PREPARATION AND CHARACTERIZATION OF NEW HYDROGELS USED AS DRUG DELIVERY SYSTEMS FOR CHRONIC DRUGS

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MASTER THESIS
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Najwa Ibrahim Yahya YAHYA

Thesis Advisors
Assoc. Prof. Dr. Nurettin ELTUĞRAL
Prof. Dr. Fawzi Habeeb JEBRAIL

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Prof. Dr. Fawzi Habeeb JEBRAIL

T.C.

Karabük University

Institute of Graduate Programs

Department of Chemistry

Prepared as

Master Thesis

KARABUK

February 2024

I certify that in my opinion the thesis submitted by Najwa Ibrahim Yahya YAHYA titled "PREPARATION AND CHARACTERIZATION OF NEW HYDROGELS USED AS DRUG DELIVERY SYSTEMS FOR CHRONIC DRUGS" is fully adequate in scope and in quality as a thesis for the degree of Master of Science.

Assoc. Prof. Dr. Nurettin ELTUĞRAL .....

Thesis Advisor, Department of Medical Engineering

Prof. Dr Fawzi Habeeb JABRAIL .....

Thesis Advisor, Department of Chemistry (University of Mosul)

This thesis is accepted by the examining committee with a unanimous vote in the Department of Chemistry as a Master of Science thesis. February 2, 2024

Examining Committee Members (Institutions)	**Signature**
Chairman : Assoc. Prof. Dr. Nurettin ELTUĞRAL (KBU)	.....
Member : Prof. Dr. Fawzi Habeeb JEBRAIL (UM)	.....
Member : Assoc. Prof. Dr. Yasin KANBUR (KBU)	.....
Member : Assist. Prof. Dr. İsmail YILMAZ (KBU)	.....
Member : Assoc. Prof. Dr. Ümit TAYFUN (BU)	.....

The degree of Master of Science by the thesis submitted is approved by the Administrative Board of the Institute of Graduate Programs, Karabük University.

Assoc. Prof. Dr. Zeynep ÖZCAN .....

Director of the Institute of Graduate Programs

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Najwa Ibrahım Yahya YAHYA

ABSTRACT

Master Thesis

PREPARATION AND CHARACTERIZATION OF NEW HYDROGELS USED AS DRUG DELIVERY SYSTEMS FOR CHRONIC DRUGS

Najwa Ibrahim Yahya YAHYA

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Department of Chemistry

Thesis Advisors:
Assoc. Prof. Dr. Nurettin ELTUĞRAL
Prof. Dr. Fawzi Habeeb JABRAIL
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Chitosan blend synthetic polymers can produce hydrogels carrying extra properties in addition to their biocompatibility, non-toxicity and biodegradability. The blend hydrogels will be thermally stable and mechanically strong. Therefore, chitosan was blended with polyacrylonitrile, and poly (acrylic acid) and the final hydrogel was cross-linked physically using sodium hexametaphosphate (SHMP). The prepared hydrogels were characterized for their chemical structure using 1H NMR, and their crystalline structure using X-ray diffraction, whereas their thermal and morphological state were examined by TGA, DTA, DSC, and FESEM analyses. The different analyses of the prepared hydrogels (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) have shown semi-crystalline structure, and thermally stable composites with homogeneous blend materials, have folded surface containing pores. The prepared hydrogels are experimentally examining their controlled drug delivery

behaviour. For that, the degree of swelling (DS) of the hydrogels were carried out under ambient conditions. The hydrogel (CH-co-PAAc/SHMP) shows higher DS%=120% in comparison with (CH-co-PAN/SHMP) hydrogel DS%=90% duo to its highly hydrolysable functional group. The hydrogels were loaded with hydroxychloroquine drug which used as model and (CH-co-PAAc/SHMP) hydrogel shows high maximum loading percentage Lmax%=39%, whereas (CH-co-PAN/SHMP) hydrogel shows Lmax%=36%. FESEM analysis was used for characterization of the loaded hydrogels, where FESEM images of both hydrogels presents that the drug particles were distributed inside and outside the hydrogel surface and in between its folds. Finally, the loaded hydrogel microspheres were allowed to release in buffered phosphate release solution pH=7.4 and at 37 ^{o}C. The hydrogel (CH-co-PAAc/SHMP) showed higher cumulative release percentage Rcum%=29.6% compared with (CH-co-PAN/SHMP) hydrogel with Rcum%=23.5% and for along controlled release time 30 hrs, while (CH-co-PAN/SHMP) hydrogel release for 24 hrs. The FESEM images of both hydrogels after release have shown the drug molecules are absent and the hydrogel microspheres are diffused their loaded drug, and they are still integrated.

Keywords **:** Hydrogels, Drug delivery systems, chitosan, biocompatibility.

Science Code : 20107

ÖZET

Yüksek Lisans Tezi

KRONİK İLAÇLAR İÇİN İLAÇ DAĞITIM SİSTEMLERİ OLARAK KULLANILAN YENİ HİDROJELLERİN HAZIRLANMASI VE KARAKTERİZASYONU

Najwa İbrahim Yahya YAHYA

Karabük Üniversitesi
Lisansüstü Eğitim Enstitüsü
Kimya Anabilim Dalı

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Doç. Dr. Nurettin ELTUĞRAL
Prof. Dr. Fawzi Habeeb JABRAIL
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Kitosan karışımı sentetik polimerler biyouyumluluk, toksik olmama ve biyolojik olarak parçalanabilirliklerinin yanı sıra ekstra özellikler taşıyan hidrojeller oluşturabilirler. Bu karışım hidrojellerin termal olarak stabil ve mekanik olarak güçlü olması beklenir. Bu nedenle kitosan, poliakrilonitril ve poli(akrilik asit) ile karıştırıldı ve nihai hidrojel, sodyum heksametafosfat (SHMP) kullanılarak fiziksel olarak çapraz bağlandı. Hazırlanan hidrojeller, kimyasal yapıları 1H NMR kullanılarak, kristal yapıları ise X-ışını kırınımı difraktometre ile karakterize edilmiş; termal ve morfolojik durumları ise TGA, DTA, DSC ve FESEM analizleriyle incelenmiştir. Hazırlanan hidrojellerin (CH-co-PAN/SHMP) ve (CH-co-PAAc/SHMP) farklı analizleri yarı kristal yapıyı ve homojen karışım malzemelerine sahip termal olarak stabil kompozitlerin katlanmış yüzeye dökülmeler içerdiğini

göstermiştir. Hazırlanan hidrojeller kontrollü ilaç dağıtım davranışlarını deneysel olarak incelenmiştir. Bunun için hidrojellerin şişme derecesi (DS) ortam koşullarında gerçekleştirildi. Hidrojel (CH-co-PAAc/SHMP), yüksek derecede hidrolize edilebilir fonksiyonel grubuna göre (CH-co-PAN/SHMP) hidrojel %DS=%90 ikilisiyle karşılaştırıldığında daha yüksek %DS=%120 göstermiştir. Hidrojeller, model olarak kullanılan hidroksiklorokin ilacı ile yüklenmiştir ve (CH-co-PAAc/SHMP) hidrojel, yüksek maximum yükleme yüzdesi Lmax%=%39 strike, (CH-co-PAN/SHMP) hidrojel, Lmax%=36 göstermiştir. İlaç yüklenen hidrojellerin karakterizasyonu için FESEM analizi kullanılmış; burada her iki hidrojel de FESEM görüntüleri incelendiğinde ilaç parçacıkları hidrojel yüzeyinin içinde ve dışında ve kıvrımları arasında dağılmış görünmektedir. Son olarak yüklenen hidrojel mikroküreleri, tamponlu fosfat salma çözeltisi pH=7,4 içinde ve 37 ^{o}C'de salınması sağlandı. Hidrojel (CH-co-PAAc/SHMP), Rcum%=%23,5 olan (CH-co-PAN/SHMP) hidrojel ile karşılaştırıldığında ve 30 saatlik kontrollü salım süresi boyunca daha yüksek kümülatif salım yüzdesi Rcum% değeri %29,6 gösterirken, (CH 24 saat boyunca -co-PAN/SHMP) hidrojel salınımı Rcum% değeri %23,5 olmuştur. Her iki hidrojelin ilaç salınımı sonrasında elde edilen FESEM görüntüleri, hidrojeller üzerinde ilaç moleküllerinin bulunmadığını ve hidrojel mikroküreleri yüklü ilaçlarını dağıttıklarını ve hala bütünleşik olduklarını göstermiştir.

Anahtar Kelimeler : Hidrojeller, ilaç taşıma sistemleri, kitosan, biyouyumluluk.
Bilim Kodu **:** 20107

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SYMBOLS AND ABBREVIATIONS

ABBREVIATIONS

BMA	: Butyl methacrylate
CH	: Chitosan
CH-co-PAAC	: Chitosan Copolymerization Polyacrylic acid
CH-co-PAN	: Chitosan Copolymerization Polyacrylonitrile
DDS	: Degree of swelling
DMSO	: Dimethyl sulfoxide
DS	: Drug delivery system
DSC	: Differential scanning calorimetry
DTA	: Differential thermal analysis
FESEM	: Field emission scanning electron microscopy
LCST	: Low critical solution temperature
PAAC	: Polyacrylic acid
PAAm	: Polyacrylamide
PAN	: Polyacrylonitrile
SEM	: Scanning electron microscope
SHMP	: Sodium hexametaphosphate
TGA	: Thermal analysis
TGA	: Thermogravimetry
UCST	: Upper critical solution temperature
XRY	: X-ray diffraction

PART 1

INTRODUCTION

Hydrogels can absorb enormous amounts of water or biological fluids, however in their three-dimensional structures, they are insoluble in physiological conditions [1]. As smart polymer materials advance [2,3] The domains of materials science and medicine are paying more attention to functional medical materials [4]. Functional polymer materials have been developed that modify their chemical structures and qualities to suit the requirements of various situations and environmental changes [5–7], in contrast to conventional medical materials. Because of its exceptional qualities, such as its high swelling/de-swelling ratio, non-toxicity, biocompatibility, and biodegradability, a dynamic crosslinked hydrogel stands out among these polymer materials. It is a promising biomaterial for biomedical applications, including [8] controlled drug and protein delivery [2], wound dressing [9], and tissue engineering [10]. Furthermore, they are employed in biomedicine as antimicrobial materials [11]. Hydrogel dressings for injuries have been made using a variety of biopolymers. For example, chitosan and poly (acrylic acid) (PAA) are frequently used in the preparation of hydrogels due to their non-toxicity, affordability, and biocompatibility. Natural polysaccharide chitosan is typically used in tissue engineering; more significantly, though, it can be chemically altered by adding amino and/or hydroxyl groups to create complexes and add functions that are required for particular uses. Chitosan, however, has a weak mechanical property. A simple method to overcome this issue is to combine it with other polymers, including Since it features a carboxyl group in every repeating unit and promotes metal ion adsorption [13], poly (acrylic acid) (PAA) [12] has gained a lot of attention. It is a typical pH-responsive polyelectrolyte that gels at pH values higher than its pKa (4.75), Cu (II) in aqueous solution has been successfully removed by using biodegradable, ultra-high content grafted chitosan-g-poly (acrylic acid) powder as an adsorbent in a homogenous system [14].

Chemical crosslinking is the usual method used to create Cs–AA hydrogels. In diluted acidic solutions, Cs is soluble, and in water [15], it forms a rubbery hydrogel. To enhance the water sorption and hydrophilicity of Cs while maintaining its desired biological characteristics, AA grafting on the Cs chain might be a useful technique.

Interesting hydrogels with potential applications as biomaterials exhibiting different properties depending on the composition and type of interactions within the network, attending to chemical crosslinking and hydrogen bonding interactions, will result from the combination of the hydrophilic properties of acrylic polymers with the biodegradable nature of chitosan-based blends.

Hydrogels were also created using chitosan, a hydrophilic polymer, by combining it with other hydrophobic polymers, including poly (acrylonitrile) [16], which are mechanically stronger. One advantage of polyacrylonitrile (PAN), a semicrystalline vinylic homopolymer with the repeating unit-(CH2-CHCN)-, is that it is relatively straightforward to modify its physicochemical properties. PAN is typically found in the atactic form. Because it contains a nitrile group, polyacrylonitrile has this special quality [17,18]. The mechanical strength and thermal stability of PAN systems are comparable to that of fibers [19]. While PAN is most commonly associated with its usage in upholstery, it is also a crucial precursor to carbon fibers [20].

Researchers discovered that Ch-g-PAN graft copolymers adsorb a greater amount of heavy metal ions compared to Ch alone. This adsorption effect is especially strong when it comes to their amidoxime derivatives [21]. Additionally, it was demonstrated that the capacity of Ch to attract more molecules of dye rises with increasing graft %. This enhancement is also observed for amidoxime derivatives [22]. The temperature and pH responsiveness of chitosan and polyacrylonitrile (PAN) 23 hydrogels were investigated by Seon et al.

Following implantation, PAN swells in water and/or bodily fluids to create hydrogels that are both biocompatible and biodurable, with little irritation. What makes PAN special is that it mimics the properties of natural tissues, including cartilage and the

nucleus pulposus of intervertebral disc [19], in terms of both elasticity and tensile strength (19). As a result, PAN has been refined for minimally invasive spinal procedures [24]. Despite PAN's many biological benefits, its hetero-chemical interaction with sodium hydroxide and/or amine limits control over its hydrophilic and hydrophobic portions. Therefore, practical development efforts have focused on creating a straightforward preparation technique for PAN copolymers with a controlled composition.

