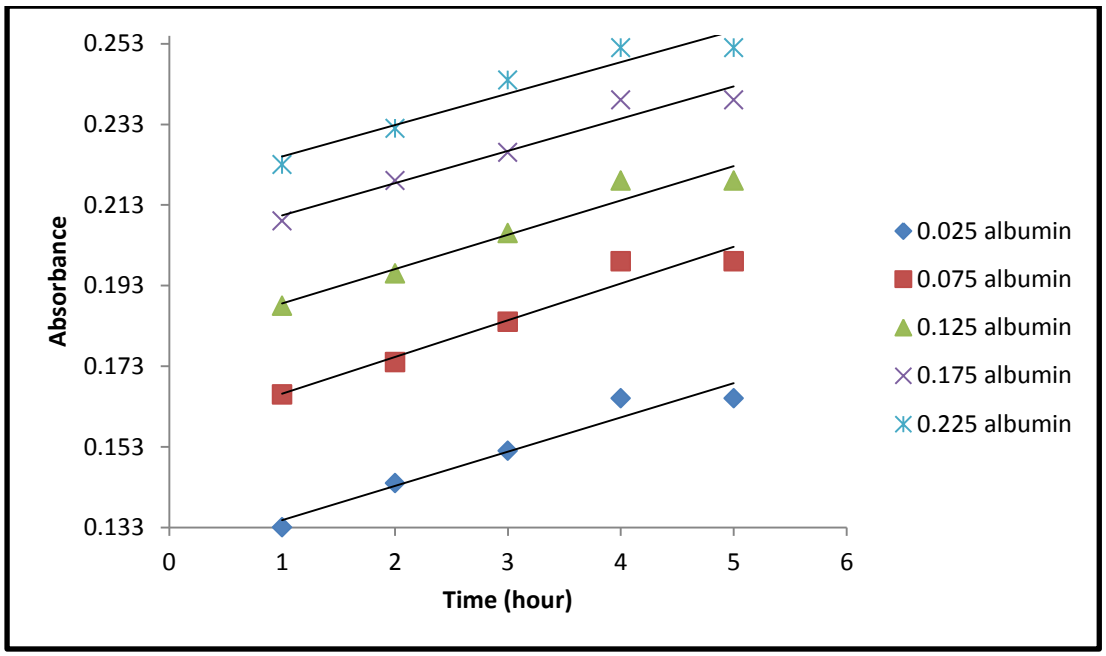

Figure (3-36): Release of albumin curves and time(hour), of modified resin containing 0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

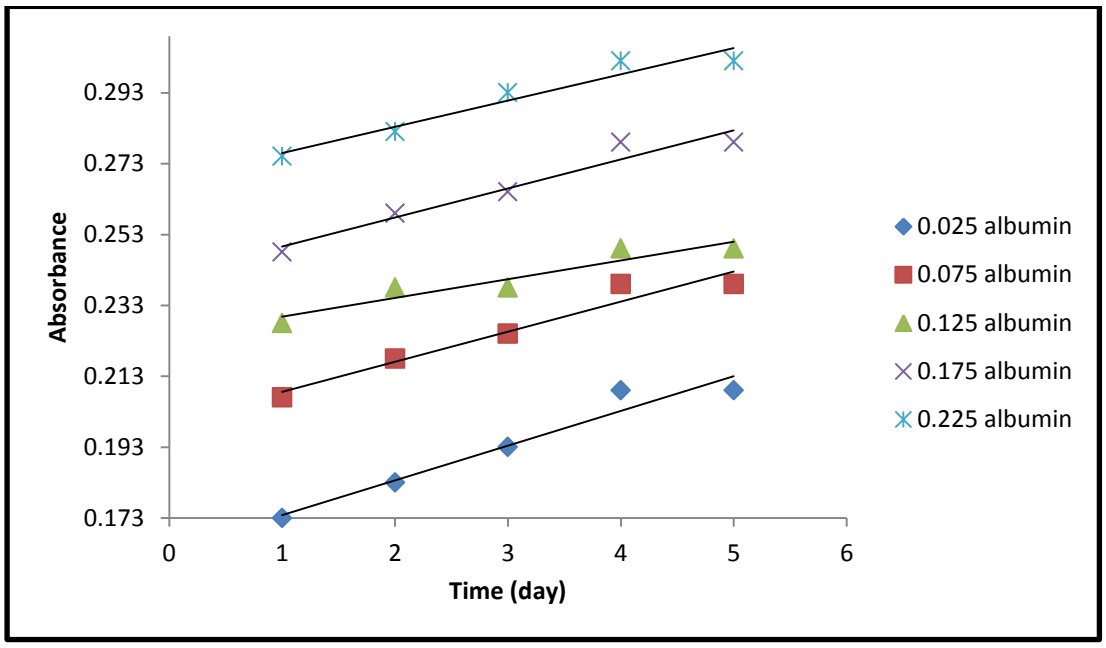

Figure (3-37): Release of albumin curves and time(day), of modified resin containing 0.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

