MARMARA UNIVERSITY

INSTITUTE FOR GRADUATE STUDIES

IN PURE AND APPLIED SCIENCES

FABRICATION OF HYDROGEL FOR CONTROLLED DRUG DELIVERY BY USING PHOTOPOLYMERIZATION TECHNIQUE

SALİSE OKTAY

MASTER THESIS

Department of Chemical Engineering

Thesis Supervisor

Assc. Prof. Dr. NESLİHAN ALEMDAR YAYLA

ISTANBUL, 2018

MARMARA UNIVERSITY

INSTITUTE FOR GRADUATE STUDIES

IN PURE AND APPLIED SCIENCES

FABRICATION OF HYDROGEL FOR CONTROLLED DRUG DELIVERY BY USING PHOTOPOLYMERIZATION TECHNIQUE

SALİSE OKTAY

(524516006)

MASTER THESIS

Department of Chemical Engineering

Thesis Supervisor

Assc. Prof. NESLİHAN ALEMDAR YAYLA

ISTANBUL, 2018

MARMARA UNIVERSITY INSTITUTE FOR GRADUATE STUDIES IN PURE AND APPLIED SCIENCES

Salise OKTAY, a Master of Science student of Marmara University Institute for Graduate Studies in Pure and Applied Sciences, defended her thesis entitled "**Fabrication of hydrogel for Controlled Drug Delivery by Using Photopolymerization Technique**", on ..... and has been found to be satisfactory by the jury members.

Jury Members

Assc. Prof Neslihan ALEMDAR YAYLA (Advisor)
Marmara University

Prof. Dr. Atıf KOCA (Jury Member)
Marmara University

Prof. Dr. Mehmet Ali Faruk ÖKSÜZÖMER (Jury Member)
Istanbul University

APPROVAL

Marmara University Institute for Graduate Studies in Pure and Applied Sciences Executive Committee approves that Salise OKTAY be granted the degree of Master of Science in Department of Chemical Engineering, Chemical Engineering Program on 23.07.2018 (Resolution no: 2018/17-02).

Director of the Institute

Prof. Dr. Bülent EKİCİ

ACKNOWLEDGEMENT

In the realization of this study, I would like to thank in particular my thesis advisor Assc. Prof. Dr. Neslihan ALEMDAR YAYLA, and also Prof. Dr. Atıf KOCA, Prof. Dr. Mehmet EROĞLU and their team member for academic support.

I would also like to express my gratitude to the Marmara University Scientific Research Project Coordination Unit (BAPKO) for the financial support and Institute for Graduate Studies in Pure and Applied Sciences, Marmara University for their educational conditions and support.

Finally, I would like to thank my family for their support.

LIST OF CONTENT

ACKNOWLEDGEMENT i

LIST OF CONTENT ii

ABSTRACT iv

ÖZET v

SYMBOLS vi

ABBREVIATIONS vii

LIST OF FIGURES x

INTRODUCTION 1

1.1 Hydrogels 1

1.1.1 Smart Hydrogels 2

1.1.1.1 pH Sensitive Hydrogels 2

1.1.1.2. Temperature Sensitive Hydrogels 2

1.1.1.3 Electric Field Sensitive Hydrogels 2

1.1.2 Applications of Hydrogels 3

1.1.2.1.1. Skin Drug Delivery Systems 6

1.2. Conducting Polymers 11

1.2.1. Poly (3, 4-ethylenedioxythiophene) (PEDOT) 12

1.3. Gelatin methacryloyl (GelMA) 13

2. MATERIALS AND METHOD 16

2.1 Materials 16

2.2 Synthesis of GelMA 16

2.3 Fabrication of GelMA hydrogels 16

2.4 Synthesis of PEDOT/PSS Polymer 16

2.5 Encapsulation of PEDOT/PSS into the GelMA hydrogel 17
2.6 Characterization of Hydrogels 17
2.6.1 Cytotoxicity Test for GelMA 17
2.6.2 Electrical Conductivity of Hydrogels 17
2.6.3 Swelling Characterization 18
2.6.4 Drug Loading and Releasing 18
3. RESULTS AND DISCUSSSON 20
3.1 Synthesis of Gelatin Methacryloyl 20
3.2 Fabrication of GelMA hydrogels 21
3.3 Synthesis of PEDOT/PSS polymer 22
3.4 Encapsulation of PEDOT/PSS into the GelMA hydrogel 23
3.5 Characterization of GelMA-PEDOT/PSS Hydrogels 24
3.5.1 Cytotoxicity of GelMA-PEDOT/PSS Hydrogels 29
3.5.2 Electrical conductivity of GelMA-PEDOT/PSS hydrogels 29
3.5.3 Swelling tests 30
3.5.4 Release Behaviour of 5-FU-loaded GelMA-PEDOT/PSS Hydrogels 33
4. CONCLUSIONS 36
REFERENCES 37

ABSTRACT

FABRICATION OF HYDROGEL FOR CONTROLLED DRUG DELIVERY BY USING PHOTOPOLYMERIZATION TECHNIQUE

Smart hydrogels are polymeric materials that undergo mechanical and physical changes in structures due to the effects of external stimuli such as pH, temperature and electricity. Among of smart hydrogels, electrically conductive hydrogel which is susceptible to electrical stimulation is often used for controlled drug release due to the amount of flexible dosage and temporal treatment at a good level. The conductive hydrogel to be used for controlled drug release should have a good conductivity, biocompatibility, biodegradability and low toxicity. Herein, poly (3, 4 ethylenedioxytiophene)/poly (styrene sulfonate) (PEDOT/PSS) which is a biocompatible conductive polymer with high electrical conductivity and good chemical resistance was encapsulated into the gelatin methacrylamide (GelMA) to fabricate electrically sensitive hydrogel for controlled drug delivery. One of the areas where controlled drug delivery systems are used effectively is skin diseases such as Bowen's disease, superficial basal cell carcinoma. One of the most effective drugs used in the treatment of such diseases is 5-fluorouracil (5-FU). The obtained electrically-sensitive hydrogels were characterized by FT-IR and SEM analyses. Cytotoxicity tests were performed to determine biocompatibility. Swelling tests were conducted to determine the swelling capacity of hydrogels. The release of 5-FU from the hydrogel was provided in efficient and controlled manner at simulated skin cancer (pH=5.5) and under 0 V and 1.5 V. The higher amount of 5-FU from the hydrogel was observed when voltage applied to the hydrogels. The obtained results was shown that GelMA-PEDOT/PSS hydrogels can be used in electrically controlled drug delivery systems.

ÖZET

FOTOPOLİMERİZASYON TEKNİĞİ KULLANILARAK KONTROLLÜ İLAÇ SALIMI İÇİN HİDROGEL ÜRETİMİ

Akıllı hidrojeller, pH, sıcaklık ve elektrik gibi dış uyaranların etkilerinden dolayı yapılarında mekanik ve fiziksel değişimlere uğrayan polimerik malzemelerdir. Akıllı hidrojellerin arasında, elektriksel uyarana karşı hassas olan elektriksel olarak iletken hidrojel, iyi bir seviyede esnek dozaj ve geçici tedavi miktarı nedeniyle kontrollü ilaç salımı için sıklıkla kullanılır. Kontrollü ilaç salımı için kullanılacak olan iletken hidrojel iyi bir iletkenliğe, biyouyumluluğa, biyo-bozunmaya ve düşük toksisiteye sahip olmalıdır. Burada, yüksek elektrik iletkenliğine ve iyi kimyasal dirence sahip biyo-uyumlu bir iletken polimer olan poli (3, 4 etilendioksitiofen)/poli (stirensülfonat) (PEDOT/PSS), kontrollü ilaç salımı için elektriksel olarak duyarlı hidrojel sentezlemek üzere jelatin metakrilamid (GelMA) içerisine kapsüllenmiştir. Kontrollü ilaç salım sistemlerinin etkin kullanıldığı alanlardan biri, Bowen hastalığı, yüzeysel bazal hücreli karsinom gibi cilt hastalıklarıdır. Bu tür hastalıkların tedavisinde kullanılan en etkili ilaçlardan biri 5-flurourasil'dir (5-FU). Elde edilen elektriğe duyarlı hidrojeller FT-IR ve SEM analizleriyle karakterize edildi. Biyouyumluluğun belirlenmesi için sitotoksisite testleri yapıldı. Hidrojellerin şişme kapasitesini belirlemek için şişme testleri yapıldı. 5-FU' nun hidrojelden salınımı simüle edilmiş cilt kanserinde (pH = 5.5) ve 0 V ve 1.5 V altında etkili ve kontrollü bir şekilde sağlandı. Hidrojellere voltaj uygulandığında hidrojelden daha yüksek miktarda 5-FU salımının gerçekleştiği gözlemlenmiştir. Elde edilen sonuçlar, elektrik kontrollü ilaç salım sistemlerinde GelMA-PEDOT / PSS hidrojellerinin kullanılabileceğini göstermiştir.

SYMBOLS

I	: Current	(A)
V	: Voltage	(V)
s	: Probe space	(m)
σ	: Conductivity	(S/m)
ρ	: Sheet resistivity	(Ω.m)
W_s	: Swollen weight of hydrogel	(g)
W_d	: Dry weight of hydrogel	(g)

ABBREVIATIONS

Irgacure 2959	:	2-hydroxy-1- [4- (2-hydroxyethoxy) phenyl] -2-methyl-1-propanone
EDOT	:	3,4 ethylenedioxythiophene
5-FU	:	5-Fluorouracil
AK	:	Actinic keratosis
RGD	:	Arginine-glycine-aspartic acid
BCC	:	Basal cell carcinoma
BD	:	Bowen's disease
DC	:	Direct current
DI	:	Distilled water
FT-IR	:	Fourier transform infrared
GelMA	:	Gelatin methacrylamide
IPN	:	Interpenetrating polymer network
$Fe(NO_3)_3.9H_2O$	:	Iron (III) nitrate nonahydrate

LAP	:	Lithium acylphosphinate salt
MMP	:	Matrix metalloproteinase
MA	:	Methacrylic anhydride
ECM	:	Natural extracellular matrix
PBS	:	Phosphate buffer saline
PDT	:	Photodynamic therapy
PEDOT	:	Poly(3,4ethylenedioxytiophene)
PEDOT/PSS	:	Poly(3,4ethylenedioxytiophene)/poly(styrenesulfonate)
PAA-PEDOT: PSS	:	Poly (acrylic acid)-Poly(3,4ethylenedioxytiophene):poly(styrenesulfonate)
PEG-PEDOT: PSS	:	Poly(ethylene glycol)-Poly(3,4ethylenedioxytiophene):poly(styrenesulfonate)
NaPSS	:	Poly(sodium-4-styrene sulfonate)
PSS	:	Poly(styrenesulfonate)
SEM	:	Scanning electron microscopy
UV	:	Ultraviolet

LIST OF FIGURES

Figure 1.1 Mechanism of drug release from hydrogels [24] 5

Figure 1.2 A cross-sectional representation of the skin [28]. 7

Figure 1.3 Chemical Structure of 5-Fluorouracil [42]. 10

Figure 1.4 Chemical Structure of PEDOT/PSS [60, 61]. 13

Figure 1.5 Synthesis gelatin metacrylamide (GelMA). Gelatin macromers containing primary amine groups were reacted with methacrylic acid group to introduce methacrylate-pendant groups (A). To form a hydrogel network, the methacrylated gelatin was cross-linked using UV radiation in the presence of a photoinitiator (B) [66]. 14

Figure 2.1 The experimental set-up that have been used to study electro-responsive drug delivery from hydrogels in this study. 19

Figure 3.1 (a) Purification of gelatin methacryloyl in membrane dialysis tubing (b) Purificated gelatin methacrylamide in membrane dialysis tubing. 20

Figure 3.2 Synthesis of GelMA hydrogels. Reaction of methacrylate and methacryamide side groups with amine and hydroxyl groups on the gelatin (A), Cross-linked hydrogel build-up by photopolymerization technique (B). 21

Figure 3.3 Schematic shown of PEDOT/PSS synthesis. 22

Figure 3.4 Schematic diagram of synthesis procedure of GelMA-PEDOT/PSS hydrogels. 23

Figure 3.5 Pure GelMA (A) and GelMA-PEDOT/PSS hydrogel (B). 23

Figure 3.6 FT-IR spectrums of PEDOT/PSS (A), pure GelMA (B) and GelMA-PEDOT/PSS-1.5 wt. % (C). 25