1.1. AIMS OF THE PRESENT WORK

Two hydrogel copolymers systems are prepared, where chitosan (CH) is the main polysaccharide present beside polyacrylonitrile (PAN) and polyacrylic acid (PAAc). The prepared systems copolymerize to, (CH-co-PAN), and (CH-co-PAAc). They are cross-linked using ionic (physical) cross-linker called sodium hexametaphosphate (SHMP) salt. Moreover, the prepared hydrogel systems are characterized by 1H NMR, XRD, SEM, thermal analysis. The prepared hydrogel systems are examined for drug delivery. Therefore, they were loaded with Hydroxychloroquine as drug model. The maximum drug loading percentage (Lmax %) is calculated. The loaded particles were characterized by SEM. Finally, the loaded hydrogel systems were allowed to release at pH=7.4 to simulate plasma blood fluid and at 37 ˚C. The released particles were characterized by SEM. A comparison studies were done for (CH-co-PAN) and (CH-co-PAAc) hydrogel systems as for the better controlled drug delivery system.

PART 2

PREFACE

Hydrogel is a material that is neither solid nor liquid nor gas. Like a solid, hydrogel does not flow [25]. Like a liquid, small molecules diffuse through a hydrogel [26]. Hydrogels have some advantages in industrial applications such as pharmaceutical, oil recovery, textile, water treatment, and agriculture [27].

Hydrogels are currently shown as water insoluble materials due to their cross-linked structure, and are three dimensional networks of polymer chains which include solvent (mostly water) that fills the spaces between polymer chains [27].

Hydrophilic polymers can be cross-linked through chemical, physical bonds, or cross-linkers leading to formation of a hydrogel.

A cross-linked hydrosol is named a hydrogel which can only swell in its surrounding liquid to a certain degree of swelling, depending on the cross-linking density [28] as shown in Figure 2.1[29].

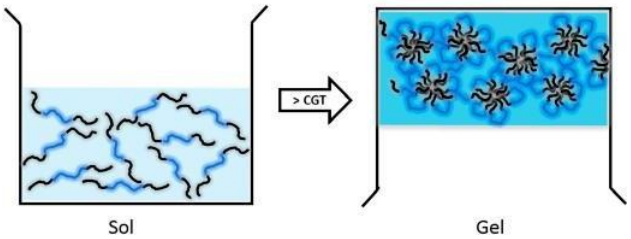

Figure 2.1. Illustration of a sol-to-gel transition.

Generally, hydrogels are known as soft materials composed of insoluble, hydrophilic, cross-linked polymer chains with three-dimensional networks that can uptake a huge

amount of water inside its network [30,31]. Hydrogels may shrink from 10-20% and swell up to thousands of times of their dry weight in water [32].

hydrogels sometimes appear as colloidal gels where water is the dispersion medium [33,34]. Hydrogels can absorb water because of their cross-linking network structure where the polymer carries hydrophilic groups such as –OH, –COOH, –NH2, –SO3H, and –CONH, [35]. The three-dimensional network gives the polymer matrices the capability for imbibing large amounts of water, or other biological fluids [36,37].

Hydrogels have properties such as biocompatibility, integrity, imbibing large amounts of water and biological fluids, and flexibility. These properties are the reason behind its different applications ranging from clinical applications to food additives to pharmaceuticals. Synthetic hydrogels prepared from different kinds of monomers have shown many applications especially in drug delivery devices, tissue-engineering scaffolds, and carriers for implantable devices [36,37].

Hydrogels respond to different external stimuli such as solvent, ionic strength, pH, temperature, and electric fields, for example by changing their wetting characteristics and/or volume.

Cross-linking is one of the bases where hydrogels are classified into two categories are chemical gel and physical gel. Chemically the hydrogels are cross-linked covalently and are never dissociated only by complete degradation. While physical gels are formed when the polymer chains are held together and their entanglements are formed if one of the following secondary forces are present such as ionic, hydrophobic interactions, or hydrogen bonding. Some physical interactions are reversible and sometimes disrupted by changes in physical conditions Figure 2.2.

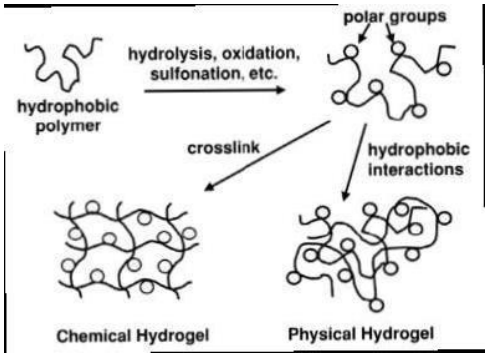

Figure 2.2. Types of cross-linking.

Smart hydrogels can change some properties, especially their shape, according to a change in environment. Smart hydrogels show a sharp and a large change in response to small changes either in physical or chemical conditions. The most common stimuli are temperature, pH, solvent composition, radiation, ionic strength, electrical potential, pressure, and chemical and biological agents. But the common stimuli for most smart hydrogels are temperature, pH, and ionic strength.

The polymer chains for hydrogels most have hydrophilic functional groups. Some polymers have carboxylic acid groups (RCOOH), where acids are present as side groups on the polymer backbone. In the water, the hydrogen of the carboxylic acid group may dissociate and carboxylate ion ($RCOO^-$) with a negative charge would form. The negative charges along its backbone repel each other and the result is forcing the polymer to uncoil. At the same time the negative charge increases the attraction of the hydrogel to water. This uncoiling state of the polymer arises from its attraction to water form swelling of the hydrogel [25].

2.1. CLASSIFICATION OF HYDROGELS

Hydrogels are classified depending on different points of view including physical properties, nature of swelling, method of preparation, origin, ionic charges.

2.1.1. Polymer Origin

Hydrogels are classified as either natural, semi- synthetic, or synthetic [26,27]. They are from natural origin like proteins, examples such as collagen and polysaccharides

like alginate, cellulose, and dextran. They are biocompatible and biodegradable. Hydrogels serve as semi synthetic or synthetic. Chitosan based hydrogels is an example to semi-synthetic ones [27]; while synthetic hydrogels can be prepared by blending aqueous solutions of vinyl acetates [26].

2.1.2. Ionic Charges

Hydrogels can carry charges through functional groups and they can be categorized based on ionic charges as neutral (no charge) like dextran, anionic (negative charge) like carrageenan, cationic (positive charge) like chitosan, and ampholytic (positive or negative charge) like collagen [26].

2.1.3. Cross-Linking Agents

One common method to prepare hydrogels is to use cross-linking agents for polymerization [26,28]. The polymer chains of a hydrogel are cross-linked (interconnected). A Physical cross-linker includes such as sodium hexametaphosphate (SHMP), or chemical cross-linker such as glutaraldehyde (Glu).

The physical connections are weaker and more reversible because the polymers chains of physically connected hydrogels are held together by hydrogen bonds, chain entanglements, electrostatic forces, van der Waals interactions [38], or polymer chains of chemically connected hydrogels are held together by permanent covalent bonds. Figure 2.3 shows hydrophobic interactions involving hydrogel formation whereas covalent bond is represented by sharing of pairs of electrons between chain atoms as shown in Figure 2.4 [26].

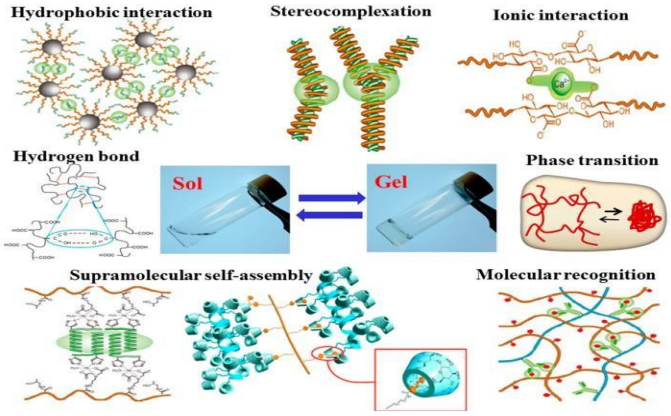

Figure 2.3. A schematic representation of the formation of physically cross-linked hydrogels [39].

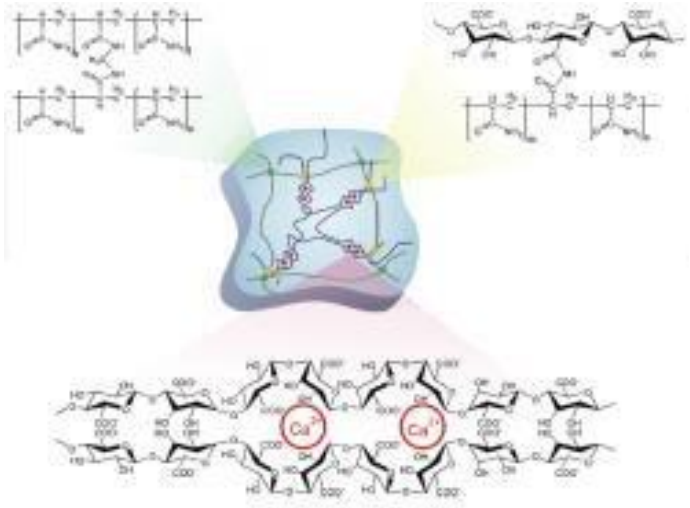

Figure 2.4. A schematic drawing for the chemical cross-linking and ionic interaction between alginate and calcium ions [40, 41].

2.1.4. Physical Structure of the Polymer Chains

The classification based on physical structure of the polymer chains includes amorphous, means random (non-crystalline); semi-crystalline, represent regions of partially ordered structure; or hydrogen-bond, where the network is held together by hydrogen bonds.

2.1.5. Method of Hydrogel Preparation

Hydrogels can also be classified by the method of preparation including homopolymer, made from (one type of monomer); copolymer, made from (two type of monomer); multipolymer, made from (more than one type of polymer); or interpenetrating polymer where the second polymer network enters within the structure and polymerizes around the first polymer network with non-covalent linkages connecting both networks as shown in Figure 2.5.

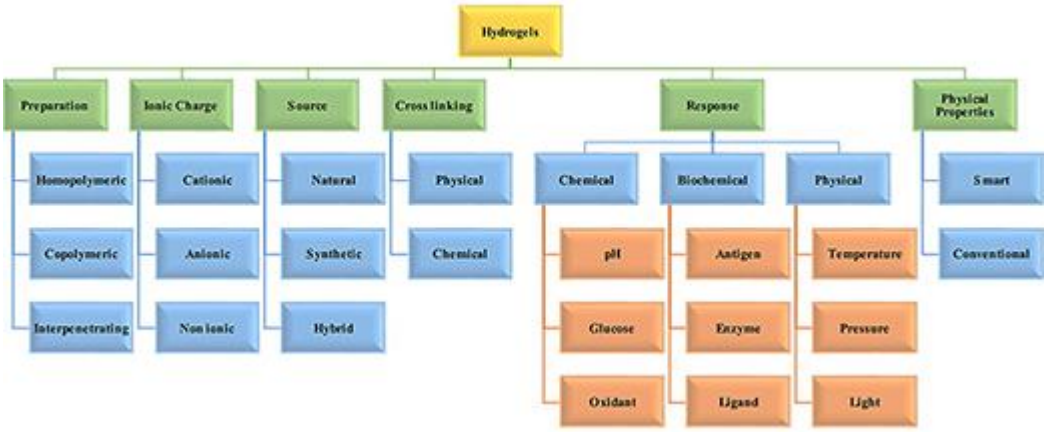

Figure 2.5. Classification of hydrogels based on the different properties [26].

2.2. pH SENSITIVE HYDROGELS

pH sensitive hydrogels are formed from endosome/lysosome, and tumor sites and their pH range occurring at pathological, physiological, or sub-cellular sites such as the gastro intestine, or stomach. pH sensitive hydrogels, shown in Figure 2.6, with their ionic groups accept or donate protons according to changes in environmental pH change. The pKa or pKb (degree of ionization) shows changes in response to pH change [42]. The pH change shows sudden volume transition which creates large osmotic swelling force.

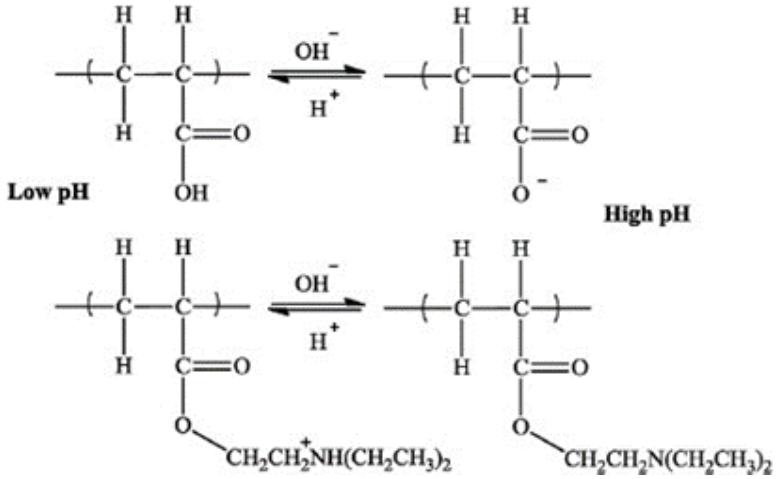

Figure 2.6. pH sensitive hydrogel [19].

2.3. TEMPERATURE SENSITIVE HYDROGELS

Temperature sensitive hydrogels swell or shrink as temperature changes in the environment. Where the swelling of the hydrogels and their deswelling behavior mostly depend on the surrounding temperature as shown in Figure 2.7.