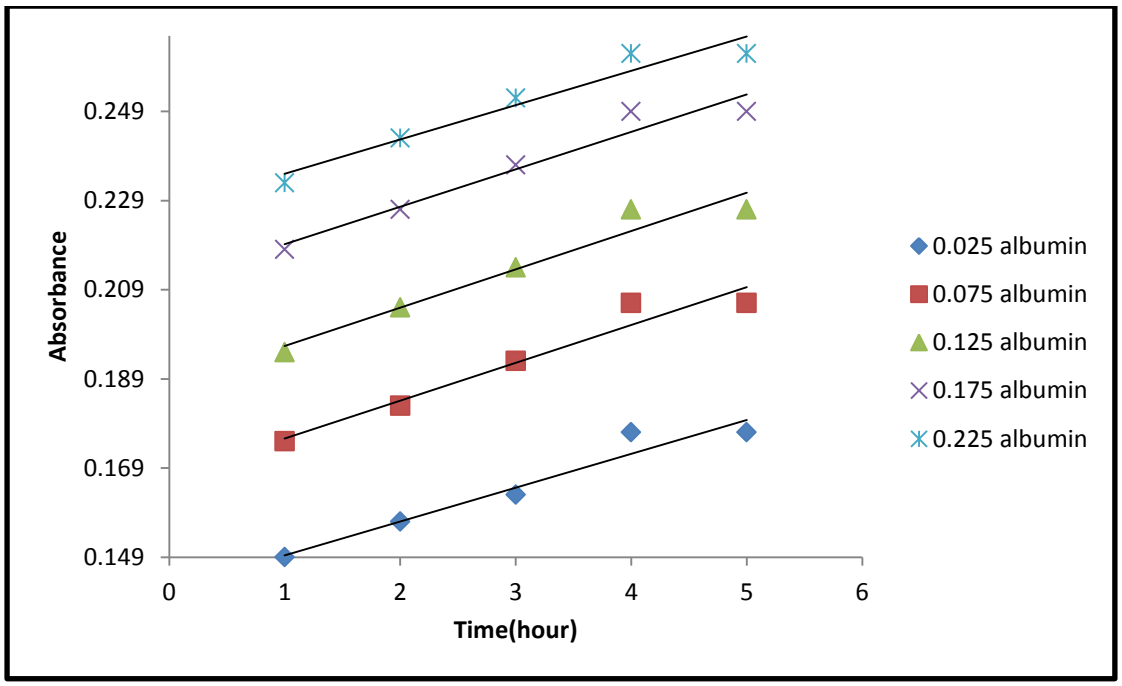

Figure (3-38): Release of albumin curves and time(hour), of modified resin containing 1.0 mole of acrylic acid monomer at pH=8.0, Temp.=310K