Figure 3.7 FT-IR spectrums of 5-FU (A), GelMA-PEDOT/PSS hydrogel (B) and drug loaded GelMA-PEDOT/PSS hydrogel (C). 27

Figure 3.8 SEM images of PEDOT/PSS (A), pure GelMA (B) and GelMA-PEDOT/PSS-1.5 wt. % hydrogel (C). 28

Figure 3.9 Viability of L929 cells on the GelMA, GelMA-PEDOT/PSS-1.5 wt. % and polystyrene well (control sample) 29

Figure 3.10 Conductivity of the GelMA-PEDOT/PSS hydrogels..... 30

Figure 3.11 Effect of 1.5 wt. % PEDOT/PSS on swelling ratio without voltage..... 31

Figure 3.12 Effect of DC electric field set at 0 V and 1.5 V on swelling capacity of GelMA-PEDOT/PSS-1.5 wt.% 32

Figure 3. 13 The effect of an electric field on a polyelectrolyte gel [84]. 33

Figure 3.14 Time-dependent release of 5-FU from the GelMA and GelMA-PEDOT/PSS 1.5 wt% hydrogels under 0 V. 33

Figure 3.15 Time-dependent release of 5-FU from the GelMA and GelMA-PEDOT/PSS 1.5 wt.% hydrogels when a DC electric field set at 0 V and 1.5 V was applied. 35

INTRODUCTION

1.1 Hydrogels

Hydrogels are three dimensional, cross-linked and hydrophilic polymeric network structures that are insoluble in water or biological fluids and do not lose their structure. Large amounts of water or biological fluids have absorptive capacity. These three dimensional structures are formed by cross-linked polymer chains. Cross-linking between hydrogel chains; such as covalent (chemical cross-linking), hydrogen, ionic or hydrophobic (physical cross-linking). They are insoluble in water, but they can retain 20-100 times their weight of water by keeping their shape and mechanical stability. The hydrogels overlying the 100% swelling capacity are called superabsorbent hydrogels [1].

Hydrophilic groups, such as; hydroxyl (-OH), carboxyl (-COOH), amide ($-CONH_2$), sulphonic provide hydrophilic properties to the network; insolubility and shape stability are due to the presence of three dimensional network structure. Because of these groups, the cross-linked polymer starts to swell by increasing in volume and mass due to the water in the bound state until equilibrium point. Swelling degree decrease by increasing crosslinking density. Because cross-linking inhibits the ability of the polymer chain to move, thus reducing the amount of gel swelling. Swelling degree increase by increasing number of hydrophilic groups in the crosslinked polymer [1, 2].

Hydrogels may exhibit "swelling-shrink" behavior depending on the external environment. These hydrogels, which show large changes in swelling rates against changes in pH, temperature, ionic strength, solvent composition and electric field coming into the environment, are called stimuli-response hydrogels. Since the water absorption rate of hydrogels is limited by water diffusion, hydrogels in the small size lead to rapid swelling [2].

1.1.1 Smart Hydrogels

Intelligent hydrogels have a variety of chemically and structurally responsive parts and react to external stimuli such as temperature, pH, ionic concentration, light, magnetic fields, electric fields and chemicals. Intelligent polymer hydrogels change the structural and volume phase transitions in response to external excitation, creating tremendous potential for scientific observations and various advanced technological applications [3].

1.1.1.1 pH Sensitive Hydrogels

The pH-sensitive hydrogels are generally formed on the polymer skeleton by acidic or basic functional groups. These groups are in aqueous media receive or give proton depending on the change of pH and ionic strength. These ionizing groups have a constant electrical negative or positive charge on the hydrogel and these electrostatic forces push each other out of the network structure the solvent ingress increases and the structure swells. The pH-sensitive hydrogel is in the polyelectrolyte structure show reversible ionization characteristics according to the pH value of the medium [4].

1.1.1.2. Temperature Sensitive Hydrogels

Temperature-sensitive hydrogels can be obtained using temperature-sensitive functional group-containing monomers or crosslinking agents. Interaction of hydrophilic and hydrophobic groups with water causes volumetric phase changes due to temperature change. The most important properties of these hydrogels are hydrophobic groups such as methyl, ethyl and propyl [5].

1.1.1.3 Electric Field Sensitive Hydrogels

The swelling and shrinkage behavior of smart polymers is also controlled by electric field control. These polymers respond to electric current by contraction [6]. Electric current sensitive hydrogels are made of polyelectrolytes [7]. Polyelectrolyte is a macromolecule (covalently bonded anionic or cationic groups macromolecule), and low-molecular counter-charged ions that provide electron-transference. Polystyrene sulfonic acid, gelatin, polyethylene imine are examples for polyelectrolytes [8]. Electric field sensitive hydrogels have many usage area. For example, they convert chemical

energy into mechanical energy, so they can be used as actuators or artificial muscles in many applications, and also they have been used in drug delivery systems [7].

In order to realize a strong actuator or biological sensor, both the fast electric field sensitivity and the high mechanical strength combination of a hydrogel must be completed. It is believed that the formation of an interpenetrating polymer network (IPN) is a promising candidate to meet these requirements because it has very strong mechanical properties, and also, as conductive polymers improve the electric field sensitivity of hydrogels, the use of conductive polymers supported hydrogels for sensors, actuators, switches and drug delivery systems may be more beneficial [9].

One of the most important electric-current sensitive hydrogels is GelMA which is an attractive biomaterial, because the gelatin backbone allows the cells to set specific physicochemical properties of biological cues and functionalization of the cells [10].

1.1.2 Applications of Hydrogels

Hydrogels have some applications in different research areas such as, wound healing, cellular studies [11], and tissue engineering [12]. They are known as ideal alternatives for surgical wound because they have the ability to transfer steam and oxygen to the wound area with high water content. Moreover, since they do not need any liquid to return to the dry gels, hydrogels are suitable for dry wounds. Tissue regeneration and repair are other applications of hydrogels that can be applied, particularly for cell transplantation and for the replacement of skeletal tissues such as bone, cartilage and muscles. Because of the tissue mimicry properties of hydrogels, they can carry growth factors to promote cell growth and promote tissue repair and regeneration [13].

One of the most important application of hydrogels is drug delivery [14], because of the controllable pore configuration required for drug release, facilitating diffusion of molecules in the gel [13].

1.1.2.1 Drug Delivery

The study of controlled and continuous drug-eluting devices has been an increasing concern over the last few decades. Controlled release systems are systems that deliver the target cell, tissue or organ by controlling the release rate of the active substance

required for the organism [15]. Widely used in many areas, from food production to agriculture and pharmaceuticals. The prominence of drug-release vehicles is increasing rapidly by shifting macromolecular biology from small molecules [16].

It is the aim of all controlled release systems to improve the safety of medicines and the effectiveness of treatment. There is a plasma range in which each agent is effective, and this is called the "therapeutic window". The goal of the agent-controlled drug release is to release the therapeutic dose at the most appropriate site of the drug's body. In addition to this, reducing the side effects of the drug, providing the patient with the least dose is to keep the pharmacological effect of the drug for a long time [17].

Today there are many areas where controlled drug delivery systems are applied. For example; medicine, agriculture, food and cleaning materials. These systems have significant clinical advantages in medical practice like reducing side effects, using small drug dosages [15].

Biologics require higher release concentrations, greater protection against metabolic interactions, and more targeted release than small molecule drugs. Due to these requirements, more sophisticated means of release are needed [15]. Hydrogels are generally chosen as drug release means due to their advantageous properties such as high water content, biocompatibility, biodegradability [18], stimulus-response rate [19] and high porosity compared to biological membranes and other materials. Physically cross-linked hydrogels are particularly attractive for the construction of drug delivery vehicles because the preparations do not contain any toxic compounds [20].

The hydrogels in the drug release system can be used to deliver drugs over a period of time through the controllable release mechanism. The use of hydrogels offers many advantages, such as reduced drug dosages, costs and side effects. It is based on the swelling ability of the use of hydrogels in drug release systems. The swelling mechanism is caused by the increase in the distance between the cross-linked polymer chains; which allows the drug molecules to be released and absorbed into the bloodstream [21].

Loading of the drug into the hydrogel generally involves two methods. In a first approach, the polymer to be used for the hydrogel is mixed with the drug, if necessary, allowed to polymerize in the matrix of the drug with an initiator and a cross-linker.

However, in the second approach, a preformed hydrogel is allowed to swell to the balance in a drug solution. In both mechanisms, the drug is dried after the drug has been loaded. The drug loading in the hydrogel is affected by several factors such as the interaction between the polymer and the solvent, the cross-linking density of the polymeric network, and the presence of a solvent. All these parameters greatly affect the swelling dimension [22].

Most of the hydrogels are glassy in the dehydrated state and drug release usually involves simultaneous absorption of water through a swelling-controlled mechanism and absorption of the drug. The speed control factor that mediates drug delivery is the volume increase and shape change resistance of the polymer. When the glassy hydrogel comes into contact with water or other thermodynamically compatible medium, it allows the solvent to penetrate into the free spaces in the surface between the macromolecular chains. When enters enough water to the matrix, the glass transition temperature of the polymer drops to the test temperature. The presence of a solvent in a glassy polymer causes the development of stretches, which are seen as macroscopic swelling, with a radius of rotation and an increase in the end-to-end distance of the polymer molecules. The movement of the solvent molecules into the dry (glassy) polymer matrix takes place with a well-defined velocity gradient and simultaneous reversal time increase in the thickness of the swollen (rubbery) region [23].

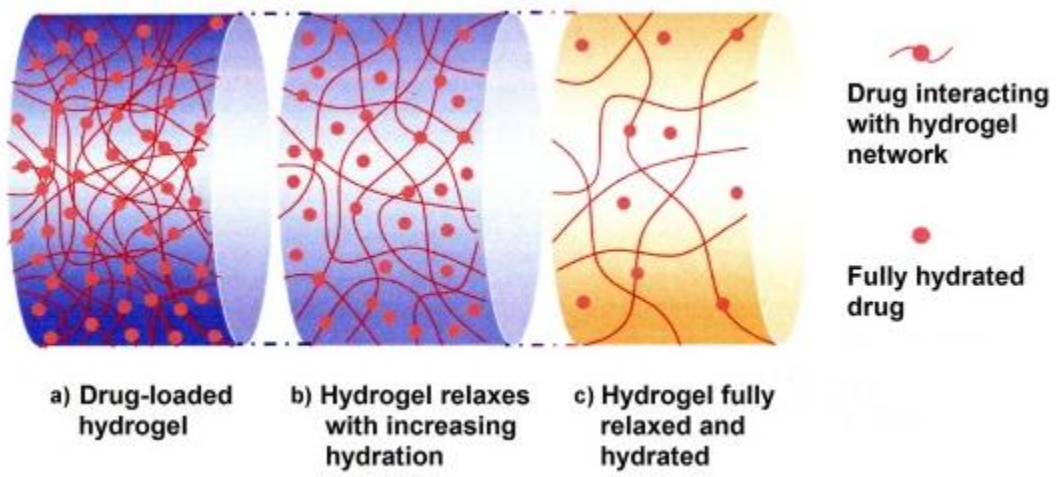


Figure 1.1 Mechanism of drug release from hydrogels [24]

One of the most used areas of controlled drug release is skin diseases with the following advantages. Firstly, the transdermal release bypasses the first pass metabolism and prevents the harsh environment of the gastrointestinal tract, potentially improving drug bioavailability. Most biological drugs are compatible for transdermal drug delivery. Secondly, the skin has a large surface area and is easily accessible. Thirdly, transdermal release may persist drug release and potentially reduce dose frequency. Continuous release is likely to reduce peak plasma drug levels and drug toxicity. Finally, transdermal delivery can be accomplished with no needles, painless, self-administering and good patient compliance [25].

1.1.2.1.1. Skin Drug Delivery Systems

The skin, the largest organ in the body, occupies about 16% of the total body weight of a person. Basically a complex barrier, the skin consists of three structural layers: epidermis, dermis and hypodermis, each with different composition and functions. The epidermis actually provides barrier function, innate immune and UV protection. Dermis: It is an integrated system with many resident cells such as fibroblasts, macrophages, mast cells, vascular, lymphatic and neural networks. Hypodermis: Supports mechanical and physiological support and contains a large number of vessels and nerves [26]. Stratum corneum is the outermost layer of skin and is the main barrier for skin transport and systemic circulation along the skin. The stratum corneum consists of 10 to 15 layered nucleated corneocytes with thicknesses ranging from 10 to 15 μm in dry state and 40 μm in the case of hydration. These corneocytes are filled with a matrix of cross-linked keratin fibers that are negatively charged in physiological conditions and responsible for the mechanical formation of the stratum corneum. It is organized in a brick-mortar-like structure with intercellular matrix composed of keratin-rich corneocytes, long-chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulfate and sterol / wax esters and the intracellular space occupies 5-20% of the stratum corneum volume [27].