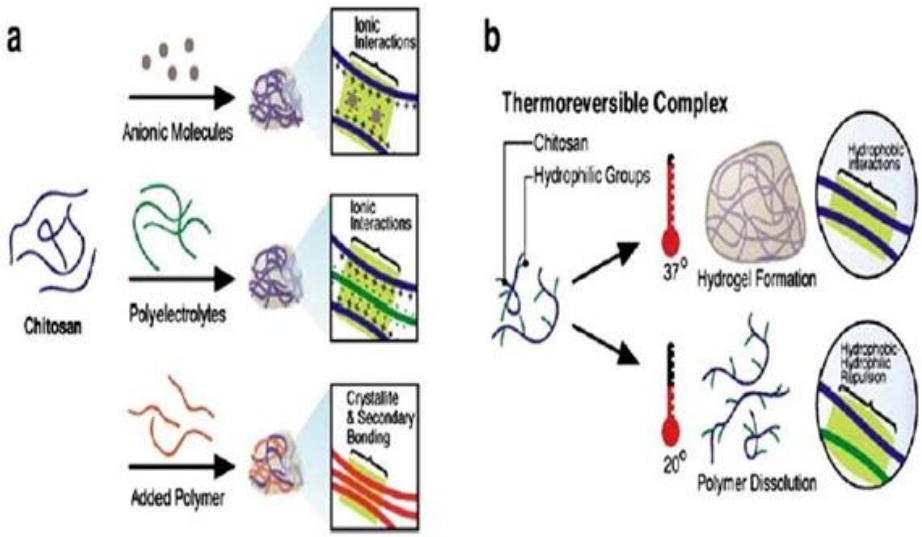

Figure 2.7. A schematic drawing for temperature sensitive hydrogels [42].

Temperature sensitive hydrogels are classified as positive or negative systems [42]. Where positive temperature hydrogels have specific upper critical solution temperature (UCST) [42]. This UCST temperature is required for hydrogel swelling higher UCST. Below the UCST dehydration occurs, where the hydrogels shrink after

release solvents or fluids from their matrix means the hydrogels shrink at low temperatures while they swell at high temperatures. polyacrylamide (PAAm), Poly (acrylic acid) or Poly (AAm- co-BMA) are examples of positively thermo-sensitive hydrogels.

Negative temperature hydrogels are hydrogels that have low critical solution temperature (LCST). Shrinkage of hydrogel occurs at temperature above the LCST and swell below LCST. Examples of negative temperature hydrogels include poly N-isopropylacrylamide and Polyvinylpyrrolidone [42].

2.4. CHITOSAN

Chitosan, as a natural polymer [44], is commercially obtained by deacetylation of the amino acetyl group present in chitin [45]. Chitosan is composed from(B1-4) linked residues of both N-acetyl-2deoxy-D- glucose and 2-amino-2-deoxy-D-glucose as shown in Figure 2.8, which is produced from the most abundant polysaccharide chitin in the world [46]. Chitosan has acceptable biocompatibility and non-toxic properties [47]. Therefore, chitosan is a sustainable and renewable material. In addition, due to its interesting properties, chitosan is suitable for use in biomedical, cosmetic, biotechnological, and pharmaceutical applications [44]. It has a wide range of applications, like in medical, cosmetic, food, pharmaceutical etc. [47] because of its gel forming capabilities with different types of solvents.

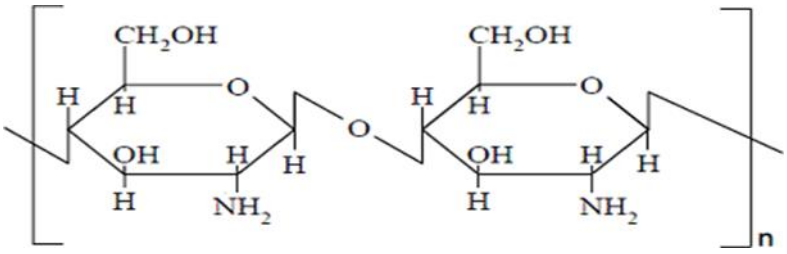

Figure 2.8. Chemical structure of chitosan [45].

Chitosan has active amino and hydroxyl groups which can be used to change chemically its properties occur under mild reaction conditions. It is a weak base with gel forming ability at low pH and it is bio-adsorber [28]. Chitosan is insoluble in

water and all organic solvents, and its solubility in water occurs in dilute acidic solutions of organic acid like formic acid, acetic acid or mineral acids like hydrochloric acid (HCl), and nitric acid (HNO_3) [44].

Because chitosan has the advantage of inhibitory growth of fungus, stopping bleeding, anti-cholesterol properties, antibacterial, it has a wide range of pharmaceutical and biomedical applications including controlled drug delivery systems [48].

2.5. ACRYLIC ACID (AA)

The monomer of propanoic acid or acrylic acid with chemical formula (CH2=CHCOOH) is a clear and colorless liquid above 13°C [49]. Acrylic acid has vinegar odor [34], infinite solubility in water and it is soluble in organic solvents and other solvents.

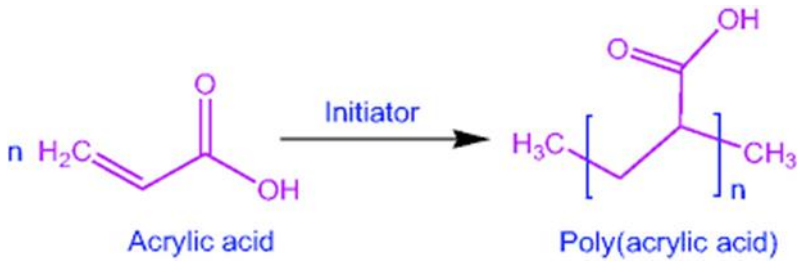

Figure 2.9. Preparation of poly (acrylic acid).

Poly(acrylic acid) PAA, is an acrylate polymer, and it is synthesized through a process called free radical polymerization, in addition, graft polymerization may also be used. In free radical polymerization the monomer acrylic acid (CH2=CHCO2H) is converted into a polymer chain by the action of free radicals as shown in Figure 2.9 [50].

2.6. POLYACRYLONITRILE (PAN)

Polyacrylonitrile, or Poly(propenonitrile)(PAN) [51]is a vinyl polymer, and it is a derivative of acrylate family of polymers. Polyacrylonitrile is a highly crystalline polymer and has melting temperature 319 ˚C and glass transition temperature 87 ˚C. Studies on polyacrylonitrile have been concentrated on melting behavior of acrylonitrile polymers. The monomer acrylonitrile is polymerized to Polyacrylonitrile by free radical vinyl polymerization, which is shown in Figure 2.10 [52].

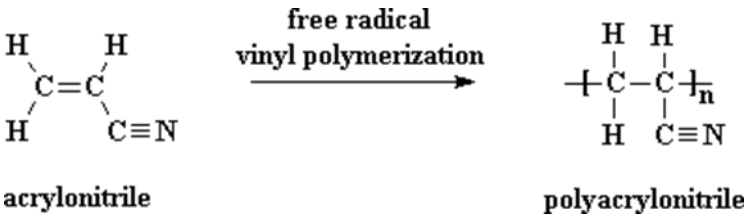

Figure 2.10. Preparation of polyacrylonitrile (PAN)

Polyacrylonitrile is highly used in copolymers, where it's present with 85% as propenonitrile units, making the copolymer much softer. Also, it is used as fabrics where it is a very harsh fiber, is used to reinforce the concrete and in road construction. Polyacrylonitrile (PAN) is suitable for preparing a semi-IPN (interpenetrating polymer network) hydrogel that is composed of polyacrylonitrile (PAN) and another hydrogel like chitosan to form copolymer [53].

2.7. CONTROLLED DRUG DELIVERY SYSTEMS

In controlled drug delivery system (DDS) usually constant drug concentration level is kept in blood plasma and tissue for a long period. The pharmacokinetics curves of conventional and controlled drug delivery system between drug concentrations in blood plasma vs. time is presented in Figure 2.11[54].

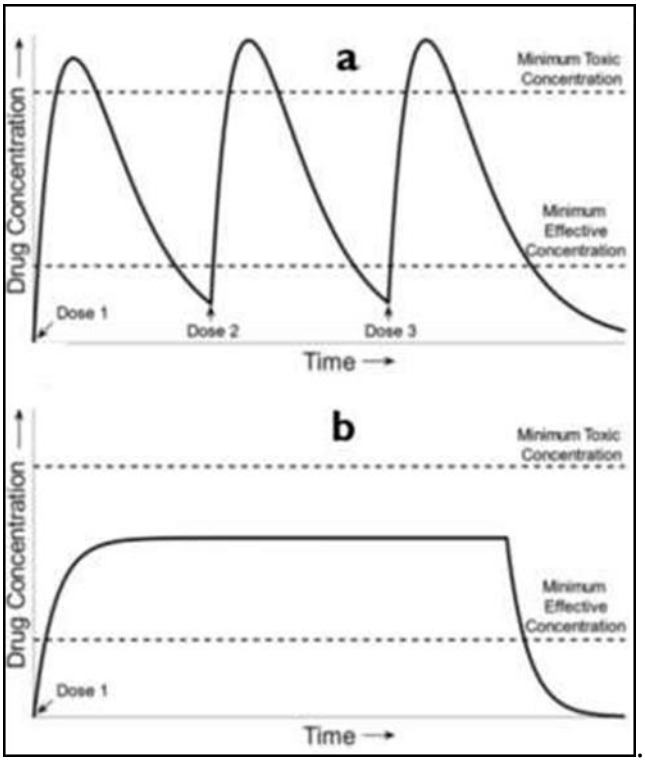

Figure 2.11. A typical drug bolus of a-Conventional DDS, b-Controlled DDS.

The conventional DDS shows the typical bolus pharmacokinetics curve for multiple dosing either taken by injections or by oral tablets, where the drug level shows fluctuation below and above the effective and toxic concentration, respectively. On the other hand, the figure shows a zero-order pharmacokinetics is recorded by controlled delivery system where just a single dose is given from a specific formulation or device. In controlled drug delivery system, the drug levels are maintained constant within the therapeutic window [54], that is by releasing the sufficient dose of the therapeutic agent at each time and it is continued for a pre-determined duration. Therefore, DDS could reduce fluctuation in drug and help in improving patient compliance. At the same time the drug toxicity reduces and grows in the overall efficacy of the dose [55].

2.8. CLASSIFICATION OF CONTROLLED DRUG DELIVERY SYSTEMS

Controlled-release drug delivery systems are classified as diffusion-controlled, water penetration-controlled, chemical-controlled and dissolution-controlled drug release systems [56].

2.8.1. Diffusion-controlled Dissolution System

The diffusion-controlled drug delivery systems are classified into membrane control reservoir systems and, monolithic matrix systems in which the drug is trapped or encapsulated in releases via diffusion through water insoluble polymeric membranes (reservoir systems) or polymeric matrices (monolithic systems) which are depicted Figure 2.12 [57,58]

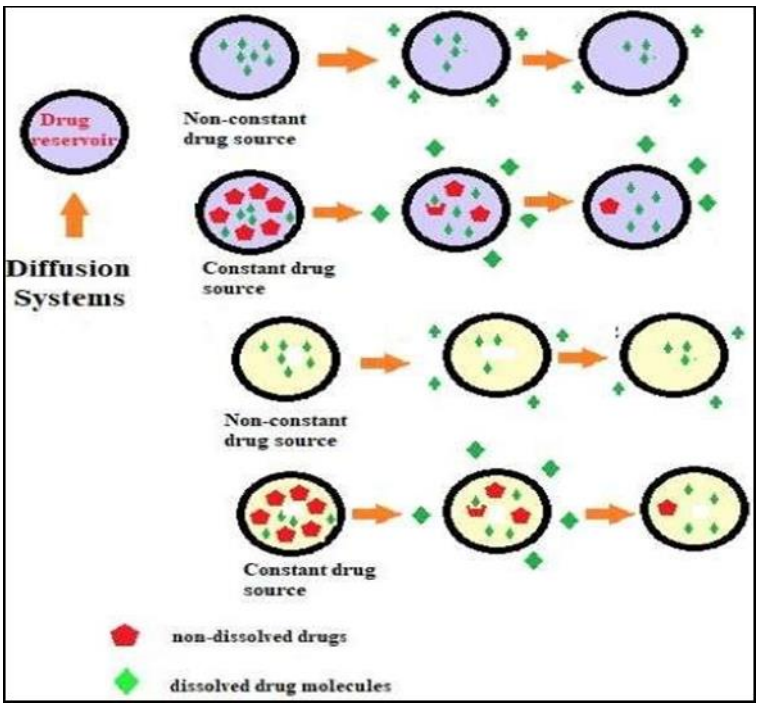

Figure 2.12. Schematic of the diffusion-controlled dissolution system

2.8.2. Water Penetration-controlled Drug Delivery Systems

Water penetration-controlled delivery systems include osmotic-controlled drug delivery systems (Figure 2.13) and swelling controlled drug delivery systems [59,60].

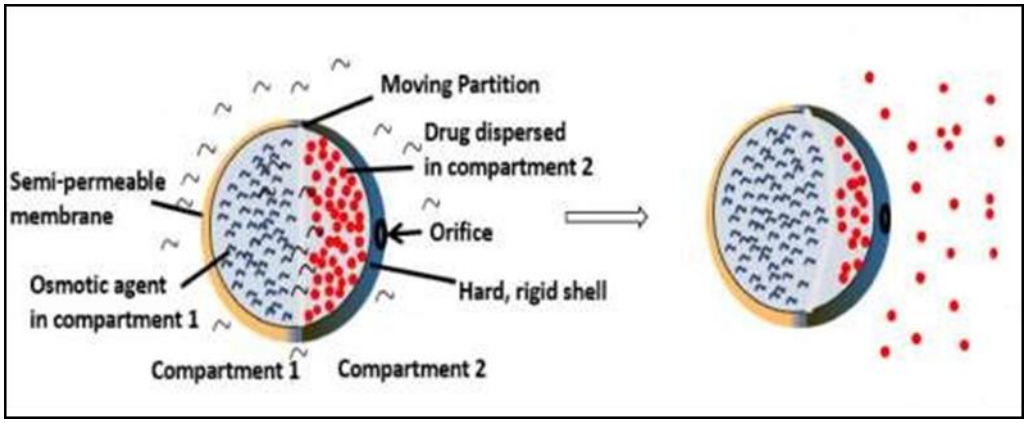

Figure 2.13. Schematic of the water penetration-controlled drug delivery system.