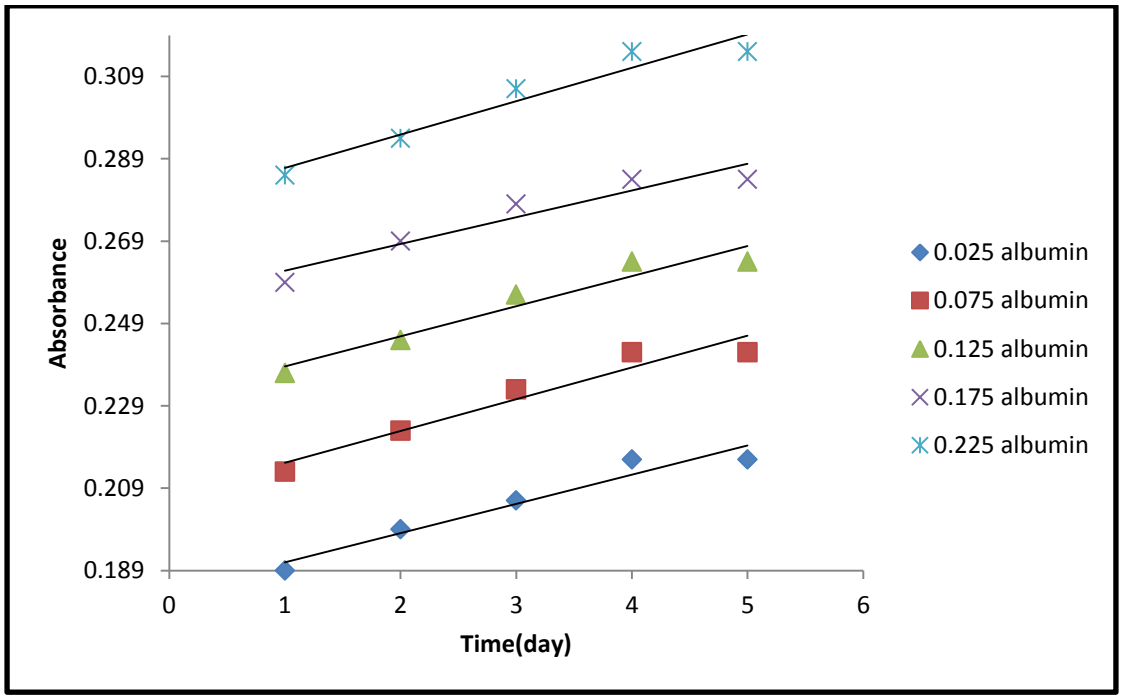

Figure (3-39): Release of albumin curves and time(day), of modified resin containing 1.0mole of acrylic acid monomer at pH=8.0, Temp.=310K

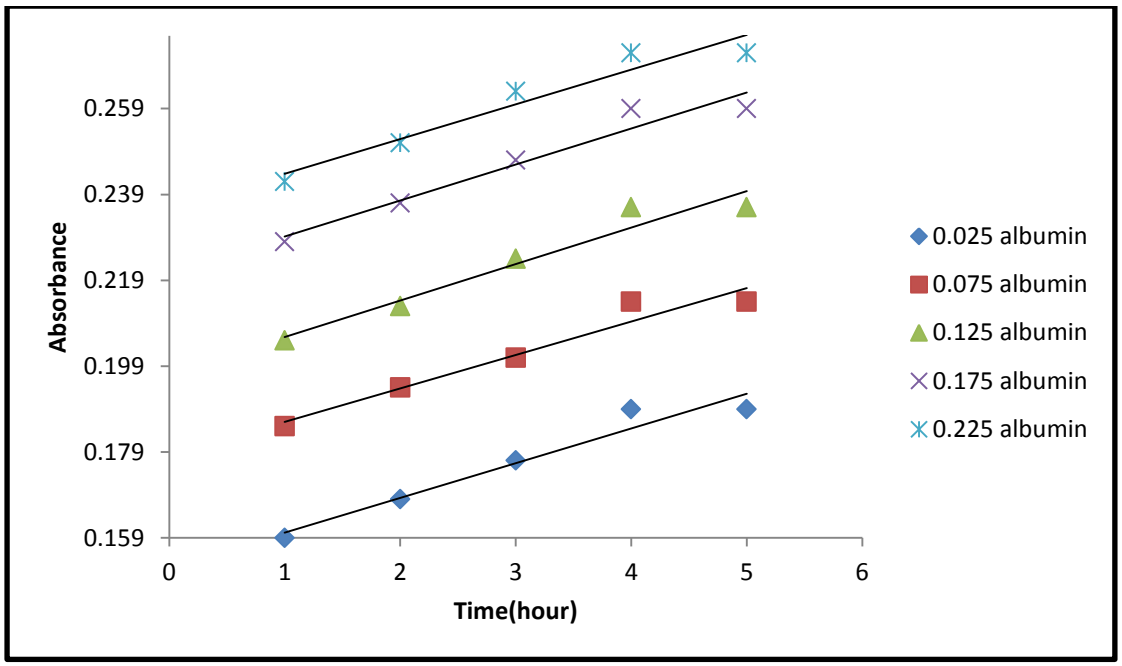

Figure (3-40): Release of albumin curves and time(hour), of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