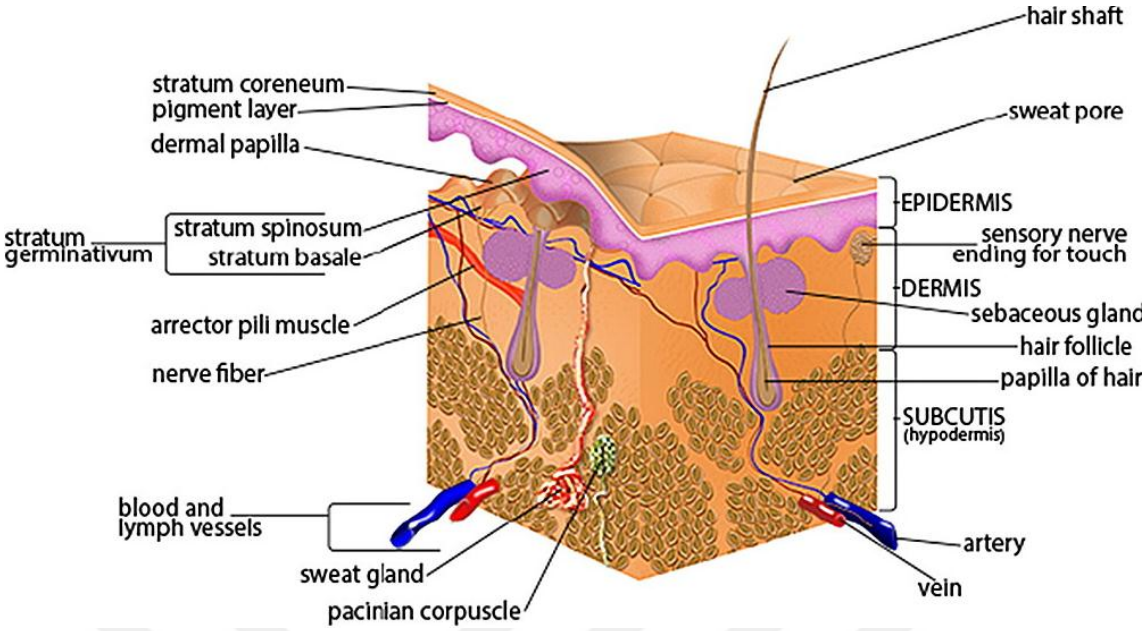


Figure 1.2 A cross-sectional representation of the skin [28].

The drug delivery market can be divided into eight categories: oral, pulmonary, transdermal, injectable, ocular, nasal, implanted and transmucosal drug delivery. Oral release has the largest market share (more than 50%) followed by transmucosal (26.2%) and transdermal (12%), respectively. However, parenteral release is one of the most commonly used methods for drug administration [29].

The release of dermal and transdermal drugs, generally defined as skin drug delivery, is an attractive approach in the treatment of many diseases. Dermatological pathologies, e.g. skin cancer, inflammation disorders, cutaneous infections are known to be difficult to treat. Indeed, drug formulations are usually intended for the oral route or for those parenteral in the most severe cases. However, in skin disorders, such routes of administration may be of limited interest, since they are inadequate to provide a clinical enrichment due to the low amount of drug in the skin tissue. Indeed, active substances must overcome different biological barriers before reaching the skin layers. Accordingly, an effective concentration in the skin is generally achieved by giving high doses that enhance the side effects of the drug. Thus, direct and localized access to the pathological region will be more promising and more relevant in the treatment of diseases by topical release [30].

The administration of drugs in a systemic circulation transdermal route provides a suitable route of administration for various clinical indications. In addition to preventing hepatic first-pass effects and chemical degradation of drugs in the gastrointestinal tract, patient compliance can be improved by reducing the frequency of dosing due to continuous drug ingestion [31]. Furthermore, transdermal drug delivery has been recognized as a potential non-invasive drug administration role, with advantages of long-term therapeutic action, reduced side effects, ease of use [32].

Despite the advantages of transdermal delivery: only small potent lipophilic drugs with passive diffusion can be given at therapeutic rates. Moreover, the transport of most medicines through the skin is very slow and the latency of reaching steady-state conditions is several hours. For this reason, achieving a therapeutically effective drug level is difficult without increasing skin penetration. Several approaches have been developed to increase and control transport throughout the skin and to broaden the range of drugs delivered. These include chemical and physical methods based on two strategies: to increase permeability to the skin and / or to provide an effective propellant on the drug [33].

It has been shown that chemical penetration enhancers substantially enhance the transdermal transport of both small lipophilic and hydrophilic compounds by affecting the stratum corneum structure. An electric field can also be used to enhance transdermal delivery. Iontophoresis uses a low intensity electrical current (0.1 to 0.5 mA / cm^2) applied over a relatively long period of time (from minutes to hours). Electroporation occurs from the application of short (100 to 1000 V) high voltage pulses (from 100 μs to less than 1 s). Iontophoresis acts primarily as a secondary effect on the drug, with changes in skin structure including electro repulsion and electro osmosis, whereas electroporation directly causes changes in tissue permeability on the skin [34].

There are two method of transdermal drug delivery as active and passive transdermal drug delivery. In the case of active transdermal drug release, the permeability of the drug through the skin, temperature, ultrasound, under voltage current, or by external stimuli such as any chemical enhancer; In the case of passive transdermal drug release, such an external stimulant / drug is not used to increase drug permeability [35].

The design of polymeric systems used for topical or transdermal drug delivery is a challenging task due to the strong penetration barrier imposed by the epidermis. However, transmission through skin surfaces is an attractive way to minimize the possible side effects of localization of delivery to the target site and systemic drug administration. Various polymeric and lipid-based devices such as liposomes, nanospheres, micelles, micro emulsions and bulk hydrogels have been developed for topical application. Among them, hydrogel matrices with buried nano-vehicles have high loading capacity, large surface area and mechanical stability as opposed to non-matrix nano carriers. These hydrogels are generally used as an inert matrix for encapsulating the active compounds or as a mechanical support for embedding drug loaded nanoparticles [36].

Skin cancer is the most common type of cancer worldwide and its incidence continues to increase. It is usually divided into cancers that originate from melanocytes (melanoma) and epidermally derived cells (non-melanoma skin cancers). These groups represent the majority of skin cancers (95%), with other skin tumors thus constituting only a very small percentage. High prevalence and commonness make them an important public health problem. The risk of developing skin cancer stems from a combination of genetic and environmental factors; The most common cause is ultraviolet (UV) light exposure [37]. Most skin cancers are not melanomatous. Malignant nonmelanoma skin cancer is caused by keratinized epithelial cells. These cancers include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Melanoma only accounts for about 2% of malignant skin cancers, but it causes a majority of deaths. BCC is the most common form and is usually slow-growing and locally invasive. SCC is the second most common form of nonmelanomatous skin cancer and accounts for about 20-30% of cases [38].

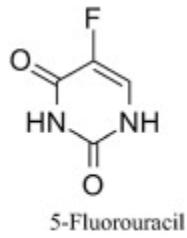
Basal cell carcinoma (BCC) is the most common type of skin cancer and its increasing incidence is a major burden on health care worldwide. BCC can be divided into three major histological subcategories: superficial, nodular and aggressive. Although many subtypes require surgery, superficial BCC (SBCC) can be treated topically with alternatives such as photodynamic therapy (PDT), imiquimod cream, fluorouracil cream, cryocortical or electrodessication and curettage. The main advantages of noninvasive treatments such as PDT, imiquimod and fluorouracil are the potential for

good cosmetic results, protection of surrounding tissue, and the application of both creams at home [39].

Actinic keratosis (AKs) or solar keratosis is a cutaneous leucosis that manifests as a proliferative growth of atypical epidermal keratinocytes and represents a step in the development of squamous cell carcinoma (SCC). The diagnosis of AKs is more important for the geriatric population than younger individuals because the incidence of malignant skin lesions increases with age and the diagnosis of AKs puts patients at higher risk for later development of skin cancer [40].

Bowen's disease (BD) is an in situ squamous cell carcinoma (SCC). It usually affects elderly patients and usually indicates that a slowly growing, solitary, scaling plate can reach a significant size. Lesions are found at the beginning, in the neck or in the extremities [41].

FU also known as 5-Fluorouracil has been approved for topical treatment of actinic keratosis (AK), superficial basal cell carcinoma (BCC), and Bowen's disease. FU appeared in the potentially 1960s years of actinic keratosis management and lesions disappeared in patients receiving systemic FU for other cancers. FU inhibits the enzyme responsible for thymidine synthesis, one of the pyrimidine nucleosides of DNA. FU is slightly soluble in water. Originally FU was formulated in hydrophilic petrolatum or simple propylene glycol gel vehicles for topical application. Only 5% preparations are used in BCC treatment [42].



5-Fluorouracil

Figure 1.3 Chemical Structure of 5-Fluorouracil [42].

1.2. Conducting Polymers

Conductive polymers are polymers with a conductivity between metals and insulators. Conductive polymers are often referred to as synthetic metals or organic metals, as some material properties that do not naturally exist in metals and semiconductors are gained by conducting polymers [43]. Since the discovery of polyacetylene (1976), conductive polymers have become a focus for researchers, technology specialists and industrialists due to their versatile electrical and optical properties. Generally, conducting polymers form the π-conjugate responsible for delocalization phenomena in the backbone. Delocalized π electrons form conductivity across the polymer chain through the formation of polarons and bipolar polymers. Their conductivity can be increased several fold by doping [44].

Conducting polymers are defined as polymers containing weakly bound electrons in the main skeleton chains. In order for the polymers to exhibit electronic conductivity, it is necessary to find suitable places in the braid that allow electrons to move along the chain. In this conditioned main chain, the conjugate provides polymers with double bonds. The main feature that differentiates conductive polymers from other polymers is that they have a chain structure consisting of alternating single and double bonds. This is called conjuncture in order to change the bond structure. For this reason, conductive polymers are also called conjugated polymers [45].

Conductive polymers have received considerable attention as biointerfaces with their unique electrical and optical properties due to their biocompatibility and polymeric properties. Relatively low cost, ease of synthesis and good biocompatibility, a number of conductive polymers have made attractive candidates specifically for applications that require communication between interfaces, especially for biomolecules. For example, conductive polymers can cause widespread use as (biological) sensors, converting chemical signals to optical or electronic signals [46].

When the conductivity of the conducting polymers was first oxidized with iodine vapor, polyacetylene was observed which increased conductivity by a factor of 10. The ambiguity of polyacetylene in the air has led to the discovery of several new conductive

polymers such as polyaniline, polypyrrole, polyazulene, polyfluorene, polythiophene, and polyaminonaphthalenes for use in both basic research and industrial applications [47].

Poly (3, 4-ethylenedioxythiophene) (PEDOT), one of the conductive polymers, has an extremely important application as an organic semiconductor polymer in today's technology [48].

1.2.1. Poly (3, 4-ethylenedioxythiophene) (PEDOT)

Poly (3, 4-ethylenedioxythiophene) (PEDOT) is one of the polythiophene derivatives that have attracted much attention in recent years due to their unique electrical properties. It combines low oxidation potential and middle band gap with good stability in the oxidized state. PEDOT has high conductivity as well as high transparency in thin, oxidized films. As a result, PEDOT derivatives are now used in a variety of industrial applications such as organic / polymer based light emitting diodes, sensors and solar cells [49].

As an excellent π-conjugated polymer, PEDOT has received considerable attention due to its excellent electrical conductivity, low density, good stability, ease of synthesis, convenient processing properties [50] and high biocompatibility [51]. Particularly excellent environmental stability, narrow band gap, low potential for oxidation, wide potential window, thermal stability and good optical transparency make PEDOT an ideal material for various applications such as electrochromic, solar cells, fuel cells and super capacitors [52]. Furthermore, PEDOT has been reported numerous as potential candidates for biomedical applications [53]. However, the water solubility of PEDOT is low and this problem is solved by using water soluble polyelectrolyte poly (styrene sulfonic acid) PSS as a charge-balancing additive. PEDOT is mixed with PSS to form a readily processable colloidal solution in water [54].