2.8.3. Chemically-controlled Drug Delivery Systems

In chemically-controlled drug delivery systems, there are basically two systems which are classified as polymer drug dispersion systems, and polymer drug conjugate systems (Figure 2.14) [61].

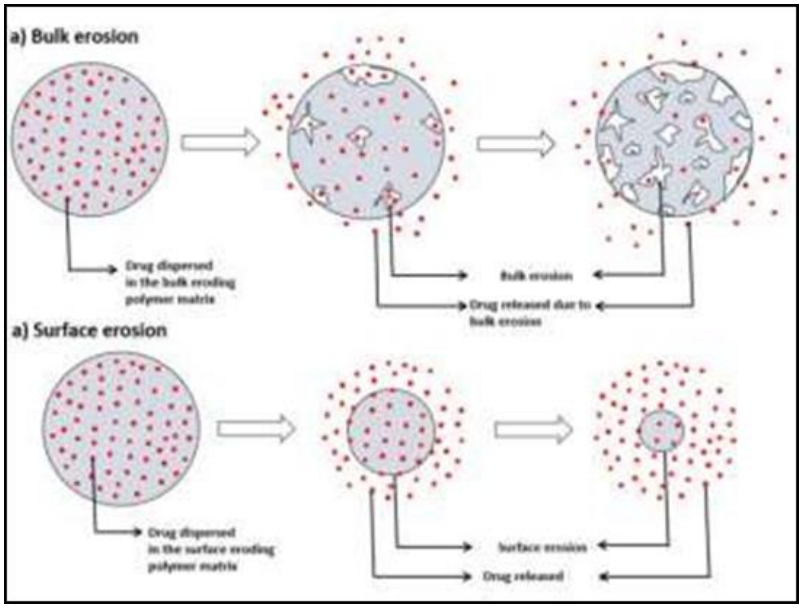

Figure 2.14. Schematic of the chemically-controlled drug delivery system.

2.8.4. Dissolution-controlled Drug Delivery Systems

Dissolution controlled drug delivery systems drugs which are coated or encapsulated in are released thorough slowly dissolving polymeric membranes (reservoir systems) or matrices (monolithic systems) [62].

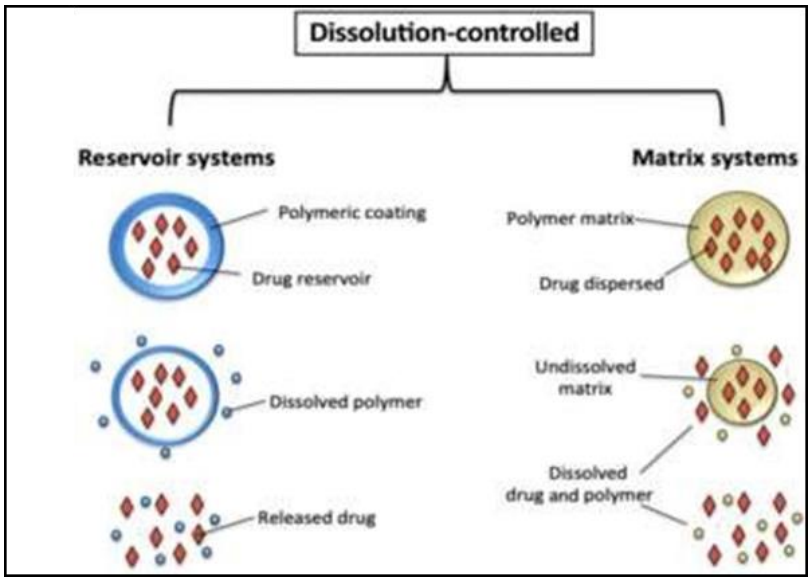

Figure 2.15. Schematic of the dissolution-controlled drug delivery system.

PART3

EXPERIMENTAL

3.1. MATERIALS AND CHEMICALS

The chemicals used in experimental part of the works are given in table 3.1.

Table 3.1. The used chemicals with their supply companies and purity percentages.

S.No.	Chemicals	Supply company	%Purity
1	Chitosan CH (MW:200,000 g.mol^{-1}), and 70wt% DDA	HiMedia Lab. Prt-ltd India	Highly viscose
2	Sodium hexameta phosphate SHMP	BDH, UK	94.5
3	Acrylic acid Aac	CAS, India	99.0
4	Acrylonitrile AN	Fluka, SW	99.4
5	Ammonium persulfate APS	PURE, USA	99.4
6	H_2O_2	Fluka, SW	99.7
7	Acetic acid	Fluka, SW	99.8
8	Hydroxychloroquen (drug model)	The state company for drugs industry and medical appliances, Samarra, IRAQ	99.0
9	Methanol	BDH, UK	99.9

3.2. APPARATUS AND INSTRUMENTS

The apparatus and instruments used for studying and characterizing the prepared hydrogels before and after loading with drug model and after releasing their loaded drug are as follows:

- Mental with mechanical stirrer, (Germany).
- Digital balance type analytical AND HR-200.
- ^{1}H NMR spectroscopy Proton Nuclear Magnetic Resonance Agilent Technologies of 499.35 MHz spectrometer freg. Germany solvent DMSO.
- X-ray diffraction type Panalytical X'Bert Pr, UK.

- Thermal analysis, instrument type DTA-60/ Simultaneous DTA-TG, Apparatus, Shimadzu/ Japan instrument.
- Field Emission Scanning electron microscope FESEM, FESEM-Imaging - EDS- Mapping Line-EBSD/ Germany
- UV-visible spectrophotometer instrument type Jasco V-630 spectrophotometer/ Japan.

3.3. PREPARATION OF CH SOLUTION

Solid chitosan (CH) of 70 wt% DDA and known average molecular weight is to be used. 1.0 g of CH is dissolved in (100mL) solvent of 2.0 %(v/v) acetic acid in distilled water under stirring for about (2hrs) at room temperature.

3.4. POLYMERIZATION OF ACRYLONITRILE (AN) AND ACRYLIC ACID (AAC)

Simple free radical polymerization is used for preparation of polyacrylonitrile (PAN) and poly (acrylic acid) (PAAc) where 5.0 g acrylonitrile monomer (AN), and 5.0 g acrylic acid monomer are poured in (250mL) round bottom flask, with (100mL) distilled water, and 0.5 g ammonium persulfate (APS) as initiator is added. The round is closed with condenser and the solution is refluxed at 70 ˚C with continuous stirring. After one hour, the heating is stopped and formed polymer is precipitated by adding methanol. The precipitate polymer is then filtered and dried [63,64].

3.5. PREPARATION OF PAN AND PAAC SOLUTION

Pure solid sample 1.0 g PAN is dissolved in 100mL distilled water and similarly 1.0 g PAAc is dissolved in 100 mL distilled water. The following mixtures are formed.

(75 mL) CH + (25 mL) PAN ----------1:0.3M of CH/PAN
(75 mL) CH + (25 mL) PAAc----------1:0.3M of CH/PAAc

The total 100mL of each previous solution is poured in beaker of 250 mL with continuous stirring. Then 10 mL of 5wt% of the ammonium persulfate (APS) initiator is added, and 2 mL hydrogen peroxide (H2O2) is added only to the CH: PAN mixture [65,66,67].

3.6. PREPARATION OF CROSS-LINKER SOLUTION

Sodium hexametaphosphate (SHMP) the cross-linker is prepared with (6.0 wt %) in 100 mL distilled water. Then the 100 mL SHMP is poured into 500 mL beaker and the solution is kept under stirring and heated at 70 ˚C using mantel with mechanical stirrer.

3.7. PREPARATION OF UNLOADED HYDROGEL MICROSPHERES

The previous mixtures of 100 mL CH/PAN, 100 mL CH/PAAc are transferred into a 5 mL syringe that has a narrow needle. The filled syringe goes to the beaker of 100 mL SHMP cross-linker solution which is kept under constant stirring. The polymer mixture is gradually injected as droplets inside the SHMP cross-linker solution for about 2 hrs and the solution is kept with gentle stirring and at 70 ˚C. After dropping of all polymer solution inside the cross-linker solution, the blend is filtered to collect copolymer microspheres and kept inside 50 ml of methanol with stirring for extra 30 min and at 25 ˚C or at ambient temperature. The formed microspheres are filtered and kept inside the vacuum oven overnight at 30 ˚C [68, 69]. The formed hydrogel microspheres are characterized by 1H NMR, XRD, FESEM, and (TGA, DTA and DSC) analysis.

3.8. DEGREE OF SWELLING OF HYDROGELS MICROSPHERES

The prepared hydrogels microspheres are examined in their degree of swelling. The microspheres sample is weighed precisely by a digital balance, and it is considered as *Wo*. The microspheres sample is transferred into a beaker containing distilled water, and the microspheres start swell, 3hr later, the swelled microspheres are removed from distilled water and transferred into sieve and even the extra drops of water are

removed by tissue paper for extra drying before weighting and it is considered as *Wt*. Furthermore, the microspheres are returned into swelling media for the next measurement. The weight processes for the microspheres are continued for every 3hr until there is no change in their weight. The degrees of swelling, *DS%,* of the microspheres are calculated according to the following equation [70].

$$DS\% = \frac{Wt - W_{\circ}}{W_{\circ}} \times 100 \quad (3.1)$$

Where, W_t is the weight of swell microspheres at *t* time, and $W_{\circ}$ is the weight of dry microspheres.

3.9. LOADING AND CROSS-LINKING THE HYDROGEL MICROSPHERES

For loading the hydrogel microspheres with drug, the previous procedure is repeated only to 100 mL SHMP solutions a 200 mg hydroxychloroquine the drug model is added, and the solution is kept under gentle stirring and heating at 70 ˚C. The mixtures (CH/PAN and CH/PAAc) are poured into the cross-linker and (drug drug/SHMP) solution using a syringe gradually for about 2hrs and the pH of the solution is adjusted to pH=7 temperature of 70 ˚C. Finally, after dropping of all polymer solution, the loaded microspheres are filtered off and kept inside 50 ml of methanol with constant stirring for another 30 min at 25 ˚C or ambient temperature. The formed microspheres were filtered and kept inside the vacuum oven overnight at 30 ˚C.

The maximum loading percentage %Lmax is calculated according to the following equation [71].

$$\%\ L_{max} = \frac{Amount\ of\ BSA\ protien\ loaded\ on\ hydrogel}{Amount\ of\ hydrogel\ taken\ for\ loading} \times 100 \quad (3.2)$$

3.10. CUMULATIVE RELEASE OF HYDROXYCHLOROQUINE FROM MICROSPHERES

The cumulative release (%Rcum) of hydroxychloroquine from hydrogel microspheres (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) are determined by keeping 100 mg loaded microspheres, in 20 mL distilled water.

The concentration of the released hydroxychloroquine after each 3 hrs from the microspheres is calculated by determining the absorbance (A) at wavelength λmax= 331 nm. A 3 mL of solution is taken from the release solution and replaced by native solution and its absorbance is measured using a UV-Visible spectrophotometer. Then through the calibration curve the concentration of the released drug is determined for each six hours until the concentration of the drug release become zero. The cumulative drug release from is given by the following equation [72,73].

$$\text{Cumulative release } (\%R_{cum}) = \frac{Wt}{W_{\circ}} \times 100 \qquad (3.3)$$

Where *Wt* is the amount of hydroxychloroquine released at time *t*, and $W_{\circ}$ is the total amount of drug release finally.

3.11. CHARACTERIZATIONS OF THE PREPARED HYDROGEL MICROSPHERES

Modern and advanced characterization analysis were applied using advanced techniques on the unloaded microspheres, beside those loaded with hydroxychloroquine, and the microspheres after drug release.

3.11.1. ^{1}H NMR Analysis

The ^{1}H NMR spectroscopy of (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels was obtained using a 500 MHz spectrometer, using deuterated DMSO solvent.

3.11.2. Thermal Characterization

To test the thermal stability of hydroxychloroquine loaded microspheres, the thermogravimetric analysis TGA, Differential thermal analysis DTA, and differential scanning calorimetry DSC, of unloaded microspheres of (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) were done. The thermal analyzer instrument was fixed at a heating rate of 10 ℃/min in nitrogen atmospheres.

3.11.3. X-ray Diffraction Measurements

X-ray diffraction (XRD) analysis of unloaded (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels were performed up to 20 scale in an angle range of 5°- 90° at a scan speed of 1°/min using Copper/Indium (0.9/0.1) 100% radiation target and nickel filter at a current of around 20 μA a voltage of 35 kv.

3.11.4. Field Emission Scanning Electron Microscopy FESEM

FESEM image was taken for (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels. The samples were mounted on aluminum studs by double adhesive taps, then coated with gold under vacuum by beam sputter.

PART4

RESULTS

4.1. CHARACTERIZATION STUDIES

Copolymerization of chitosan was done with polyacrylonitrile and cross-linked with physical cross-linker (sodium hexametaphosphate) (CH-co-PAN/SHMP) hydrogel. Besides, the copolymerization of chitosan was also carried out using poly(acrylic acid) and cross-linked with physical cross-linker (sodium hexametaphosphate) (CH-co-PAAc/SHMP) hydrogel. Both hydrogel samples were characterized, and their chemical structures have been determined by ^{1}H NMR spectroscopy analysis. In addition, the crystalline structures of the prepared hydrogels were investigated using X-ray diffraction. Moreover, the thermal behaviors of the studied hydrogels were carried out as thermogravimetric analysis (TGA), differential thermal analysis (DTA), and differential scanning calorimetry (DSC). Finally, the morphological surfaces of the prepared hydrogels were examined by field emission scanning electron microscopy (FESEM).