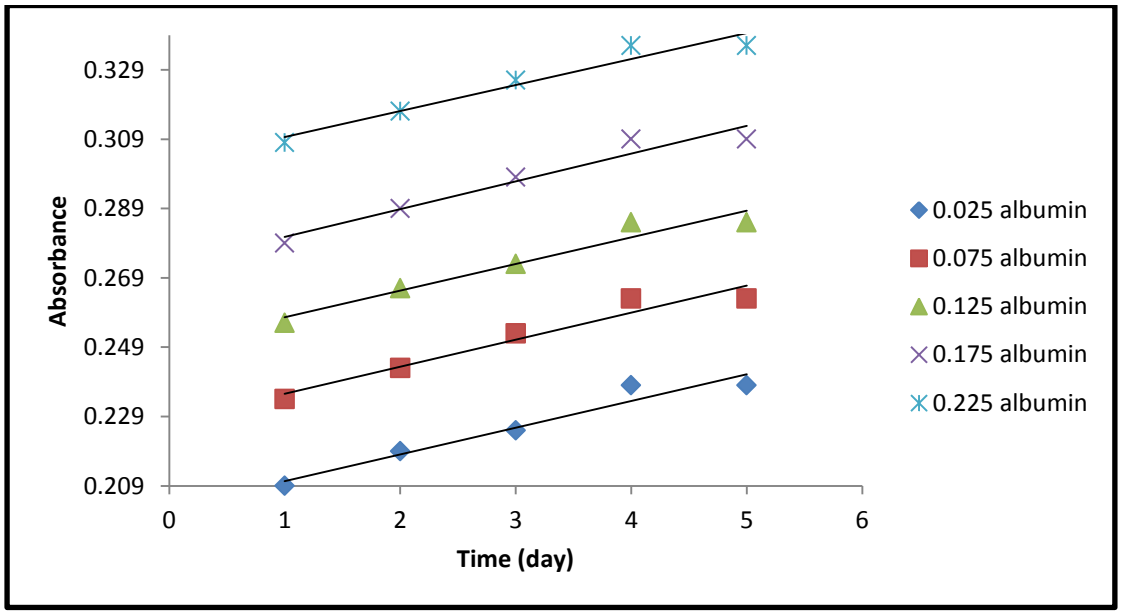

Figure (3-41): Release of albumin curves and time(day), of modified resin containing 1.5 mole of acrylic acid monomer at pH=8.0, Temp.=310K

Table (3-14): Release of albumin per time(hour and day) of modified resin containing 0.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

Time	**Absorbance**				
(hour)	**Concentration of albumin**				
	0.025	**0.075**	**0.125**	**0.175**	**0.225**
1	0.089	0.115	0.135	0.152	0.177
2	0.099	0.125	0.146	0.162	0.185
3	0.099	0.125	0.146	0.162	0.185
(day)					
1	0.108	0.133	0.152	0.173	0.207
2	0.117	0.145	0.163	0.182	0.217
3	0.117	0.145	0.163	0.182	0.217

Table (3-15): Release of albumin per time(hour and day) of modified resin containing 1.0 mole of acrylic acid monomer at pH=2.2, Temp.=310K

Time	**Absorbance**				
(hour)	**Concentration of albumin**				
	0.025	**0.075**	**0.125**	**0.175**	**0.225**
1	0.099	0.125	0.145	0.165	0.187
2	0.109	0.136	0.158	0.174	0.196
3	0.109	0.136	0.158	0.174	0.196
(day)					
1	0.117	0.144	0.166	0.188	0.218
2	0.127	0.157	0.178	0.197	0.226
3	0.127	0.157	0.178	0.197	0.226

Table (3-16): Release of albumin per time(hour and day) of modified resin containing 1.5 mole of acrylic acid monomer at pH=2.2, Temp.=310K

Time (hour)	Absorbance				
	Concentration of albumin				
	0.025	**0.075**	**0.125**	**0.175**	**0.225**
1	0.103	0.136	0.158	0.179	0.195
2	0.116	0.146	0.169	0.188	0.204
3	0.116	0.146	0.169	0.188	0.204
(day)					
1	0.133	0.165	0.189	0.209	0.236
2	0.144	0.178	0.199	0.217	0.246
3	0.144	0.178	0.199	0.217	0.246