Poly (3, 4-ethylenedioxthiophene)/poly (styrene-sulfonate) (PEDOT/PSS), consists of two oppositely charged polymers; (SO_3^-) in the sulfonate groups of the polystyrene sulfonate (PSS) neutralize the positively charged poly (3, 4-ethylenedioxythiophene) (PEDOT) and the aqueous colloidal distribution of the extra sulfonic acid groups ($SO_3^-H^+$) PEDOT/PSS complex starts. [55].

At present one of the most promising conducting polymers is poly (3,4-ethylenedioxythiophene)/poly (styrene-sulfonate) (PEDOT/PSS) due to high transparency in the visible area, solution processability, high work function, significant mechanical flexibility [56], high conductivity, compatibility with low-cost solution-processing [57], and excellent electrochemical stability [58]. At the same time, it has the highly conjugated back bone, environmental stability, biocompatibility and conformal elasticity [59].

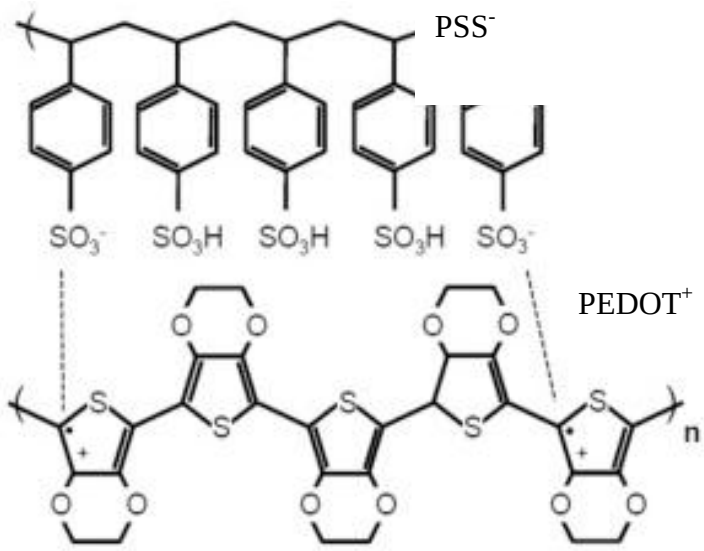


Figure 1.4 Chemical Structure of PEDOT/PSS [60, 61].

1.3. Gelatin methacryloyl (GelMA)

GelMA is a gelatin derivative mostly comprising methacrylamide groups and a minority methacrylate groups. Gelatin methacryloyl (GelMA) hydrogels are commonly used for a variety of biomedical applications due to their favorable biological properties and adjustable physical properties. GelMA hydrogels resemble some of the basic properties of the natural extracellular matrix (ECM), depending on the presence of cell motifs that respond to cell attachment and matrix metalloproteinase, allowing cell multiplication and spreading on GelMA-based scaffolds [62].

The gel is subjected to photo-initiated radical polymerization to form covalently cross-linked hydrogels. Gelatin is a fibrous protein having thermo-reversible forms derived

from the parent molecular collagen, which constitutes about 25-35% of the total body protein [63]. Compared to collagen, the advantages of gelatin include better solubility and less antigenicity. Furthermore, gelatin, is readily available, degradable and has good biocompatibility in the living organism [64]. A gelatin solution, by itself, has the unique property of gelling at low temperatures to form physically cross-linked hydrogels. Furthermore, gelatin is a fibrous protein having thermo-reversible forms derived from the parent molecular collagen, which constitutes about 25-35% of the total body protein. Conveniently, incorporation of the methacryloyl substituent groups gives photocrosslinking properties to the gelatin by photolysis with the aid of a photoinitiator due to the photopolymerization of methacryloyl substituents. This polymerization can take place under mild conditions (room temperature, neutral pH, aqueous media, etc.) and allows the reaction to be controlled temporally and spatially. This enables microfabrication of hydrogels to create unique patterns, morphologies and 3D structures to provide ideal platforms for controlling cellular behavior, examining cell-biomaterial interactions, and engineering tissues.

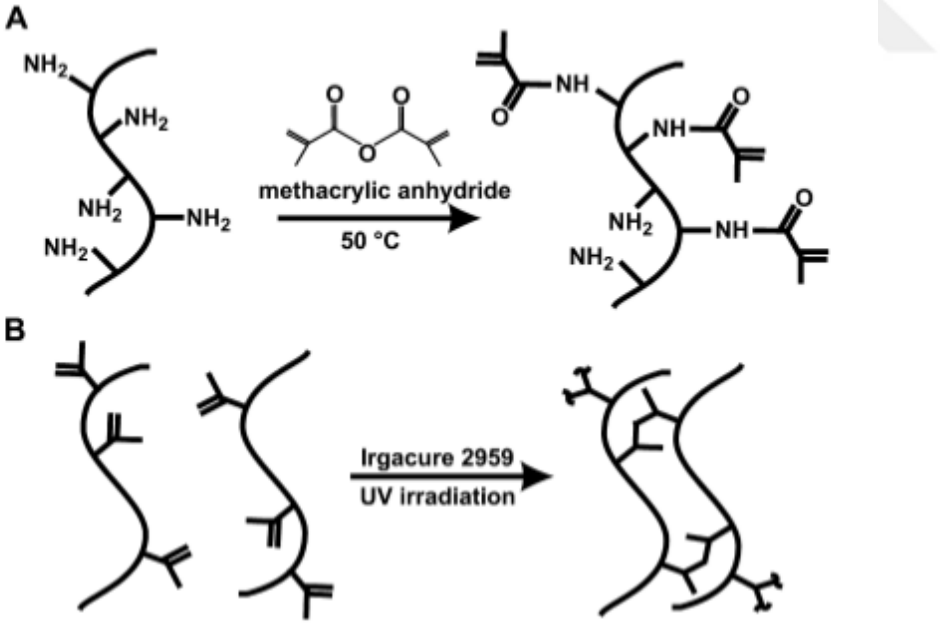


Figure 1.5 Synthesis gelatin metacrylamide (GelMA). Gelatin macromers containing primary amine groups were reacted with methacrylic acid group to introduce methacrylate-pendant groups (A). To form a hydrogel network, the methacrylated gelatin was cross-linked using UV radiation in the presence of a photoinitiator (B) [66].

Within the scope of this project, it is aimed to investigate the synthesis of electrically sensitive gelatin-based intelligent hydrogels and the electrically controlled release of 5-FU drug from the hydrogels, which is used in treatment of skin diseases in the future which are very common today, at different voltage values.

2. MATERIALS AND METHOD

2.1 Materials

Gelatin (Gel, medical grade, 280–320 bloom, Type A), Methacrylic anhydride (MA), Phosphate buffer saline tablet, 2-Hydroxy-4-(2-hydroxyetoxy)-2-methylpropiophenone (Irgacure 2959), 3,4 ethylenedioxythiophene (EDOT), Iron (III) nitrate nonahydrate ($Fe(NO_3)_3.9H_2O$), Poly(sodium-4-styrene sulfonate) (NaPSS), 5-Fluorouracil (5-FU, M_W = 130.08 Da), 12-14 kDa cutoff dialysis tubing were purchased from Sigma Aldrich (USA).

2.2 Synthesis of GelMA

20 g gel was dissolved in 200 ml phosphate buffer saline (PBS) at 50 ˚C for 1 h. Once fully dissolved, 16 ml MA was added slowly to the gel solution at 50 ˚C and the reaction was continued for 3 h under magnetic stirring. Subsequently, the mixture was diluted with 400 ml PBS, filled membrane dialysis tubes (12-14 kDa) and dialyzed to remove salts and unreacted MA.in distilled water for 7 days at 40 ˚C. After dialysis, the GelMA solution was frozen at -80 ˚C and lyophilized to obtain white GelMA foam.

2.3 Fabrication of GelMA hydrogels

Lyophilized GelMA was dissolved in PBS containing 20% w/v (g/ml) at room temperature for 15 minutes. 0.5% w/v (g/ml) Irgacure 2959 was added to the GelMA solution at 40 ˚C to prepare pre polymer solution. To fabricate crosslinked GelMA hydrogel, the pre-polymer solution was exposed to UV light at 365 nm for 25 minutes.

2.4 Synthesis of PEDOT/PSS Polymer

0.8 ml of EDOT monomer was dispersed into 15 ml of 0.1 M NaPSS solution, and the mixture was stirred vigorously for 30 minutes at room temperature. Once dispersed, 15.3 g Fe $(NO_3)_3.$ $9H_2O$ in 5 ml of distilled water was added and the reaction kept for 2 h under magnetic stirring at room temperature. End of this reaction, a deep blue powder was collected by centrifugation and dried overnight at 50˚C under vacuum [67]

2.5 Encapsulation of PEDOT/PSS into the GelMA hydrogel

GelMA-based PEDOT/PSS hydrogels were prepared by using the photopolymerization technique. Firstly, GelMA pre-polymer solution was prepared by procedure explained in section 2.3. Secondly, PEDOT/PSS 1% w/v (g/ml) was dispersed in PBS for 10 minutes into the ultrasonic bath to prepare PEDOT/PSS solution. Then, a variety of PEDOT/PSS amount (0%, 1%, 1.5% and 2.5% w/w) were put into the GelMA solution. Following that, GelMA-PEDOT/PSS solution was exposed to UV light (365 nm) during 25 minutes to obtain polymeric network.

2.6 Characterization of Hydrogels

GelMA-PEDOT/PSS hydrogels were characterized by Fourier transform infrared spectroscopy (FT-IR-ATR, Perkin Elmer Spectrum 100). SEM images were taken to determine the structure of products.

2.6.1 Cytotoxicity Test for GelMA

Cytotoxicity of the GelMA and GelMA-based PEDOT/PSS -1.5 wt. % hydrogels were investigated by WST-1 assay using the L929 cell line. For this experiment, L929 cell line from the exponential phase culture was washed with PBS and separated with 0.1% trypsin-EDTA. Second, sterilized hydrogel specimens were placed in 24-well cell culture plates. In 1 ml cell-DMEM solution, $5x10^4$ viable cells were seeded onto the film and incubated in a humidified incubator in 5% CO_2 for 24 hours at 37 °C. As a control group, $5x10^4$ viable cells in 1 ml of cell-DMEM complete medium were seeded in wells without sample. After a 24 hour period, 1000 µl of WST-1 solution was added to each well and incubation was continued for 2 hours. The absorbance value of WST-1 for each sample was then spectrophotometrically measured at 450 nm using a Promega Glomax-Multi + detection system.

2.6.2 Electrical Conductivity of Hydrogels

Lucas Labs S-302 Four Point Resistivity Probing Equipment which was connected to a Gamry Instruments power source was used to measure electrical conductivity of

GelMA-PEDOT/PSS (1 wt.%, 1.5 wt.% and, 2.5 wt.%) hydrogel. Conductivity (σ) values were found using Eq. 2.1;

$$\sigma = \frac{1}{\rho} \quad (2.1)$$

where ρ is sheet resistance and the calculation of the sheet resistance with the following Eq. 2.2:

$$\rho = 2\pi s \times \frac{V}{I} \quad (2.2)$$

where s probe interval, V is the potential difference between the two internal probes, I is the current through the external pair of probes. [68].

2.6.3 Swelling Characterization

Swelling measurements were performed gravimetrically under 0 V and 1.5 V at 37 ℃. Pre-weighted GelMA and GelMA-PEDOT/PSS-1.5 wt. % were swollen into the 15 ml of buffer solutions (pH=5.5) at 130 rpm during 2 h in an orbital shaker. Hydrogel was placed perpendicularly between a pair of electrodes conducting hydrogel to expose to the voltage from the power source. Following that, the swollen hydrogel was weighed. The capacity of water uptake as a percentage was calculated according to the Eq. 2.3 [69].

$$Swelling\ Ratio = \frac{\mathrm{Ws} - \mathrm{Wd}}{\mathrm{Wd}} \times 100 \quad (2.3)$$

where, w_s is swollen weight of hydrogel (g), and w_d is dry weight of hydrogel (g).