4.1.1. ^{1}H NMR Spectroscopy

The ^{1}H NMR spectroscopy of (CH-co-PAN/SHMP) hydrogel, and (CH-co-PAAc/SHMP) hydrogel were done using Agilent Technologies of 499.35 MHz spectrometer frequency; Germany. Solvent; Deuterated DMSO. The results are illustrated in the following Table 4.2, and Figure 4.1 for (CH-co-PAN/SHMP) hydrogel, and Table 4.1, and Figure 4.2 for (CH-co-PAAc/SH+MP) hydrogel.

Table 4.1. [1]H NMR spectroscopy results showing the chemical shifts of the main protons of the studied hydrogels.

Hydrogel	Chemical Shift (ppm)	Descriptions of proton
(CH-co-PAN/ SHMP)	1.21 1.4 2.52-3.48 4.14	(CH_2) methylene groups of chitosan and PAN (CH) Methine groups of chitosan and PAN Protons of amide group of PAN Protons of D-glucopyranose ring in chitosan
	1.21-2.51	Protons of chitosan/PAAc hydrogel [19]
(CH-co-PAAc /SHMP)	3.33	Protons of chitosan

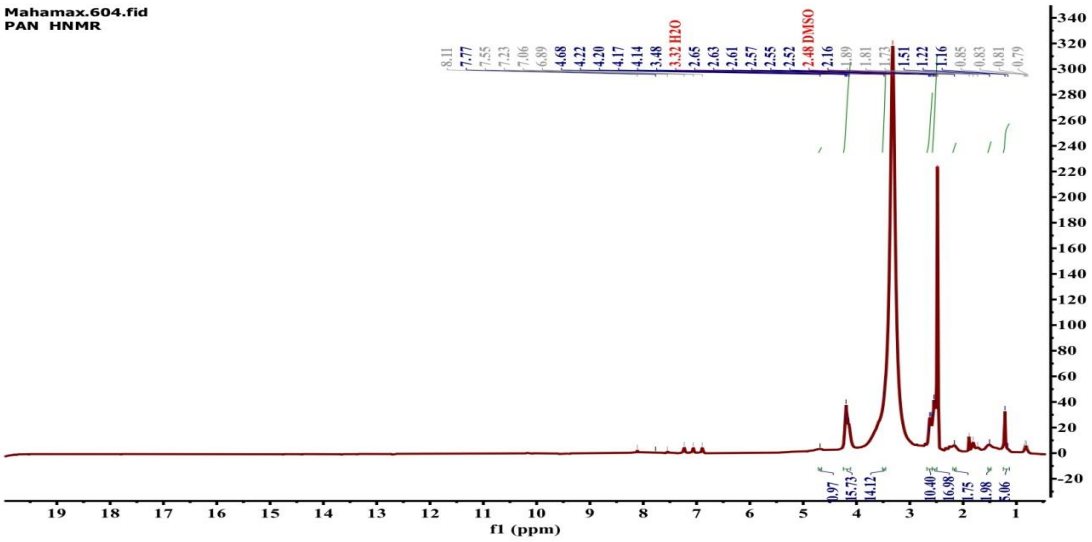

Figure 4.1. [1]H NMR spectrum of (CH-co-PAN/SHMP) hydrogel.

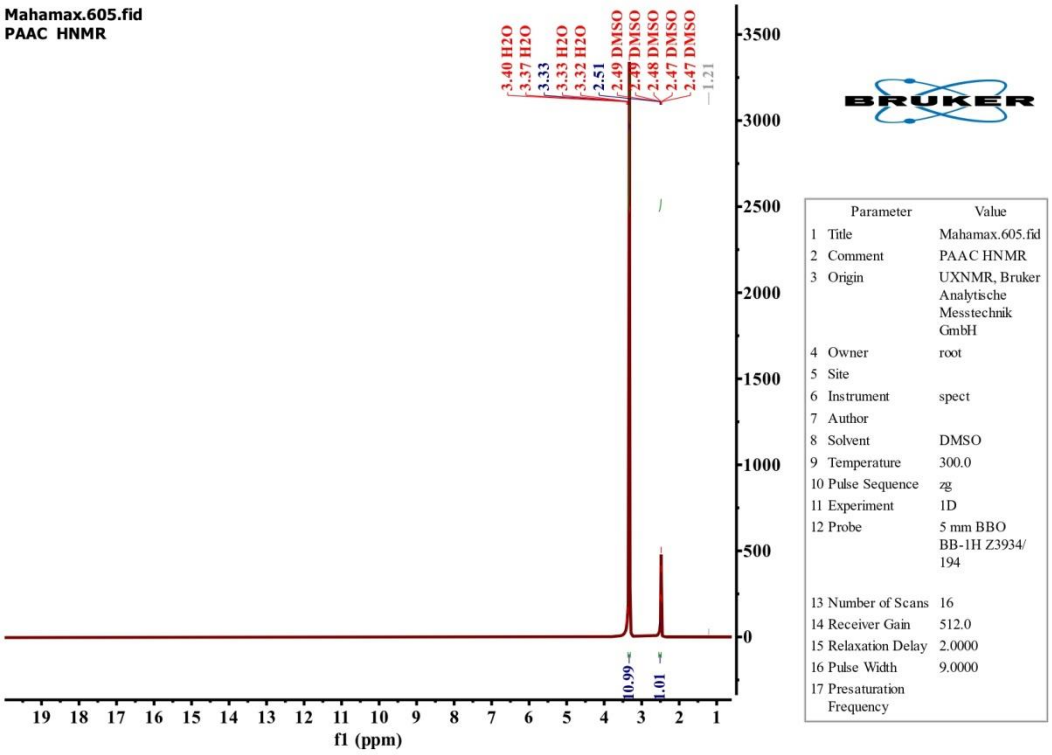

Figure 4.2. ^{1}H NMR spectrum of (CH-co-PAAc/SHMP) hydrogel.

4.1.2. X-ray Diffraction

The XRD of (CH-co-PAN/SHMP) hydrogel, and (CH-co-PAAc/SHMP) hydrogel were done using X-ray instrument kind, Panalytical X'Bert Pr, UK. The results are shown in the following Figure 4.3, Table 4.2 for (CH-co-PAN/SHMP) hydrogel, and Figure 4.4, and Table 4.3 for (CH-co-PAAc/SHMP) hydrogel.

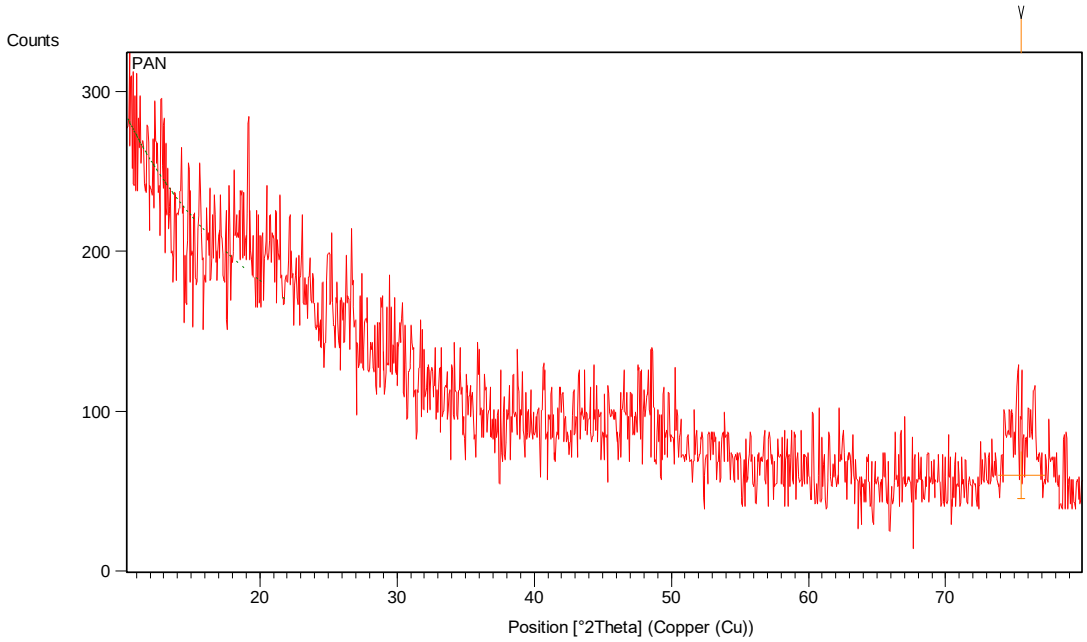

Figure 4.3. XRD pattern of (CH-co-PAN/SHMP) hydrogel.

Table 4.2. XRD data of (CH-co-PAN/SHMP) hydrogel.

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]	Tip Width	Matched by
75.47(7)	30(2)	3.4(2)	1.25857	100.00	4.0307	

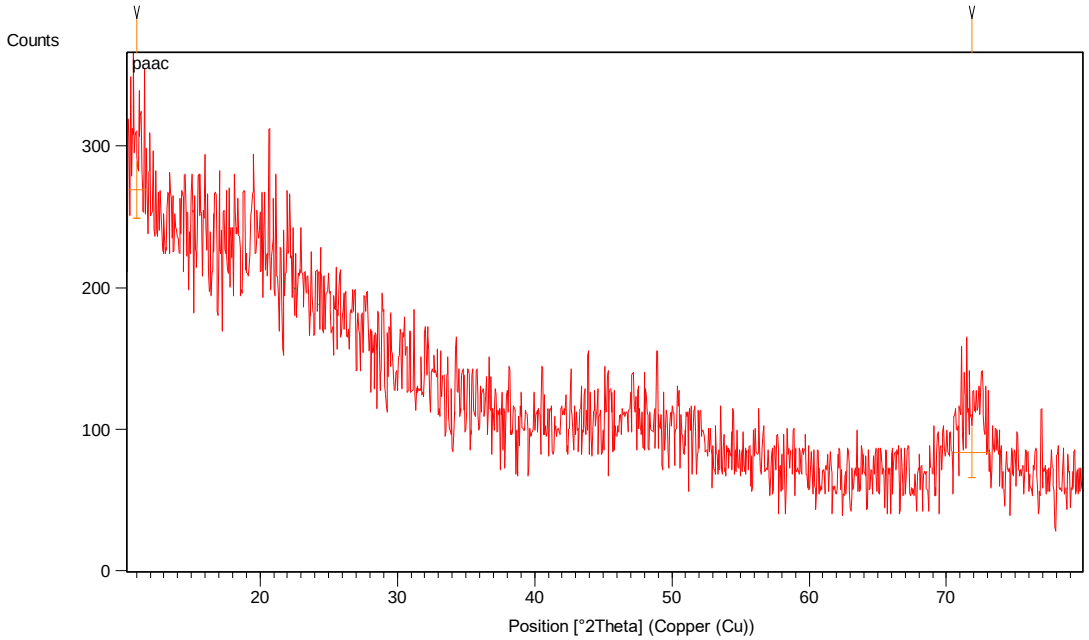

Figure 4.4. XRD pattern of (CH-co-PAAc/SHMP) hydrogel.

Table 4.3. XRD data of (CH-co-PAAc/SHMP) hydrogel

Pos. [°2Th.]	Height [cts]	FWHM Left [°2Th.]	d-spacing [Å]	Rel. Int. [%]	Tip Width	Matched by
11.01(6)	40(7)	1.2(2)	8.02632	100.00	1.4498	
71.85(5)	36(2)	2.6(1)	1.31288	90.07	3.1379	

4.1.3. Thermal Analysis (TGA, DTA and DSC)

Thermal analyses of (CH-co-PAN/SHMP) hydrogel, and (CH-co-PAAc/SHMP) hydrogel using instrument type DTA-60/ Simultaneous DTA-TG, Apparatus, Shimazdu/Japan. The results are given in the following Figures (4.5, 4.6), and Table 4.4, for (CH-co-PAN/SHMP) hydrogel, beside Figures (4.7, 4.8), and Table 4.4, for (CH-co-PAAc/SHMP) hydrogel.

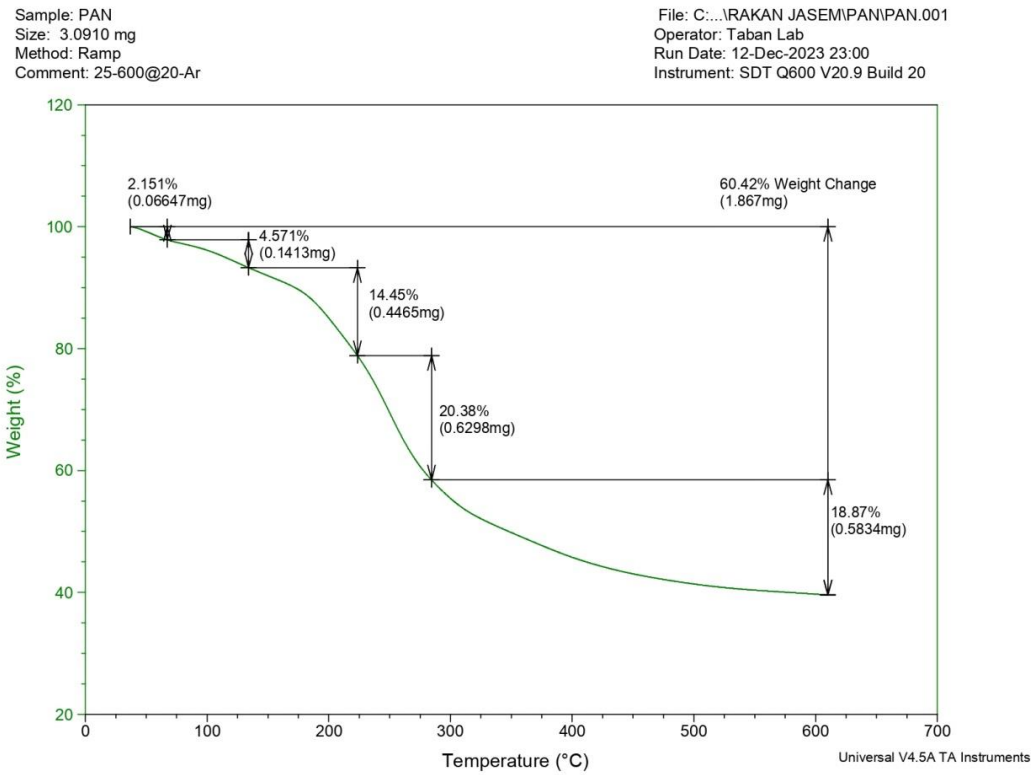

Figure 4.5. TGA thermogram of (CH-co-PAN/SHMP) hydrogel.