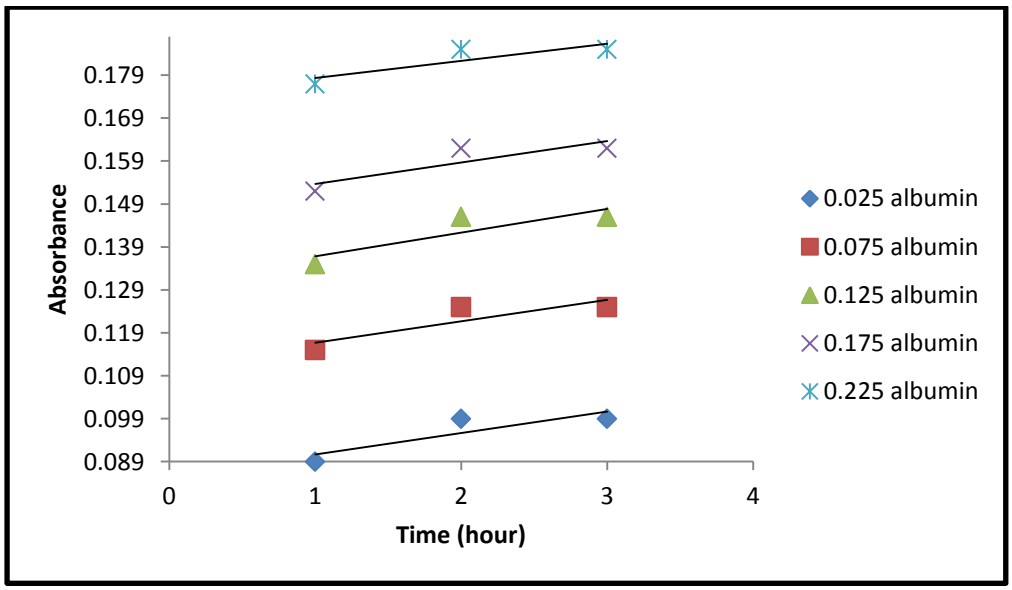

Figure (3-42): Release of albumin curves and time(hour), of modified resin containing 0.5mole of acrylic acid monomer at pH=2.2, Temp.=310K

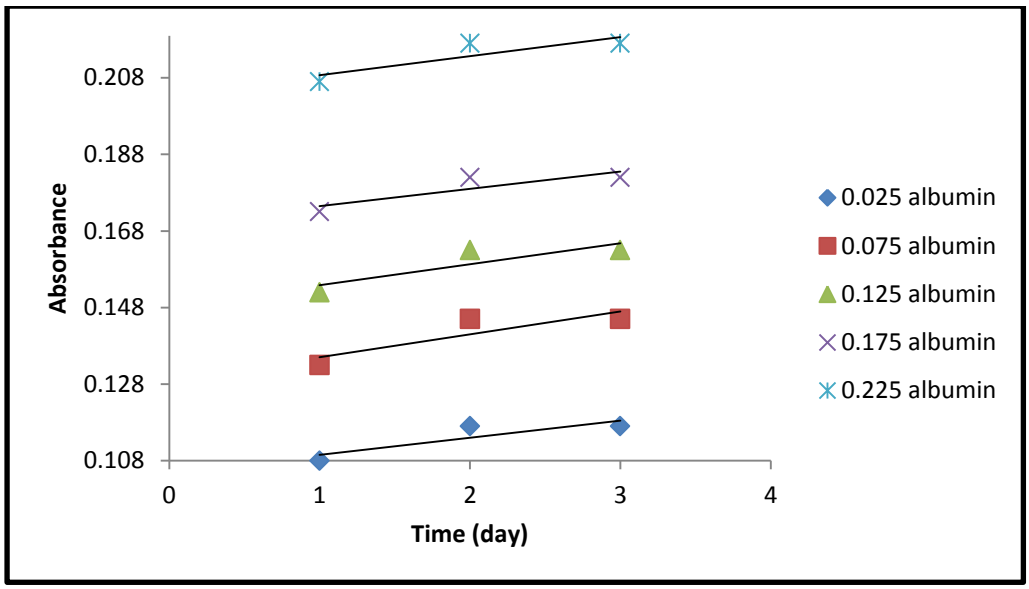

Figure (3-43): Release of albumin curves and time(day), of modified resin containing 0.5mole of acrylic acid monomer at pH=2.2, Temp.=310K