2.6.4 Drug Loading and Releasing

The drug (5-FU) was loaded to the polymeric samples during the 3 days. The loaded process was carried out at 130 rpm and 37 ℃ in an orbital shaker. Then, the samples were substracted from loading medium. The drug solution on the hydrogel samples were removed by washing with pH 5.5 solution. The drug loaded hydrogels were placed in the 15 ml of buffer solutions (pH=5.5) to mimic skin cancer conditions [70] at 37 ℃

and 130 rpm. For electric stimuli drug release, electrical voltage (1.5 V) was perpendicularly applied to the hydrogel (GelMA-PEDOT/PSS-1.5 wt. %) from the power source which has anode and cathode sides. Both of electrodes were conducted to the hydrogels. During the releasing experiment, 4.0 ml of the sample was withdrawn from the solution at predetermined intervals and was added equal amount of fresh buffer solution to maintain a constant volume of the release medium. Three replicates were used for each conditions in the release experiments. The amount of 5- FU released from hydrogels was determined UV–vis spectrophotometer (265 nm).

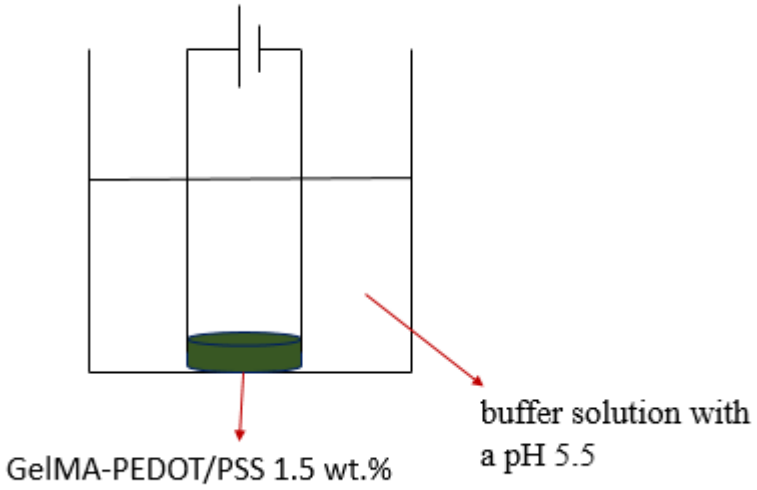


Figure 2.1 The experimental set-up that have been used to study electro-responsive drug delivery from hydrogels in this study.

3. RESULTS AND DISCUSSSON

3.1 Synthesis of Gelatin Methacryloyl

GelMA were obtained by reaction of gel with MA (Methacrylation degree: 18%). This reaction introduced methacryloyl substitution groups on the reactive amine and hydroxyl groups of the gel [71]. At the end of the reaction, toxic low molecular weight impurities such as unreacted metachrylic anhydride and methacrylic acid were removed by dialyzing in distilled water. As seen from figure 3.1, while the product color was white before purification (left side), transparent product was obtained after dialyzed process (right side).



Figure 3.1 (a) Purification of gelatin methacryloyl in membrane dialysis tubing (b) Purificated gelatin methacrylamide in membrane dialysis tubing.

3.2 Fabrication of GelMA hydrogels

To fabricate crosslinked GelMA hydrogel, the pre-polymer (GelMA) solution was irradiated with UV light in the presence of a photoinitiator. In this reaction, methacrylamide and methacrylate side groups in the GelMA macromers were polymerized to form GelMA polymeric network via short polymethacryloyl chains [10] (Figure 3.2).

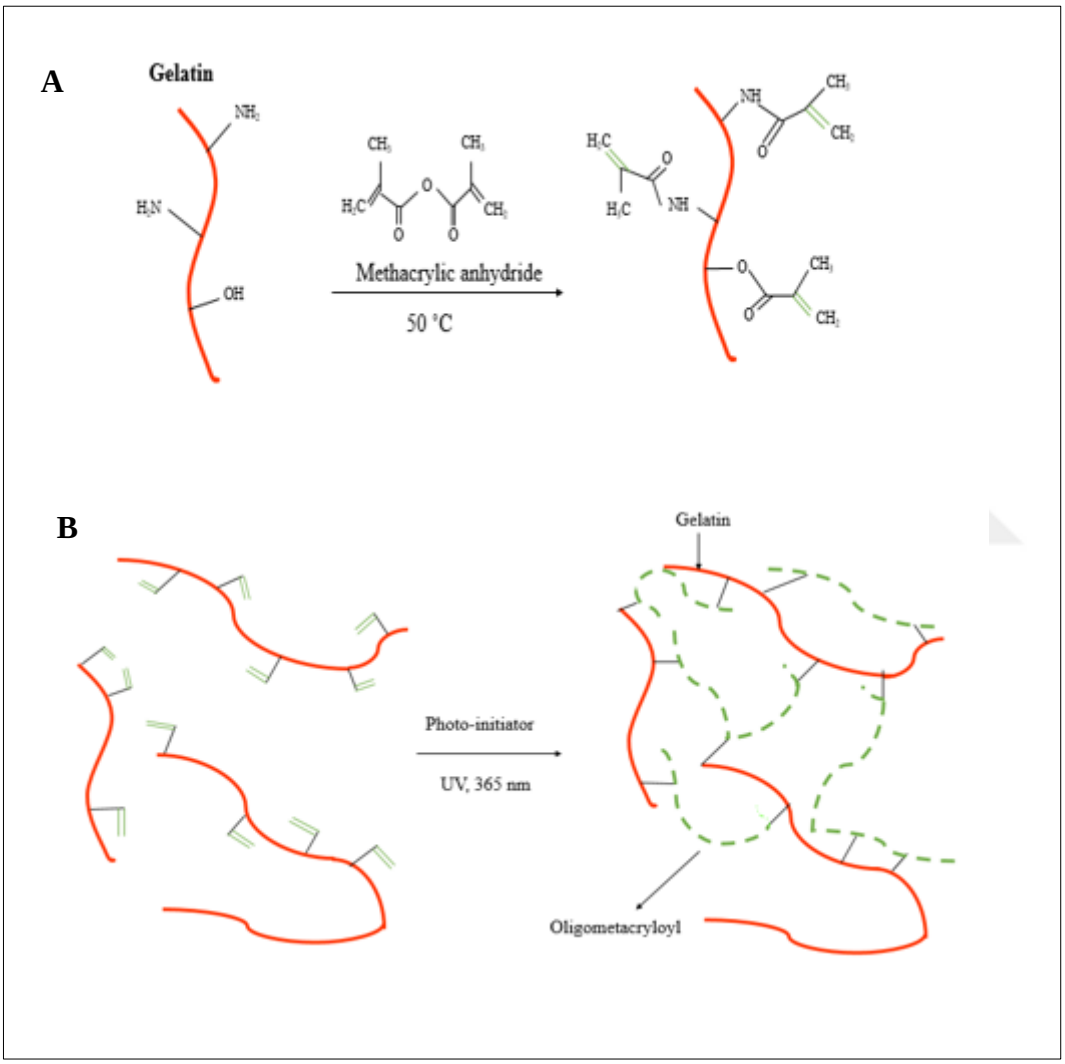


Figure 3.2 Synthesis of GelMA hydrogels. Reaction of methacrylate and methacryamide side groups with amine and hydroxyl groups on the gelatin (A), Cross-linked hydrogel build-up by photopolymerization technique (B).

3.3 Synthesis of PEDOT/PSS polymer

EDOT monomer was dispersed into the NaPSS solution to obtain easily processable colloidal solution [54]. The colour of EDOT monomers in NaPSS solution turned into from dark yellowish to dark blue with adding Fe $(NO_3)_3.$ $9H_2O$ to the solution and finally returned to almost black color due to formation of PEDOT. This transition is due to the chromic nature of the conductive PEDOT [69]. This color transition confirms that PEDOT was successfully synthesized by this method.

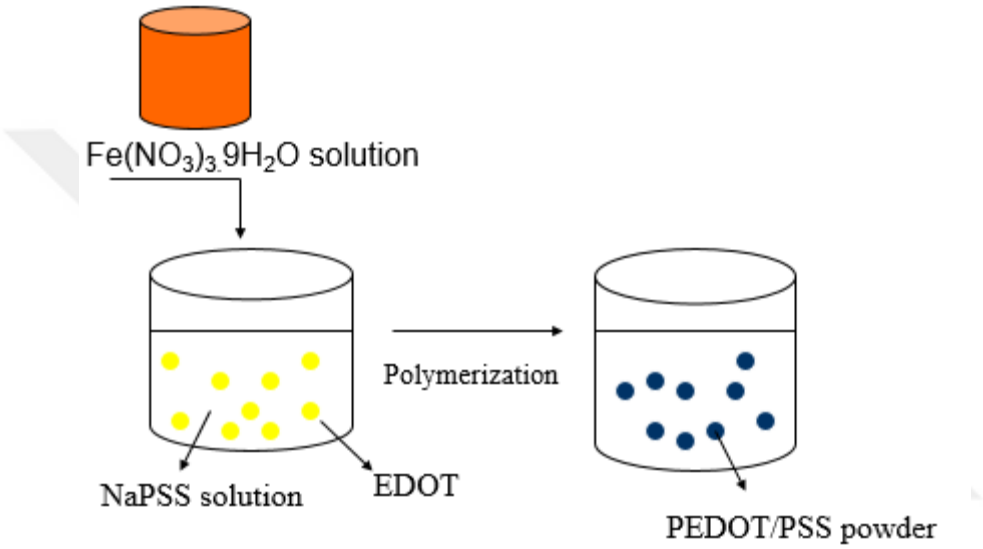


Figure 3.3 Schematic shown of PEDOT/PSS synthesis.

3.4 Encapsulation of PEDOT/PSS into the GelMA hydrogel

To obtain electro-conductive hydrogel, PEDOT/PSS was encapsulated into the GelMA hydrogel by photopolymerization technique (Figure 3.4). While the pure GelMA hydrogel is transparent, GelMA- PEDOT/PSS was almost black due to the presence of PEDOT/PSS structure within the network as shown in Figure 3.5. The conical samples with a radius of 1.5 cm and a height of 2 cm were obtained in the end of the photo-polymerization process (Figure 3.5).

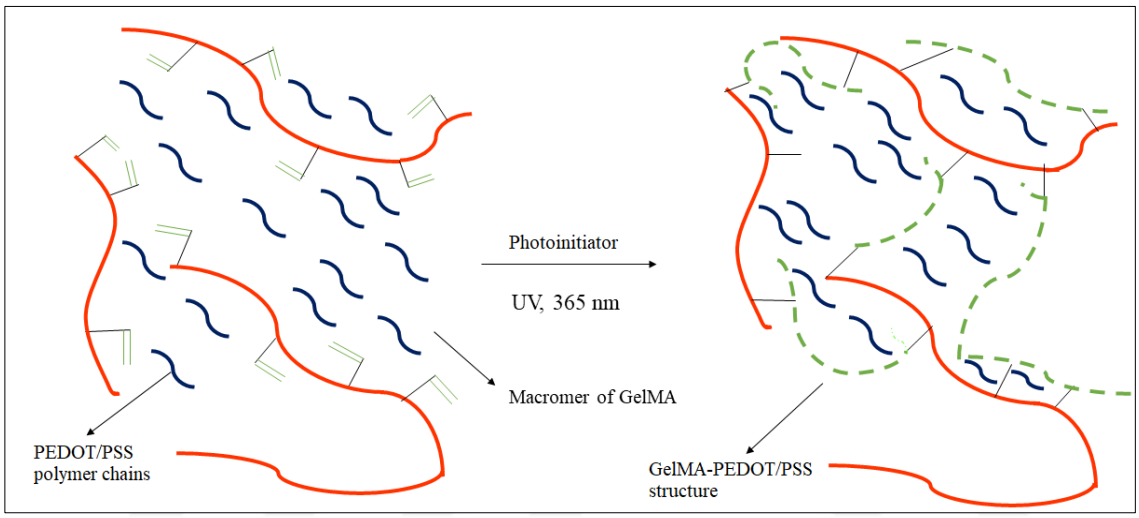


Figure 3.4 Schematic diagram of synthesis procedure of GelMA-PEDOT/PSS hydrogels.