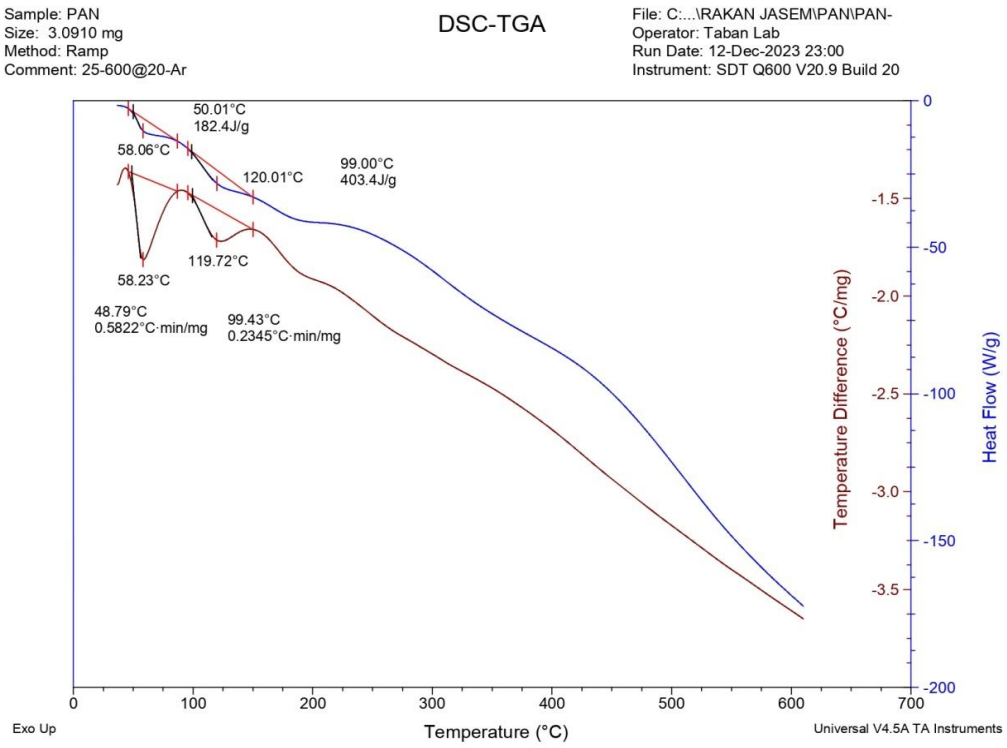

Figure 4.6. TGA and DSC of (CH-co-PAN/SHMP) hydrogel.

Table 4.4. Thermal data TGA, DTA and DSC of prepared hydrogels.

Hydrogel	**TGA weight loss (%)**				**DTA 1/℃**			**DSC (w/g)**	
	IDT ℃	FDT ℃	Tmax ℃	Tcr ℃	1st decomp 1/℃	2nd decomp 1/℃	Tg ℃	ΔH_f/ (J/g)	
(CH-co-PAN/SHMP)	2.2	40	20	22	0.5822	0.2345		182.4	403.4
	75 ℃	800 ℃	225 ℃	290 ℃	49 ℃	99.5 ℃	73	50 ℃	99 ℃
(CH-co-PAAc/SHMP)	3.2	35	15	25	0.7157	0.1055		53.33	319.5
	60 ℃	600 ℃	235 ℃	275 ℃	73 ℃	135 ℃	40	76 ℃	156 ℃

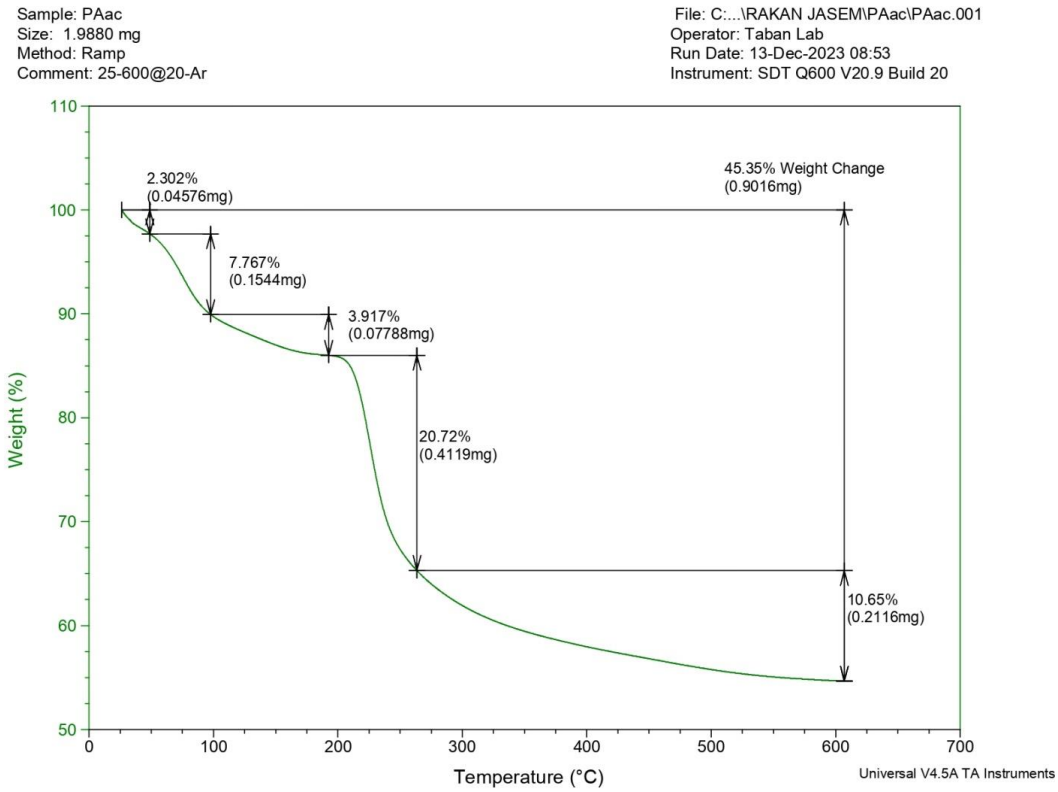

Figure 4.7. TGA thermogram of (CH-co-PAAc/SHMP) hydrogel.

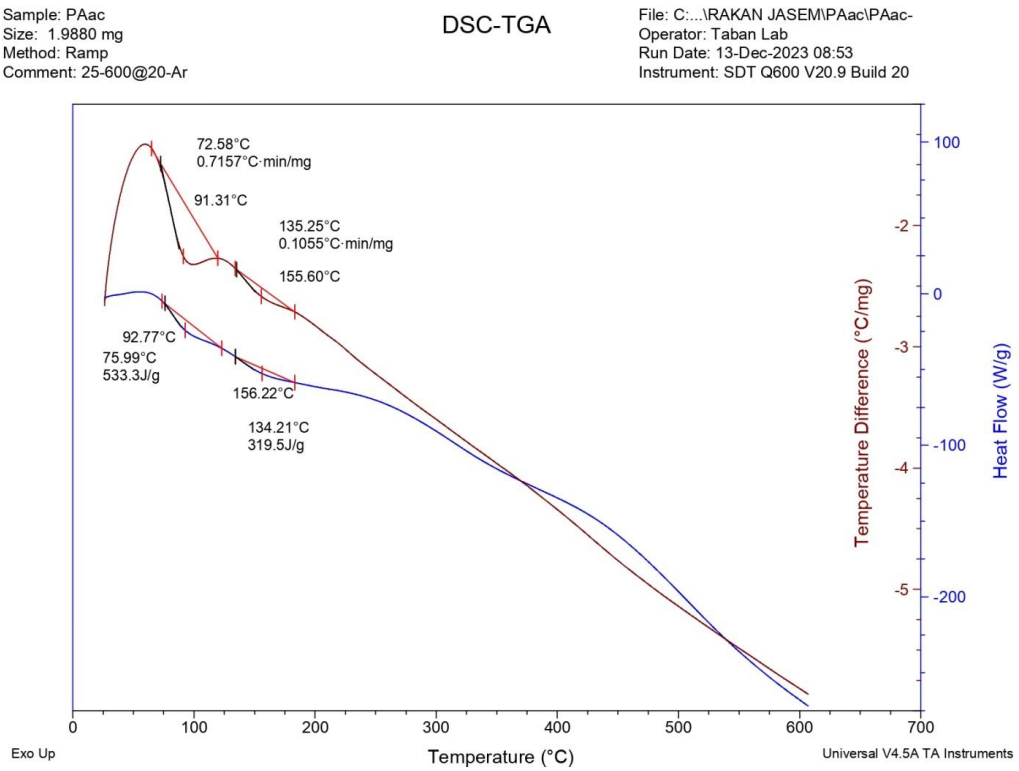

Figure 4.8. TGA and DSC of (CH-co-PAAc/SHMP) hydrogel.

4.1.4. FESEM

The field emission scanning electron microscope images of the (CH-co-PAN/SHMP) hydrogel, and (CH-co-PAAc/SHMP) hydrogel were studied using FESEM-Imaging - EDS- Mapping Line-EBSD/ Germany. The results are illustrated in the following Figure 4.9 for (CH-co-PAN/SHMP) hydrogel, and Figure 4.10 for (CH-co-PAAc/SHMP) hydrogel.

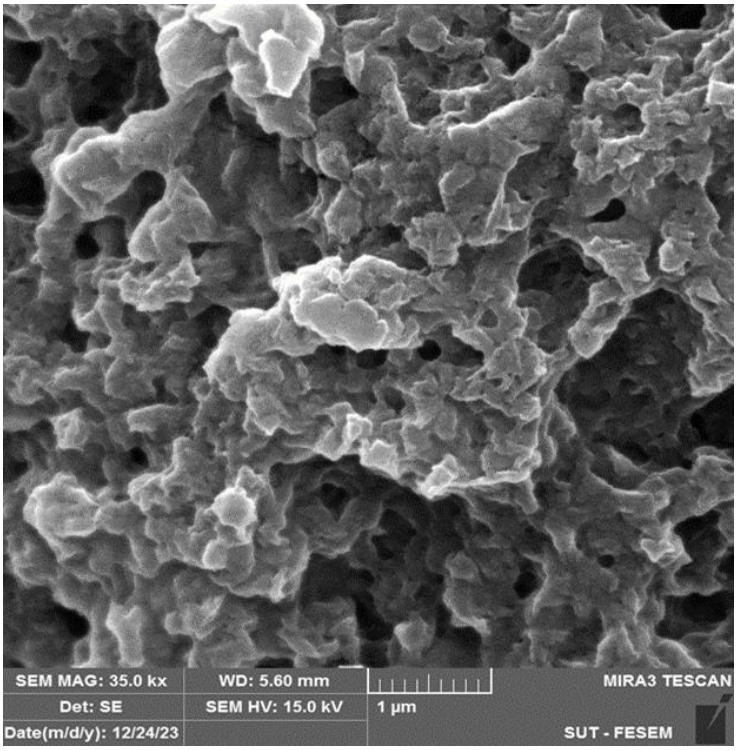

Figure 4.9. FESEM image of (CH-co-PAN/SHMP) hydrogel.

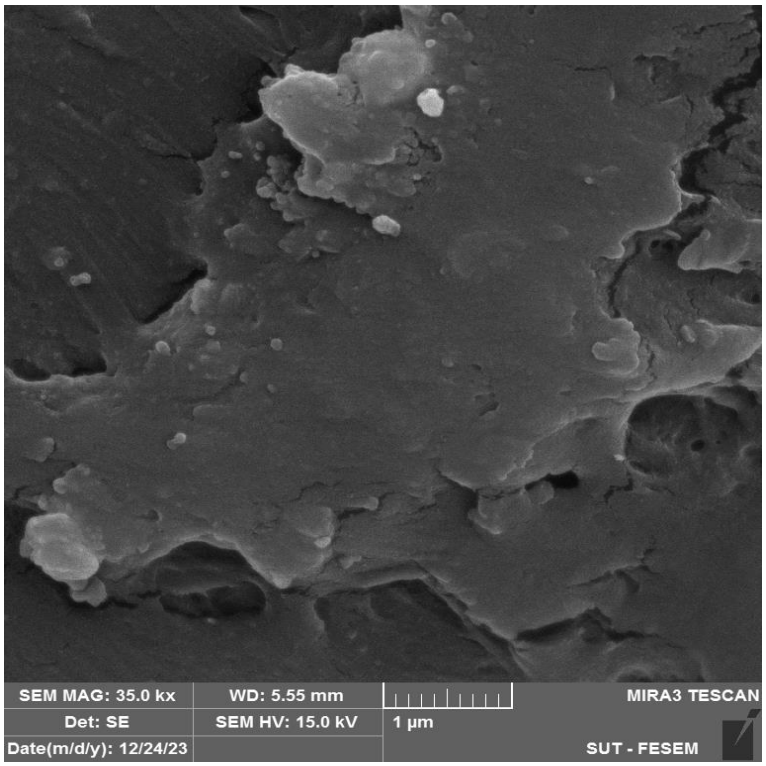

Figure 4.10. FESEM image of (CH-co-PAAc/SHMP) hydrogel.