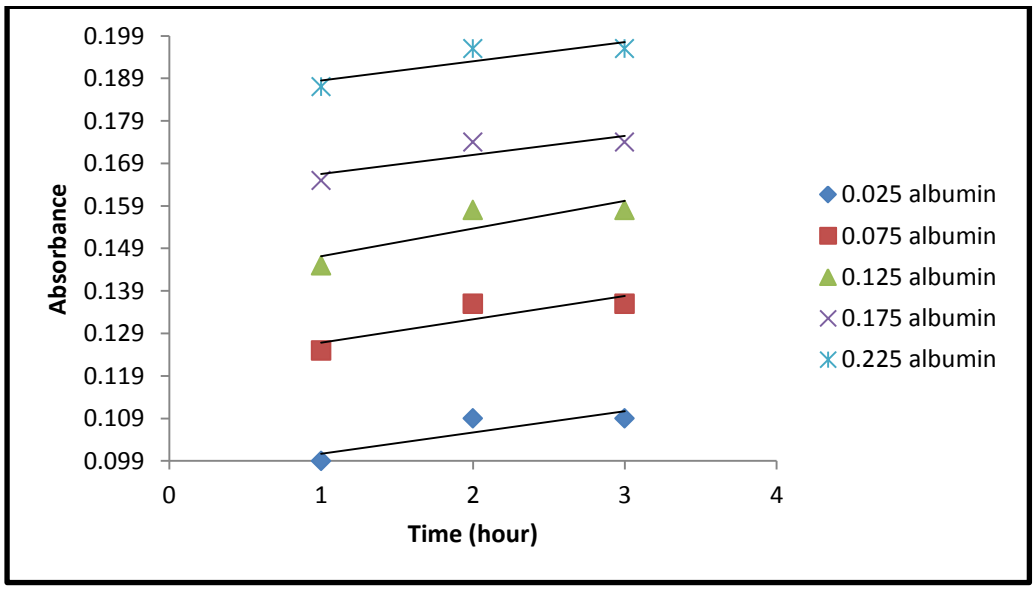

Figure (3-44): Release of albumin curves and time(hour), of modified resin containing 1.0 mole of acrylic acid monomer at pH=2.2, Temp.=310K

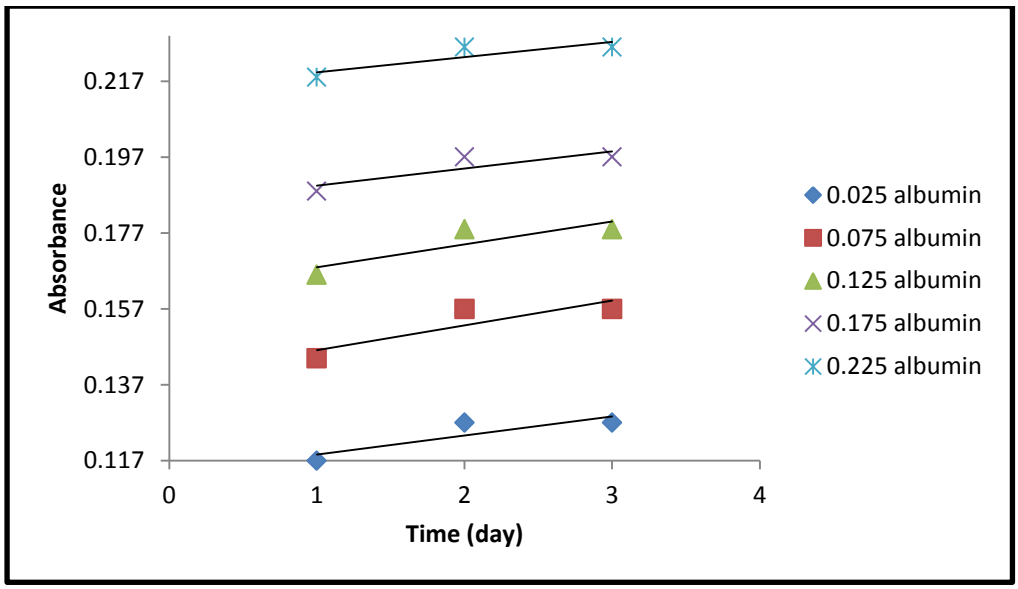

Figure (3-45): Release of albumin curves and time(day), of modified resin containing 1.0 mole of acrylic acid monomer at pH=2.2, Temp.=310K