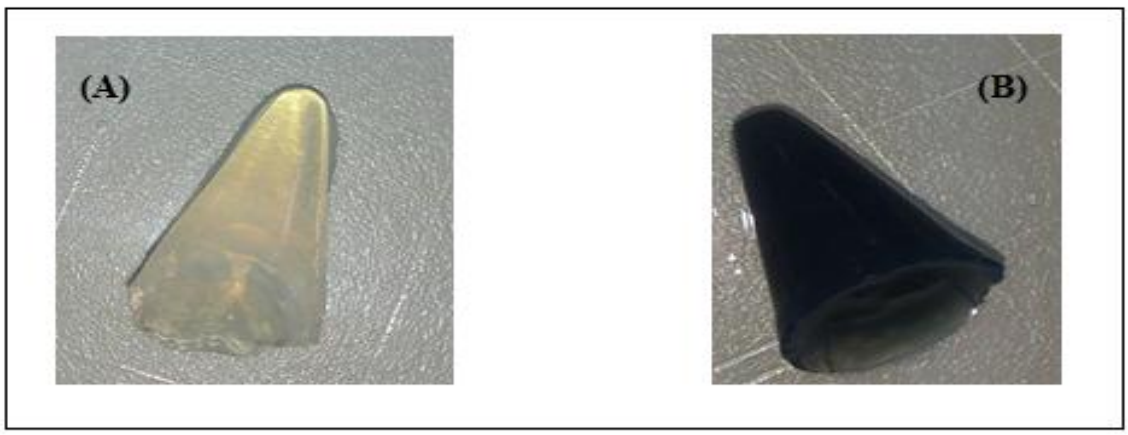


Figure 3.5 Pure GelMA (A) and GelMA-PEDOT/PSS hydrogel (B).

3.5 Characterization of GelMA-PEDOT/PSS Hydrogels

The chemical structure of PEDOT/PSS, pure GelMA, and GelMA-PEDOT/PSS-1.5 wt. % hydrogel were characterized by FT-IR analyses and their spectra were shown in Figure 3.6. As seen from FT-IR spectrum of PEDOT/PSS (Fig. 3.6 a), the vibrations of the C–S bond of the thiophene ring was found at 823 – 655 cm^{-1}. The peak at 1067 cm^{-1} was assigned to the S–C phenyl bonds in sulfonic acid. The absorption peak at 1191 cm^{-1} was attributed to the asymmetric and symmetric vibrations of S–O in sulfonate groups (SO_3H and $–SO_3–$) of PSS chains [61]. C=C and C-C stretching vibrations of the quininoid structure of the thiophene ring of PEDOT/PSS were observed at 1637 cm^{-1} [61, 72]. For GelMA (Fig. 3.6 b), the absorption peak at 3279 cm^{-1} was attributed to C-N-C group and the peak at 1635 cm^{-1} was related to C=C bonds [73]. In the FT-IR spectra of GelMA-PEDOT/PSS-1.5 wt. % (Fig. 3.6 c), GelMA characteristic peak (C-N-C) was presented at 3277 cm^{-1}. Moreover, C=C bond of GelMA which was observed at 1635 cm^{-1} and C=C and C-C stretching vibrations of the quininoid structure of the thiophene ring of PEDOT/PSS which were found at 1637 cm^{-1} overlapped at 1630 cm^{-1} in the GelMA-PEDOT/PSS-1.5 wt.%. Thus, the FT-IR spectra confirmed the encapsulation of the PEDOT/PSS within the GelMA polymeric network [74].

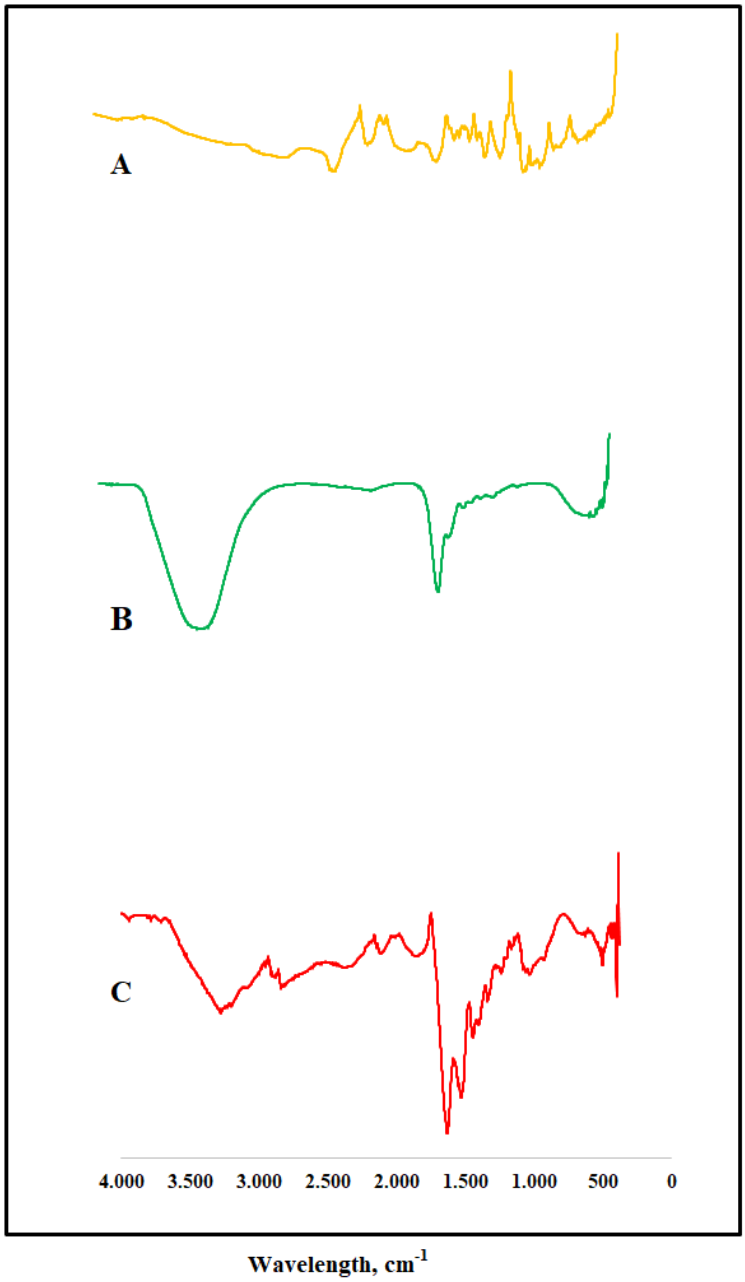


Figure 3.6 FT-IR spectrums of PEDOT/PSS (A), pure GelMA (B) and GelMA-PEDOT/PSS-1.5 wt. % (C).

To observe the structure of 5-FU and drug loaded hydrogel, FT-IR analyses was performed for these samples, as well. The peak at 3124 cm^{-1} is related to NH stretching vibrations in the spectrum of 5-FU (Fig. 3.7 a). The characteristic peak at 1720 cm^{-1} corresponded to the vibration of C=O group. The peak at 1647 cm^{-1} originated from C-N stretching and peaks at 1243 cm^{-1} and 1181 cm^{-1} were due to C-N vibration (in plane) and C-O vibration in the 5-FU structure, respectively [75]. The characteristic peaks of

GelMA-PEDOT/PSS hydrogel which was previously explained was seen in Figure 3.7 b. When the 5-FU was loaded into the GelMA-PEDOT/PSS hydrogel, the characteristic absorbance peak of 5-FU at 1647 cm^{-1} corresponding to the C-N stretching shifted to 1629 cm^{-1} because of the interaction between the NH_2 and OH side groups on gelatin and the N-H, C = O, C-N, and C-F side groups on 5-FU. The most of the characteristic peaks of 5-FU overlapped with the peaks GelMA-PEDOT/PSS polymeric structure (Fig 3.7 c). The FT-IR results reveal that 5-FU was successfully loaded into the GelMA-PEDOT/PSS polymeric matrix [75].

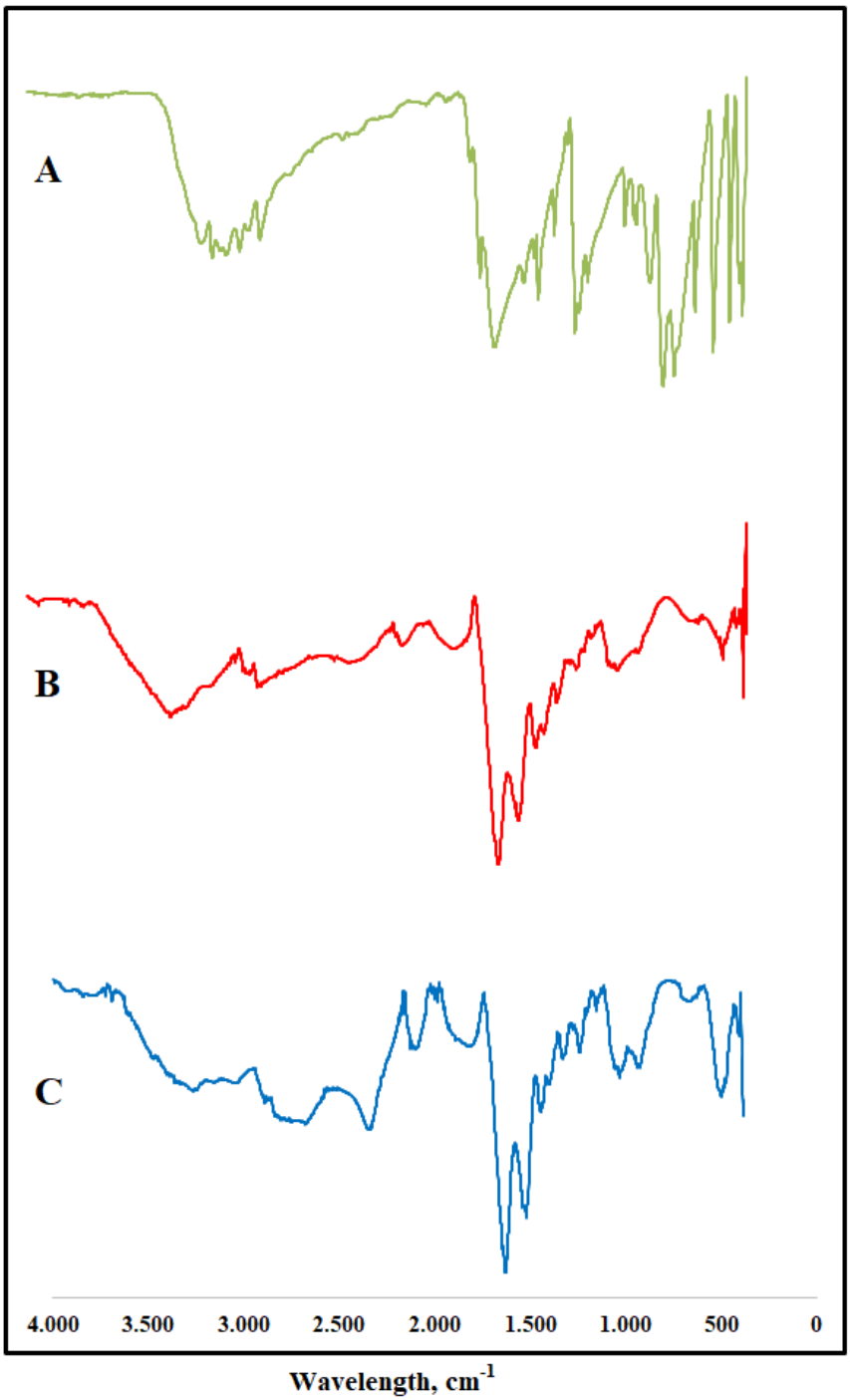


Figure 3.7 FT-IR spectrums of 5-FU (A), GelMA-PEDOT/PSS hydrogel (B) and drug loaded GelMA-PEDOT/PSS hydrogel (C).

To investigate morphologies of PEDOT/PSS and GelMA, and dispersion of PEDOT/PSS in the GelMA polymeric network, SEM analyses were performed. From Figure 3.8 (a), it is clearly observed that the obtained PEDOT/PSS particles with a black color and soft structure aggregate together. The images revealed that GelMA has porous structure and PEDOT/PSS distributed within the GelMA network (Figure 3.8 b-c).