4.2. DEGREE OF SWELLING

The degree of swelling of (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels were measured according to the procedure mentioned in the experimental part paragraph (2.8). The DS% was calculated according to the (Eq. No.1) and the data was recorded in Figure 4.11.

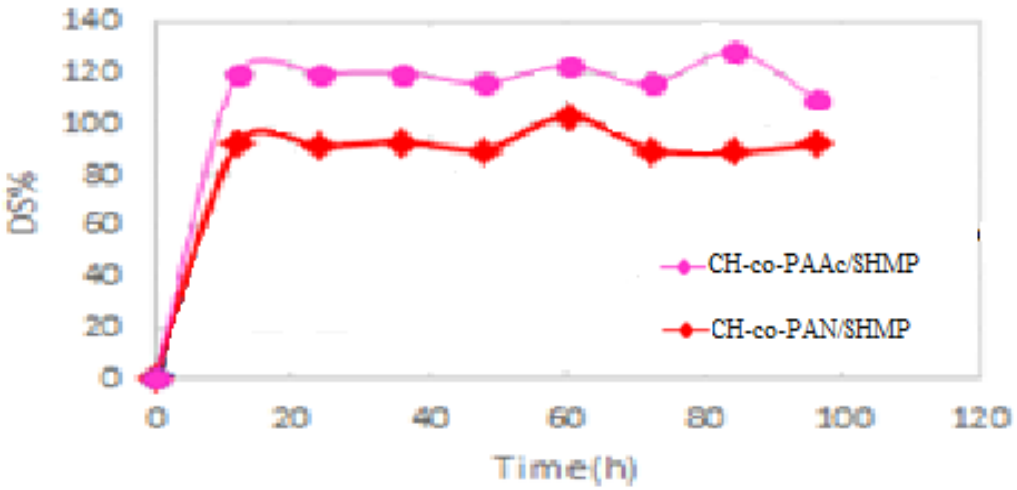

Figure 4.11. Degree of swelling percentage (DS%) of (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels, 100 mg microspheres in 20 mL swelling solution fixed at pH=7, and 37 ˚C.

4.3. LOADING OF HYDROXYCHLOROQUINE DRUG INTO HYDROGEL MICROSPHERES

The prepared microspheres of (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels were loaded with hydroxychloroquine drug and their maximum loading percentages (Lmax%) were determined according to (Eq. No. 2), using UV-Visible spectrophotometer and depends on the calibration curve of the drug. The Lmax% of both hydrogels with drug is recorded in the following Figure 4.12.

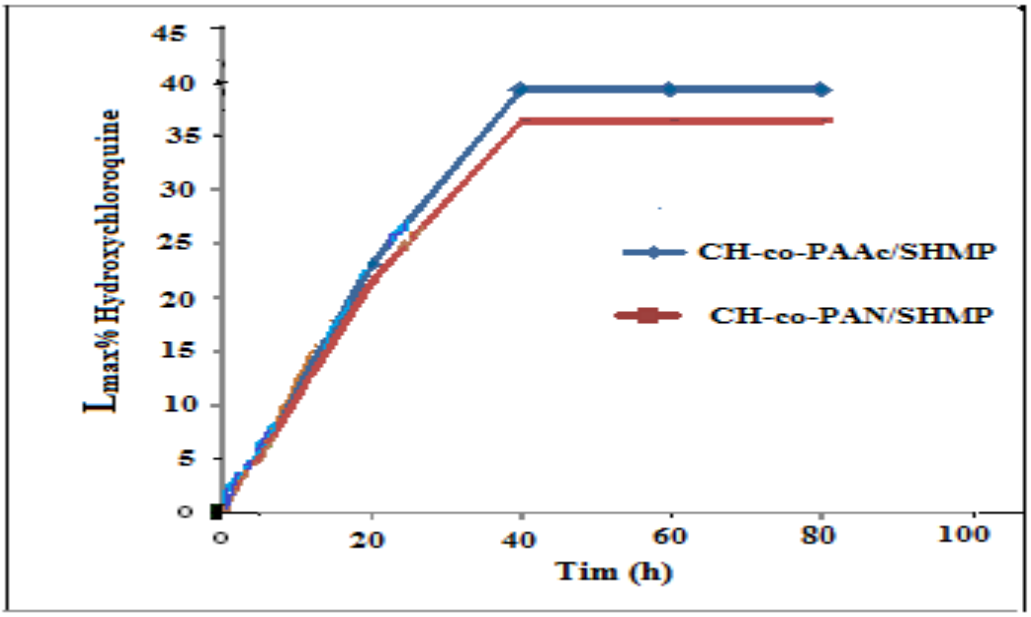

Figure 4.12. Maximum loading percentages (Lmax%) of (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels with 200 mg hydroxychloroquine for 2h loading time, and under ambient temperature in pH=7 solution.

4.3.1. FESEM of Loaded Microspheres

The FESEM images of the (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels were done after loading the microspheres with hydroxychloroquine. The following Figures 4.13 and 4.14 show the drug molecules clear on (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels respectively.

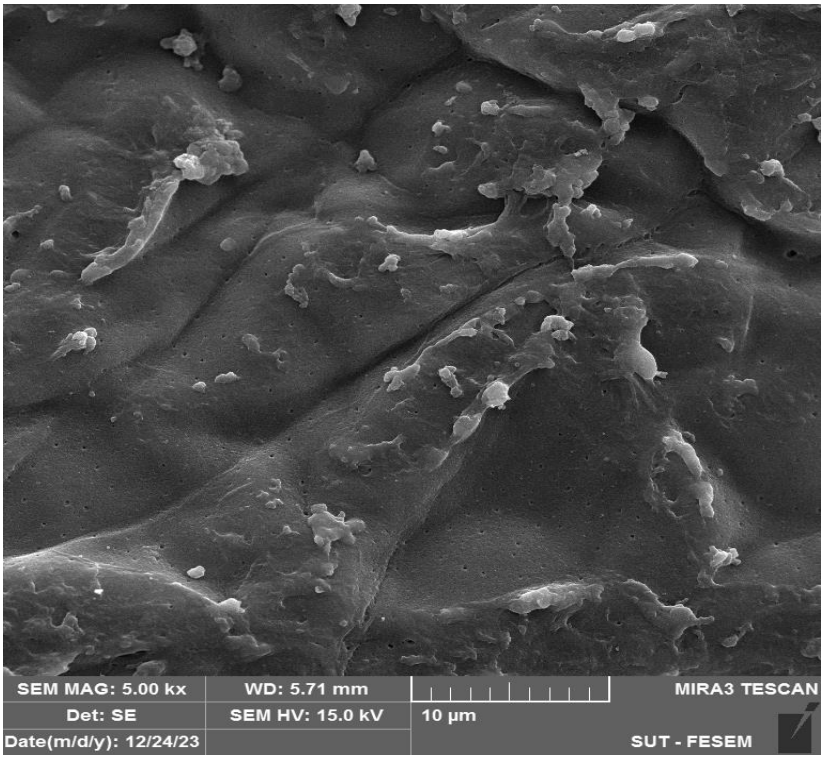

Figure 4.13. FESEM image of (CH-co-PAN/SHMP) microspheres loaded with hydroxychloroquine drug.

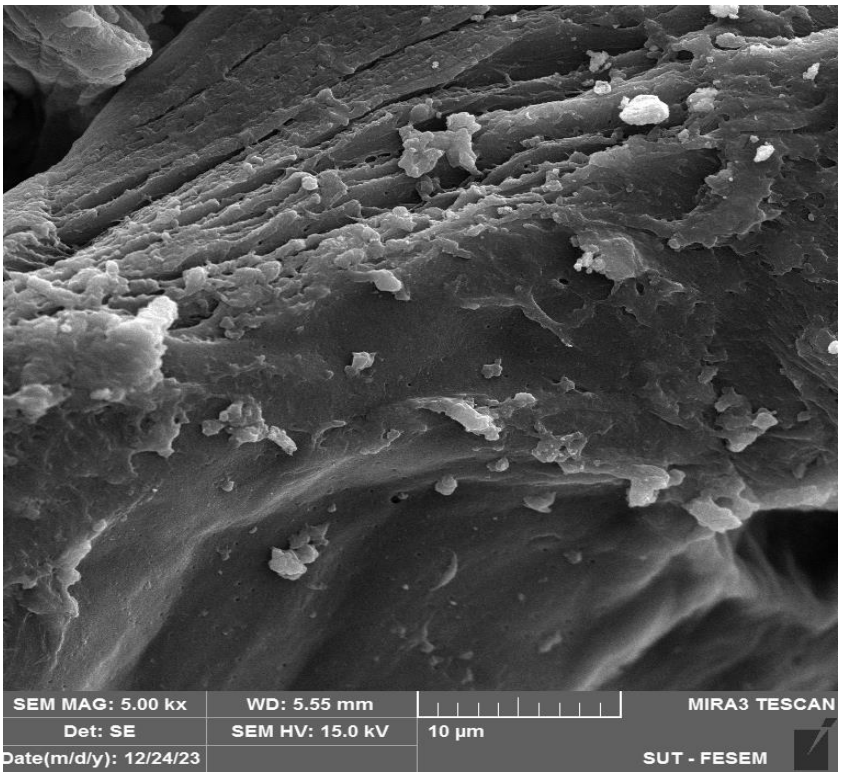

Figure 4.14. FESEM image of (CH-co-PAAc/SHMP) microspheres loaded with hydroxychloroquine drug.

4.4. CONTROLLED DRUG RELEASE BEHAVIORS OF LOADED MICROSPHERES

The controlled drug release behaviors of the loaded microspheres from (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels were studied. The concentrations of hydroxychloroquin released from microspheres were determined by measuring the absorbance (A) of the release solution after each 6hrs. The concentration of the released drug was determined depending on the previous calibration curve at wavelength λmax= 331nm. The following results are illustrated in Table 4.5, and Figure 4.15.

Table 4.5. Hydroxychloroquine loading percentage with release behaviors of the prepared microspheres shows their burst and controlled release beside controlled release time

Microscopicsample	Maximum loading L_{max} (mg)	pH of the Release solution	Burst releasemg	Controlled Release Mg	Controlled release time h
CH-co-PAAc/SHMP	39.0	7.4	6.4	29.6	30.0
CH-co-PAN/SHMP	36.0	7.4	10.5	23.5	24.0

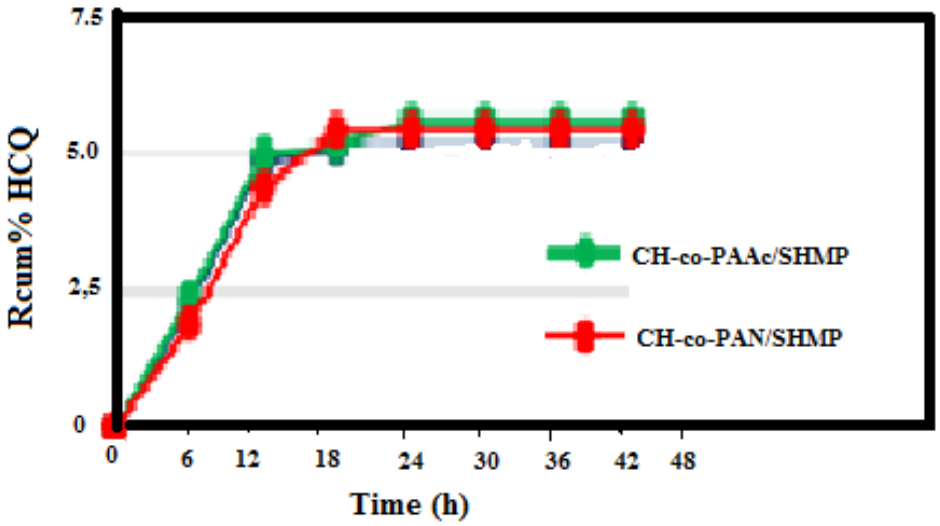

Figure 4.15. Cumulative release (%Rcum) of (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels versus time (h). 100mgmicrospheres in 20mL buffered solution pH=7.4, and at T= 37oC.

4.4.1. FESEM of Hydrogel Microspheres After Release

The FESEM images of the (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels were done after the microspheres released their loaded hydroxychloroquine. The following Figures 4.16 and 4.17 shows the microspheres shape images of the (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels, respectively.

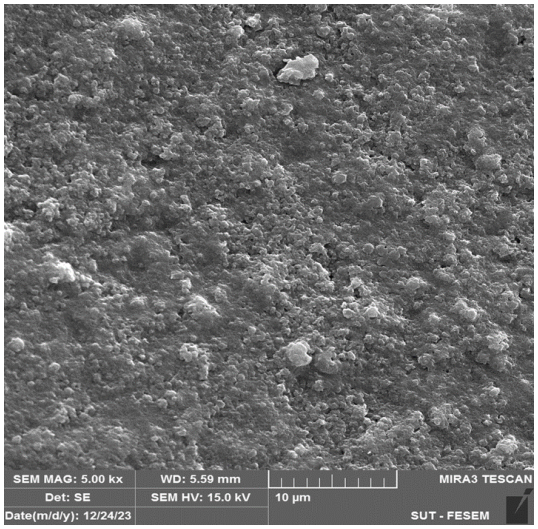

Figure 4.16. FESEM image of (CH-co-PAN/SHMP) microspheres after release of hydroxychloroquine drug.