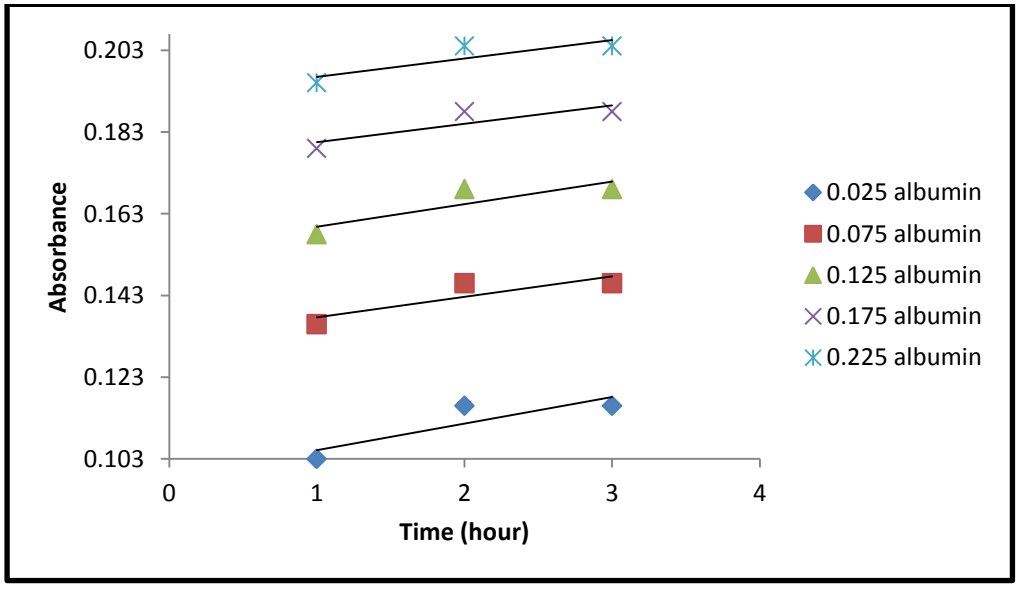

Figure (3-46): Release of albumin curves and time(hour), of modified resin containing 1.5mole of acrylic acid monomer at pH=2.2, Temp.=310K

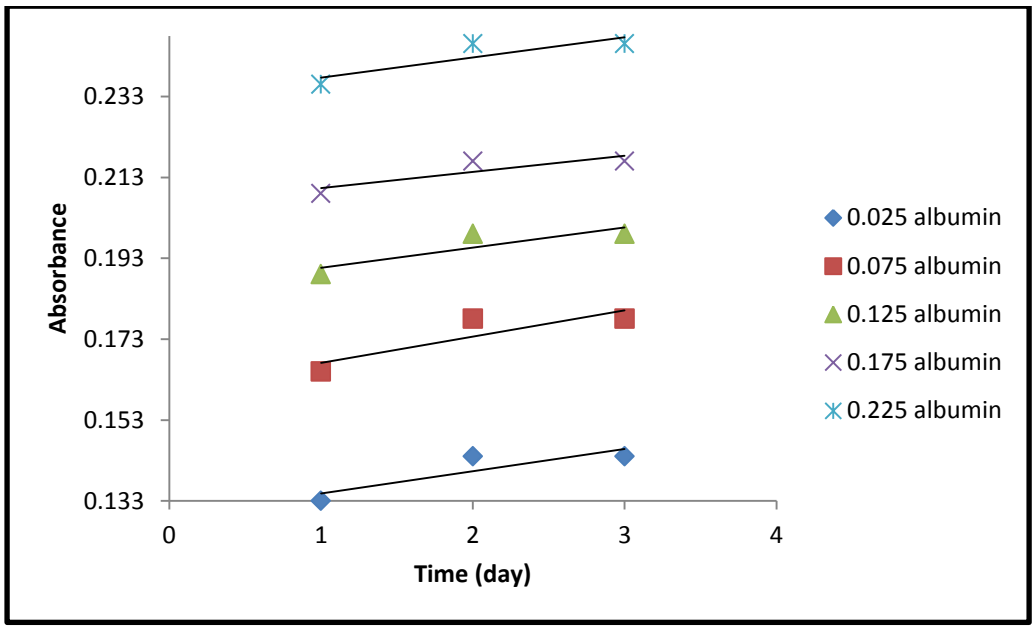

Figure (3-47): Release of albumin curves and time(day), of modified resin containing 1.5mole of acrylic acid monomer at pH=2.2, Temp.=310K

CHAPTER FOUR

Conclusion & Future Works

Conclusion

Preparation of three types of co-polymers by reaction of one mole of pentarythritol which have four hydroxyl groups, with four moles of fumaric acid monomer, which have a double bond and two groups from carboxylic acid, this reaction gave four points of cross-linked with the added monomer . When adding three different monomers of acrylic acid(0.5,1.0 and 1.5), we get on three co- polymers differed in the number of points of correlation. Thus, they differed in the number of hydrophilic groups and differ in the swelling ratio.

As clearly shown in the results, the solvent content (%)increased with increased the time (hour and day).This behavior can be explained in that compound of solvent and the structure of polymer, i.e., present of the hydrophilic groups in the dried disc, concentration and nature of the solvent. All these factors increased the solvent content (%) with the increased of time(hour and day). This corresponds with the findings of earlier research and the low values of swelling process was affected by high chain flexibility and the degree of cross linking, i.e., in the modified co-polymer with 0.5 mole of acrylic acid. The values are low comparing with the values in the modified co-polymer with 1.5 mole of acrylic acid monomer [122, 123].