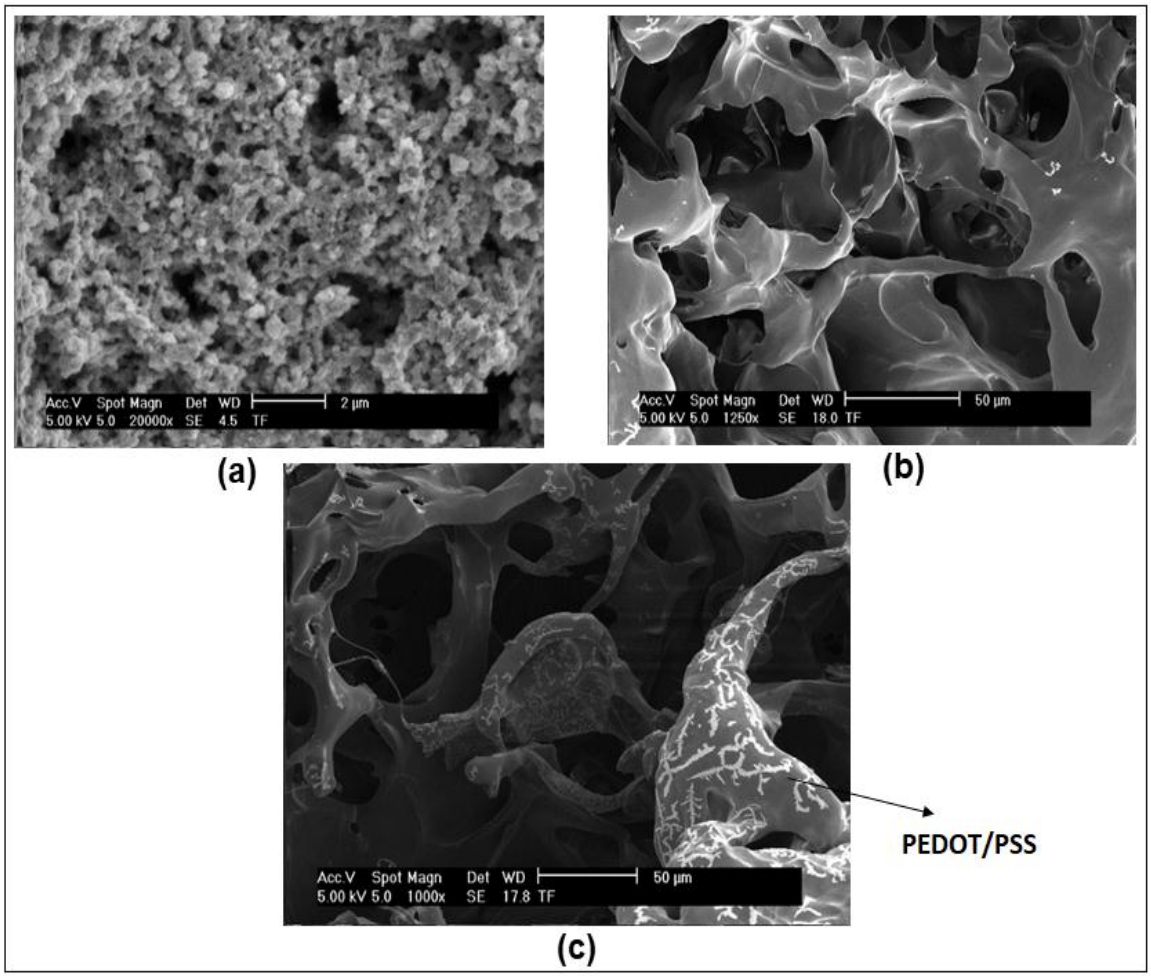


Figure 3.8 SEM images of PEDOT/PSS (A), pure GelMA (B) and GelMA-PEDOT/PSS-1.5 wt. % hydrogel (C).

3.5.1 Cytotoxicity of GelMA-PEDOT/PSS Hydrogels

According to the test results, there is no any significant difference between GelMA, GelMA-PEDOT/PSS-1.5 wt. % and control sample (Figure 3.9). The cell viability was determined as a nearly 99% for each condition.

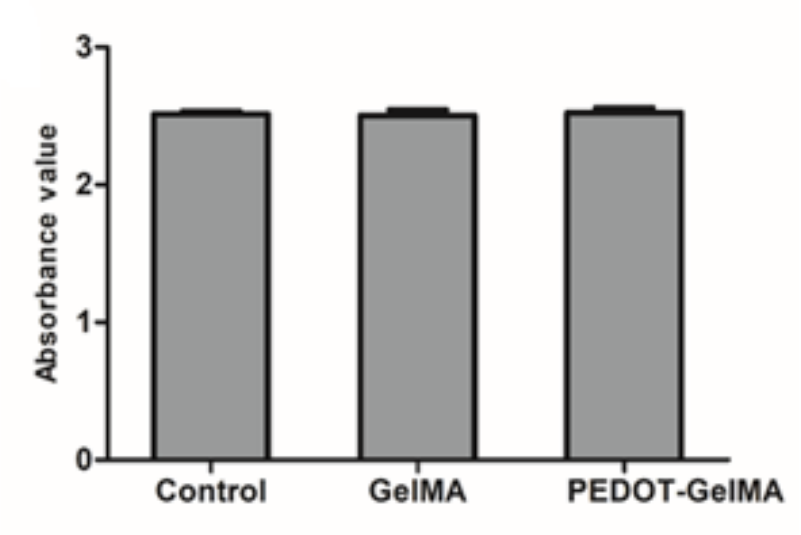


Figure 3.9 Viability of L929 cells on the GelMA, GelMA-PEDOT/PSS-1.5 wt. % and polystyrene well (control sample)

3.5.2 Electrical conductivity of GelMA-PEDOT/PSS hydrogels

The electrical conductivity of the hydrogels was measured using four-probe method and the results were showed as a graph in Figure 3.10. It was showed that the conductivity of GelMA-PEDOT/PSS significantly increased from 6.1×10^{-3} S/cm to 1×10^{-2} S/cm, with an increase in the PEDOT/PSS content from 1 wt.% to 1.5 wt.%. The cause of this phenomenon probably lie in not only the decent electrical conductivity of PEDOT/PSS which was dispersed uniformly in the polymeric network [76], but also PSS that provides the continuous transporting path for electrons [77].

However, it was also observed that the conductivity of PEDOT/PSS-2.5 wt. % was lower than that of GelMA-PEDOT/PSS-1.5 wt. %. This decrease could be attributed that PEDOT/PSS chains within the network exhibited agglomeration behaviors and so, inhomogeneous distribution occurred, which induces the reduction of electron mobility [78].

The obtained results indicated that the conductivity of the hydrogels increased by incorporating PEDOT/PSS into the structure. Additionally, it was observed that the obtained conductivity value (1×10^{-2} S/cm) in this study is higher when compared to the previous works [79.80].

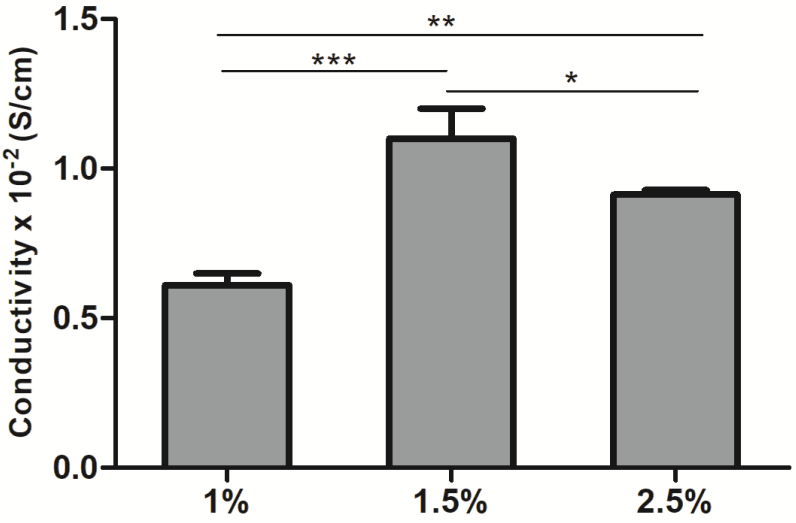


Figure 3.10 Conductivity of the GelMA-PEDOT/PSS hydrogels

3.5.3 Swelling tests

To compare the swelling ratios of pure GelMA and GelMA-PEDOT/PSS 1.5 wt. %, the swelling tests were carried out for both samples under non voltage conditions in buffer solution (pH=5.5). As can be seen from Figure 3.11, the swelling ratio of GelMA increased by incorporation of PEDOT/PSS content. This could be attributed to adding of PEDOT/PSS to the gel prepolymer solution caused reducing cross-linking degree of network. Because, PEDOT/PSS entered between the polymer chains which will be cross-linked. Decreasing of cross-linking degree, increased the swelling capacity of GelMA-PEDOT/PSS 1.5 wt. % hydrogel [81] owing to the fact that hydrogel chains relaxation increase with decreasing of cross-linking degree within the network structure [82].

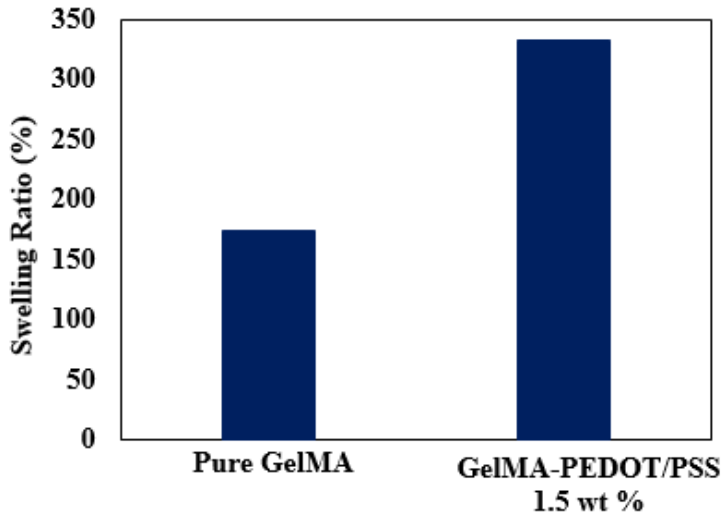


Figure 3.11 Effect of 1.5 wt. % PEDOT/PSS on swelling ratio without voltage

The swelling properties of GelMA-PEDOT/PSS-1.5 wt. % hydrogels were investigated at 0 and 1.5 V in buffer solution (pH= 5.5). As seen from Figure 3.12, GelMA-PEDOT/PSS-1.5 wt. % exhibited lower swelling ratio as voltage applied to the hydrogel. It is known that under the influence of an electric field, electro-responsive hydrogels usually deswell or bend depending on its shape and orientation of the gel. The gel deswells when the gel is perpendicular to the electrodes conducting to the gel as carried out in this study [83-85]. Because, applying voltage to the hydrogels creates an uniaxial stress along the gel axis and this stress gradient is thought to contribute to anisotropic gel deformation [86].

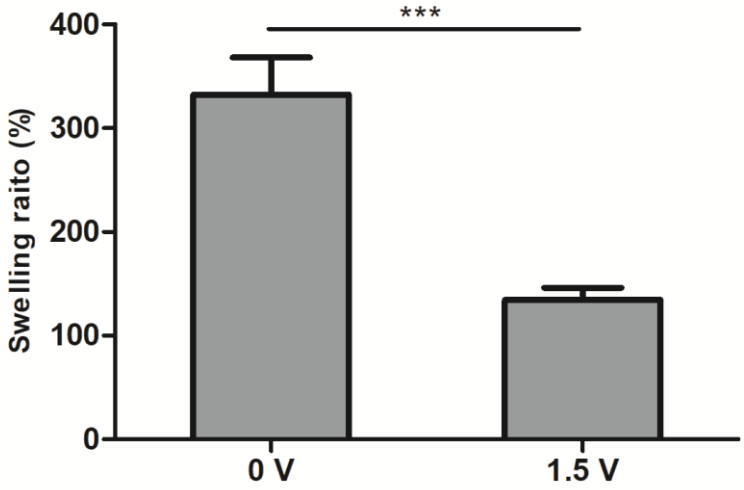


Figure 3.12 Effect of DC electric field set at 0 V and 1.5 V on swelling capacity of GelMA-PEDOT/PSS-1.5 wt.%

This phenomena can be explained as below in detail:

When the electric field is not applied, the distribution of ions that can be diffusible in the hydrogel network structure and in the buffer solution in which the hydrogels were immersed, is symmetric. Once the electric field is applied, ions in both the buffer solution and the hydrogel structure move toward their opposing electrodes, so that the distribution of the ions is not symmetrical and the ion concentration difference of the buffer and hydrogel structure widens. So when the voltage is applied, the gel becomes deswell [83]. In addition, pulling of ions toward their counter electrode, creates an uniaxial stress along the gel axis; stress is the largest in the anode and the smallest in the cathode. This stress gradient contributes to anisotropic gel deformation as well (Figure 3.13) [84].