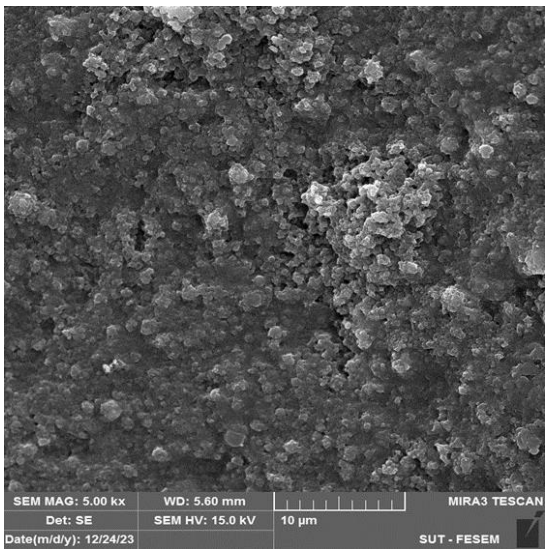

Figure 4.17. FESEM image of (CH-co-PAAc/SHMP) microspheres after release of hydroxychloroquine drug.

PART 5

DISCUSSION

From medical view chitosan the most abounded polysaccharides is biocompatible, non-immunogenic, and non-toxic material suitable to use in drug delivery systems. Furthermore, chitosan is capable for encapsulate drugs and release them in a sustained and controlled manner [74]. Different properties of the polymeric systems such as the physicochemical, thermal, mechanical, and morphological structures can play a significant role in release process of loaded drug and controlling such process. Moreover, copolymerization of chitosan, the cationic polysaccharide with synthetic polymers with hydrolysable functional group like polyacrylonitrile (PAN), and poly(acrylic acid) (PAAc) could produce hydrogels with both functional groups. The blend copolymers could swell to a wide range in different pH media, beside loading drugs and keep later for release in controlled manner and have shown long-term release under controlled in the therapeutic window.

5.1. BLEND HYDROGELS AND THEIR CHARACTERIZATIONS

The hydrogels were prepared (1:1M) by blending copolymerization of chitosan with one of the following synthetic polymers, polyacrylonitrile (PAN), and poly (acrylic acid) (PAAc), then followed with physical cross-linking using sodium hexametaphosphate (SHMP). The prepared hydrogels are given the following abbreviations.

Blend hydrogel descriptions	Abbreviation
Chitosan blend polyacrylonitrile and cross-linked with sodium hexametaphosphate	(CH-co-PAN/SHMP)
Chitosan blend poly(acrylic acid) and cross-linked with sodium hexametaphosphate	(CH-co-PAAc/SHMP)

The prepared hydrogels were characterized, and the following analyses were applied, ^{1}H NMR, X-Ray diffraction, Thermal analysis (TGA, DTA, and DSC), and finally the field emission scanning electron microscope (FESEM).

5.1.1. ^{1}H NMR Analysis

The ^{1}H NMR spectrum of (CH-co-PAN/SHMP) hydrogel given in Figure 4.1, and Table 4.1, shows the resonance (2H, s) at 1.21 ppm represents the methylene (CH2) groups presenting in chitosan and those of polyacrylonitrile. Whereas the resonance (1H, s) at 1.4 ppm belongs to methine groups present in chitosan and PAN. In addition, the resonances (^{1}H, w) at chemical shift (2.52 – 3.48) ppm are for protons of amide groups of polyacrylonitrile. The protons of D-glucopyranose ring in chitosan give resonance (^{1}H, w) at 4.14 ppm. The total regions of the important protons confirm the blend of chitosan with polyacrylonitrile in copolymer hydrogel.

On the other hand, the ^{1}H NMR spectrum of (CH-co-PAAc/SHMP) hydrogel Figure 4.2, and Table 4.1, shows the resonance (^{1}H, s) at (1.21– 2.51) ppm which represent the protons of chitosan blend poly(acrylic acid) [75]. Beside the resonance (^{1}H, w) at 3.33 ppm belongs to the protons of the chitosan. The overall descriptions prove the blend copolymerization of chitosan with poly(acrylic acid).

5.1.2. X-Ray Diffraction Analyses

The XRD pattern of (CH-co-PAN/SHMP) hydrogel given in Figure 4.3, and Table 4.2, indicates that the prepared hydrogel is between amorphous to semi-crystalline, where the structure of the hydrogel is very poor in crystalline maxima along the 2θ axis. The only maxima peak at 75.47^{o} with very narrow full width at half maximum (FWHM) has very low d-spacing magnitude (1.25857 Å) which belongs to PAN. The overall facts got from XRD analyses indicate that the hydrogel is amorphous due to the presence of the highly amorphous chitosan compound.

Similarly, the XRD pattern of (CH-co-PAAc/SHMP) hydrogel Figure 4.4, and Table 4.3, have shown the prepared hydrogel is also near amorphous state, where two

maxima peaks are shows at 11.01º and 71.85º along the 2θ axis, also with very narrow FWHM and very low d-spacing magnitude (8.02632, 1.31288 Å) respectively belongs to the PAAc polymer. Which means the presence of chitosan will force the final blend hydrogel to be amorphous.

5.1.3. Thermal Analyses (TGA, DTA and DSC)

The thermal analyses of (CH-co-PAN/SHMP) hydrogel given in Figures (4.5, 4.6), and Table 4.4, have shown from TGA thermogram Figure 4.5 and Table 4.4, the initial decomposition temperature (IDP) is 2.2 wt loss% at 75 ˚C, whereas the final decomposition temperature (FDT) is 40 wt loss% at 800 ˚C, means the hydrogel is thermally stable. Even the maximum decomposition temperature (Tmax) and crystalline decomposition temperature (Tcr) have 20 wt loss% at 225 ˚C and 22 wt loss% at 290 ˚C respectively. The DTA thermogram (Figure 4.6 and Table 4.4) has shown two decomposition curves represent the thermal decomposition of the functional groups of chitosan and PAN polymer and this is clear from the DSC thermogram (Figure 4.6, and Table 4.4) where the heat of fusion (ΔHf) at 50 ˚C and 99 ˚C as (182.4 J/g) and (403.4 J/g) respectively, indicate the (CH-co-PAN/SHMP) hydrogel is endothermic polymer.

On the other hand, the thermal analyses of (CH-co-PAAc/SHMP) hydrogel Figures (4.7, 4.8), and Table 4 have shown the TGA thermogram Figure 4.7 and Table 4.4, the IDT is 3.2 wt loss% at 60 ˚C means the free water in the hydrogel was larger than that of the previous hydrogel. The FDT was 35 wt loss% at 600 ˚C, which means the (CH-co-PAAc/SHMP) hydrogel is less thermally stable in comparison with (CH-co-PAN/SHMP) hydrogel. The Tmax and Tcr are (15 and 25) wt loss% at 235 ˚C and 275 ˚C respectively. The DTA and DSC thermogram Figure 4.8, and Table 4.4, also shows two decomposition curves and two (ΔHf) of (53.33 J/g) and (319.5J/g) at 76 ˚C and 156 ˚C respectively, and still, this means the (CH-co-PAN/SHMP) hydrogel is more stable than (CH-co-PAAc/SHMP) hydrogel, although both thermally are stable hydrogels.

5.1.4. FESEM Analyses

The FESEM image of (CH-co-PAN/SHMP) hydrogel given in Figure 4.9 shows the surface morphologies of the hydrogel have no spherical particles with long surface area. The partial white spots distributed on its surface indicate the hydrogel composites have partial crystalline region and this is clear from its XRD pattern Figure 4.3 and Table 4.2. The hydrogel surface also shows a largely folded surface with huge number of holes and pores which will help too much in loading and containing drug molecules.

Whereas the FESEM image of (CH-co-PAAc/SHMP) hydrogel given in Figure 4.10 shows a very homogeneous surface with undulate and coarse surface containing some protrusions. The highly folded and opaque structure accentual the high amorphous surface and such property help for high degree of swelling and increase drug loading percentages.

5.2. STUDIES ON DEGREE OF SWELLING

The degree of swelling percentages (DS%) of (CH-co-PAN/SHMP) and (CH-co-PAAc/SHMP) hydrogels were measured and their data recorded in Figure 4.11. Accordingly, the two hydrogels start to swell after 12 hrs and show high degree of swelling percentages from the begin and the (CH-co-PAAc/SHMP) hydrogel gives higher DS% than (CH-co-PAN/SHMP) hydrogel, where it reaches almost DS%=120% in comparison with DS%=90% for (CH-co-PAN/SHMP) hydrogel. The difference in DS% of both hydrogels belongs to the types of synthetic polymers blended to chitosan, where the amide groups of PAN polymer (Figure 4.11) are stronger in formation of hydrogen bond which increase the attraction forces between the polymer and chitosan chains which in turn means higher intra- and inter-molecular forces. Whereas the PAAC polymer (Figure 4.11) causes repulsion forces between its chains and chitosan chains helps the hydrogel to swell more.

5.3. STUDIES ON LOADING OF HYDROXYCHLOROQUINE ON HYDROGEL MICROSPHERES

Hydrochloroquine drug was selected as model for loading on both prepared hydrogels (CH-co-PAN/SHMP), and (CH-co-PAAc/SHMP) hydrogels. Hydroxychloroquine has a chemical structure shown in Figure 5.1.

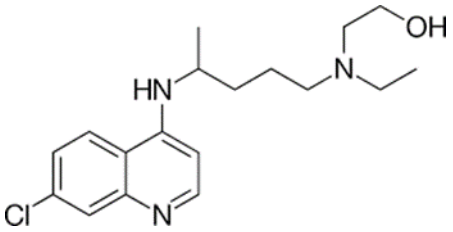

Figure 5.1. Chemical structure of hydroxychloroquine.

The loading of drug on the hydrogel microspheres depends on many factors, but in this investigation wed concentrated on difference in types of synthetic polymer blended with chitosan, although the structure of drug, pH of the loading medium and its ionic strength, functional groups of chitosan, temperature of loading media, time of loading type of cross-linker, etc. were all the same.

The maximum loading percentages (Lmax%) shown in Figure 4.12 clearly indicates that the time of loading and changing the synthetic polymer are the important variables studied in this investigation. In the UV-Visible spectroscopy measurements using the calibration curve of hydroxychloroquine drug at its wavelength λmax=331nm, the concentrations of the loaded drug on the hydrogel microspheres were determined, and according to the (Eq.No.2), the Lmax% of both hydrogels (CH-co-PAN/SHMP), and (CH-co-PAAc/SHMP) were calculated. Figure 4.12 shows (CH-co-PAAc/SHMP) hydrogel has Lmax%=39.0%, whereas (CH-co-PAN/SHMP) has Lmax%=36.0%. This proves the fact that hydrogel with more degree of swelling has the opportunity for more loading percentage.

5.3.1. Characterization of Loaded Microspheres by FESEM Analysis

The loaded (CH-co-PAN/SHMP), and (CH-co-PAAc/SHMP) hydrogel microspheres with hydroxychloroquine were characterized using FESEM analysis, and their images are shown in Figures 4.13 and 4.14

The FESEM image of (CH-co-PAN/SHMP) hydrogel given in Figures 4.13 shows the surface morphology of the sample with folds and the particles of hydroxychloroquine appear in between the folds and even some are adsorbed on its surface shows as white spots because of the difference in crystalline percentages where the drug particles are more crystalline than hydrogel microspheres.

Similarly, the FESEM image of (CH-co-PAAc/SHMP) hydrogel, given in Figure 4.14, shows the surface morphology also contain a lot of folds and holes and the particles of the drug are distributed in between the folds and inside the holes as well as their adsorption on the surface of the hydrogel surfaces. Therefore, this hydrogel shows a higher loading percentage which is clear from its FESEM image shown in Figure 4.14.

5.4. STUDIES ON CONTROLLED DRUG RELEASE FROM HYDROGEL MICROSPHERES

The controlled drug release which is calculated as cumulative drug release percentage were studies for both (CH-co-PAN/SHMP), and (CH-co-PAAc/SHMP) hydrogels, and their 100 mg microspheres were allowed to release in 20 mL loading buffered solution pH=7.4 and at 37 ˚C. The calibration curve that is used to calculate the released drug concentration after each 6 hrs by means of the recorded absorbance (A) of the drug at a wavelength, λmax= 331 nm, in addition, the (Eq.No.4) has been used for calculation of cumulative drug release (%Rcum).

Moreover, Table 4.5 and Figure 4.15 show the different parameters calculated for the loading percentages and release details for both (CH-co-PAN/SHMP), and (CH-co-PAAc/SHMP) hydrogels. The burst release concentration was found be more for (CH-co-PAN/SHMP) hydrogel which means the system need more time and drug to

release before reached the controlled way. Even the (CH-co-PAN/SHMP) system released drug less under controlled manner in comparison with (CH-co-PAAc/SHMP) system. As a result, the controlled release time was more in case of (CH-co-PAAc/SHMP) hydrogel. The main results of the drug release studies shows both hydrogel systems are suitable for loading and release under controlled conditions, but the (CH-co-PAAc/SHMP) hydrogel was shown to be a more convenient system for loading and controlled release of hydroxychloroquine drug.

5.4.1. Characterization of Microspheres After Release by FESEM Analysis

The hydrogel microspheres after releasing their loaded hydroxychloroquine drug were characterized by FESEM analysis in order view the surface morphology and to be sure the drug particles were released. Therefore, the (CH-co-PAN/SHMP) hydrogel was examined by FESEM and its image is given in Figure 4.16. It was shown the hydrogel microspheres were cracked on the hydrogel surface and the molecules of hydroxychloroquine were disappeared. In general, the microspheres were split and pushed the loaded drug out into the release solution.

Similarly, the microspheres of (CH-co-PAAc/SHMP) hydrogel Figure 4.17 has shown the particles are still integrated and they only release their loaded hydroxychloroquine molecules.

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RESUME

Najwa Ibrahım Yahya YAHYA graduated from Preparatory ALRASHIDIA for girls. She graduated from Mosul University, Faculty of Science, department of Chemistry in 2015 and she is currently working as a teacher in a girls' high school, and She Studying master's degree at Karabük University.