Future Work

We can propose the following:

1.Use new proteins to load onto polymer discs

2.Use new concentrations of drug

3 . Use of new monomers to building of the polymer network

4. study the biological activity

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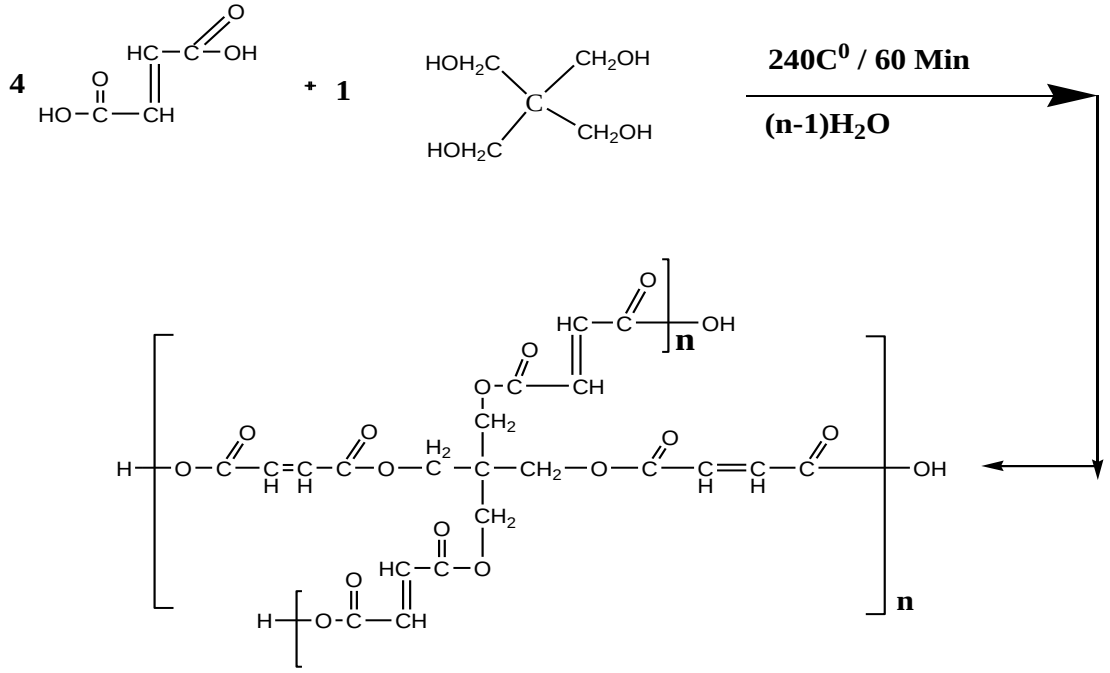
الخلاصة

في هذا العمل، تم تحضير بوليمر مشترك جديد من تفاعل بينتاايريثريتول مع حمض الفوماريك لتشكيل البوليمر المشترك الخطي في درجة حرارة $240\ C^o$ ، كما هو موضح في المخطط التالي. تم تشخيص البوليمر المشترك المحضر بواسطة مطيافية الأشعة تحت الحمراء و مطيافية الرنين النووي البروتوني المغناطيسي . وقد أضيفت ثلاث مولات مختلفة من مونومير حامض الأكريليك (0.5 ، 1.0 و 1.5 مول) للحصول على ثلاث بوليمرات مشتركة جديدة



(البوليمر المشترك الخطي)

تم قياس نسبة الأنتفاخ لجميع عينات الهيدروجيل، في ثلاث دوال حامضية مختلفة (pH=2.2) ، (pH=7.0) و (pH=8.0) وعند درجة حرارة ثابتة 310 K، كدالة للزمن.

تم تحميل الألبومين في العينات البوليمرية عن طريق غمر العينات في محاليل بفر مختلفة الدالة الحامضية (pH=2.2) و (pH=8.0) ، حيث سمح لتحميلها بالألبومين في درجة حرارة

310K، تم قياس تركيز الألبومين من خلال استخدام مطيافية الأشعة فوق البنفسجية. ودرس أطلاق الألبومين المحمل على الهيدروجيل ، حيث لوحظ عند زيادة تركيز الدواء يؤدي إلى زيادة في عملية الإطلاق.

وأظهرت النتائج أن عملية تحميل البروتين وإطلاقه في الوسط القاعدي كانت أعلى مما كانت عليه في الوسط الحامضي، مما يشير إلى أن البوليمر المشترك انتقائي في الوسط.