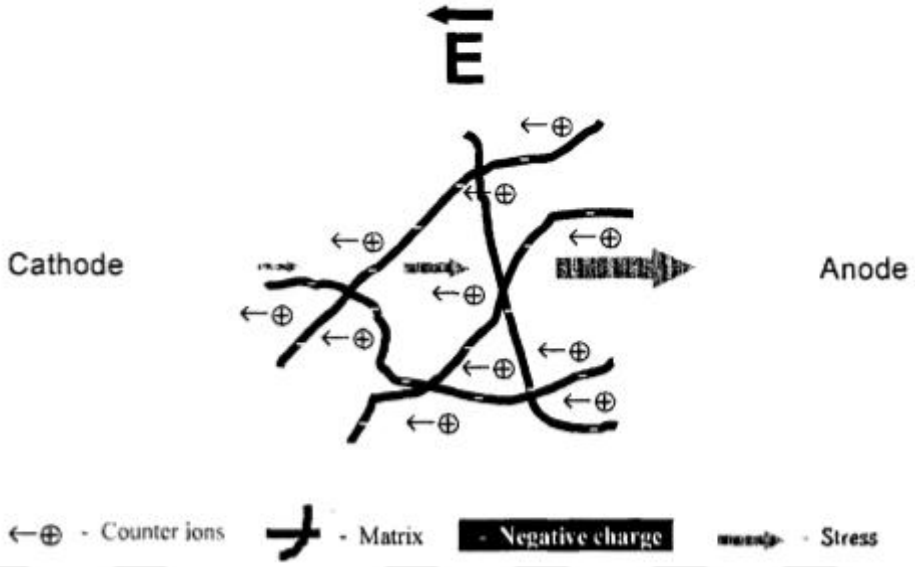


Figure 3. 13 The effect of an electric field on a polyelectrolyte gel [84].

3.5.4 Release Behaviour of 5-FU-loaded GelMA-PEDOT/PSS Hydrogels

In case of pure GelMA and GelMA-PEDOT/PSS 1.5 wt. % without an electric field, while the release amount of 5-FU was 16.9 % from the pure GelMA hydrogel during 6 h, 18.2% of the loaded 5-FU were released from GelMA-PEDOT/PSS 1.5 wt. % hydrogel in the same time interval.

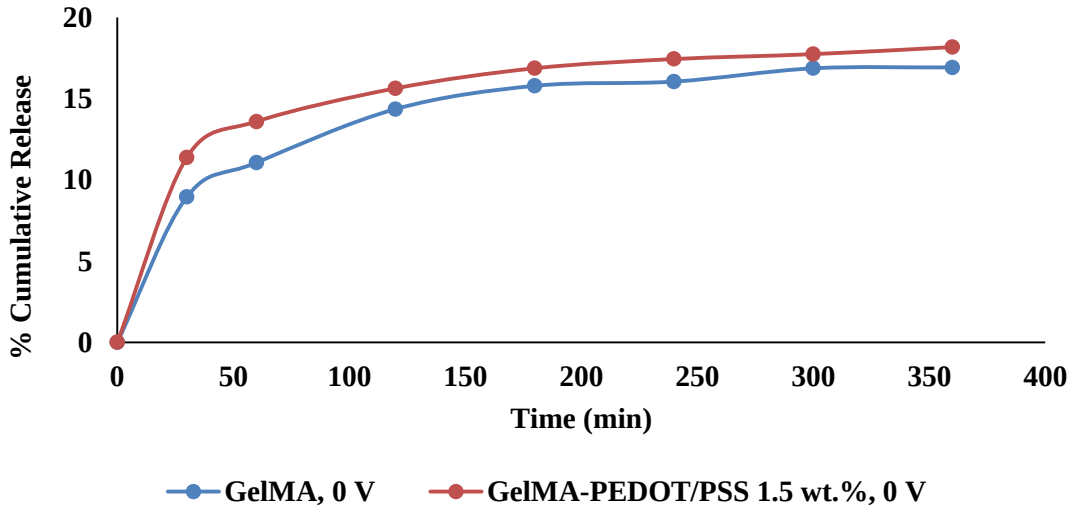


Figure 3.14 Time-dependent release of 5-FU from the GelMA and GelMA-PEDOT/PSS 1.5 wt% hydrogels under 0 V.

The high release rate of 5-FU at non voltage conditions from GelMA-PEDOT/PSS 1.5 wt.% is probably related to the increase in the swelling capacity by incorporation of PEDOT/PSS within the GelMA network. Because, the increase in swelling capacity causes an increase in hydrogel flexibility and facilitates diffusion of the drug [87].

Drug release from hydrogels by swelling, can be explained in three steps. First, the drug loaded hydrogels contain the minimum amount of water at the beginning of the process. They show minimal flexibility. Pore sizes are small and drug movement is limited. In the second step, due to the concentration difference, water starts to enter the hydrogel network, and the hydrogel has relaxed chains, increased pore size and increased drug activity with water ingress. In the final step, the hydrogel is now completely relaxed and hydrated. The size of the pore is maximized, so the diffusion of the drug from the hydrogel occurs. Because of this mechanism, there are more drugs released during the releasing time from the ones with better swelling properties [87].

The electric stimuli responsive release of 5-FU (model drug) was investigated at 0 V and 1.5 V in buffer solution with a pH 5.5 at 37 ˚C to mimic skin cancer conditions. As known from the literature, when tumor cells appear on the skin surface, the pH value in unhealthy region would be 5-6.5 [70]. The release profile (Figure 3.15) showed that the amount of 5-FU released into the buffer solution increased from 18.2% to 23.3% upon application of 1.5 V to GelMA-PEDOT/PSS-1.5 wt. %. Because, the voltage creates a uniform electric field which causes the hydrogel to deswell [88]. Shrinking the gel and changing the network size causes squeeze out of the drug molecules with liquid phase at the same time from the hydrogels [89].

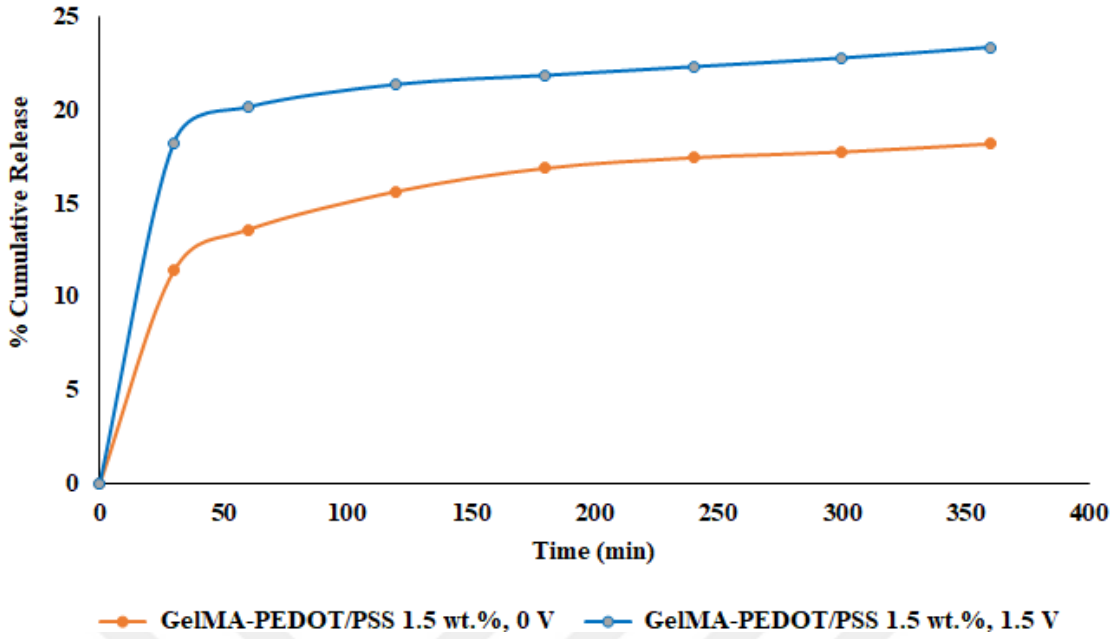


Figure 3.15 Time-dependent release of 5-FU from the GelMA and GelMA-PEDOT/PSS 1.5 wt.% hydrogels when a DC electric field set at 0 V and 1.5 V was applied.

The obtained results demonstrated that 5-FU was released from the polymeric matrix as a result of the hydrogel deswelling upon exposure to an electric field and proved that fabricated GelMA-PEDOT/PSS-1.5 wt.% successfully responded to an electric field. In addition, as a result of examining the some of studies in the literature, it can be mentioned that the amount of released drug from GelMA-PEDOT/PSS hydrogel is sufficient for skin cancer treatment [70, 90, 91].

There are studies in the literature showing that the amount of drug release increases by deswelling of hydrogels in the presence of electrical field. For example, Sawahata et al. showed that the release of the drug occurs when the applied electric field is high enough to cause dimensional changes in the gel. There was a delay of several minutes between the application of the electric field and the release of the drug in the study, which implies that the drug release only occurs when the gel is deswelled [89].

Sutani et al. reported a relatively high drug concentration in the release environment surrounding the anodic side, simultaneously with the anisotropic deswelling of anionic jellies [92].

4. CONCLUSIONS

Electrically conductive GelMA-PEDOT/PSS were synthesized by incorporating of diff erent amount of PEDOT/PSS (0%, 1%, 1.5%, 2.5% w/w) into GelMA polymeric network.

The presence of PEDOT/PSS in GelMA network was confirmed by FT-IR and SEM analysis. It was determined that GelMA-PEDOT/PSS hydrogels has biocompatible properties. Swelling experiments showed that water uptake capacity of GelMA-PEDOT/PSS hydrogels was higher than pure GelMA at non voltage conditions. On the other hand, when applying voltage, swelling capacity of GelMA-PEDOT/PSS was decreased compared to that of GelMA-PEDOT/PSS determined under non-voltage voltage conditions.

According to conductivity measurements, while the conductivities of the hydrogels increased by incorporation of PEDOT/PSS up to 1.5 wt. %, conductivity of hydrogel decreased when used 2.5 wt. % PEDOT/PSS. The highest conductivity (1×10^{-2} S/cm) was obtained by incorporating 1.5 wt. % PEDOT/PSS into the GelMA polymeric network. Therefore, 1.5 wt. % PEDOT/PSS content was chosen amount for the electro-responsive release experiments.

The results of the releasing tests performed at 0 V and 1.5 V into the buffer solutions (pH=5.5) showed that the drug release from GelMA-PEDOT/PSS 1.5 wt. % hydrogel was higher (23.3 %) under 1.5 V compared to the determined release amount (18.2 %) under 0 V condition, which confirms that the releasing of 5-FU from the fabricated electro-conductive GelMA-PEDOT/PSS hydrogel is electric dependent. Additionally, the released amount of 5-FU from the pure GelMA hydrogel was determined as a 16.9 % at the non-voltage condition.

From the all results, it can be envisaged that GelMA-PEDOT/PSS conductive material can be used as a drug carrier for the electric-stimuli controlled delivery of 5-FU in the cure of skin cancer in the future works.

REFERENCES

[1]: Brahima, S. (2016) pH ve Sıcaklığa Duyarlı Hidrojellerin Sentezlenmesi ve İlaç Salım Davranışlarının Modellenmesi. Yüksek Lisans Tezi, İnönü Üniversitesi Fen Bilimleri Enstitüsü, Malatya, Türkiye, 6-7.

[2]: Sop, E.S. (2013) Doku Genişletme Amaçlı Hidrojel Sentezi, Karakterizasyonu ve Şişme Kinetiği. Yüksek Lisans Tezi, Hacettepe Üniversitesi Fen Bilimleri Enstitüsü, Ankara, Türkiye, 4-7.

[3]: Samal, S.K., Dash, M., Dubruel, P., Vlierberghe, V.S. (2014) Smart polymer hydrogels: properties, synthesis and applications. Smart Polymers and Their Applications, 237-270.

[4]: Selen, F. (2015) UV Işıkla Çapraz Bağlanma Derecesi Değişebilen Hidrojellerin Sentezi ve Çeşitli Özeliklerinin İncelenmesi. Yüksek Lisans Tezi, Yalova Üniversitesi Fen Bilimleri Enstitüsü, Yalova, Türkiye, 3-7.

[5]: Ekren, H. (2015) Boyar madde Soğurumu için Çapraz Bağlı Terpolimer Sentezi ve Karakterizasyonu, Yüksek Lisans Tezi, Adnan Menderes Üniversitesi Fen Bilimleri Enstitüsü, Aydın, Türkiye, 9-17.

[6]: Bahar, D. (2015) Süper Absorban Polimer Geliştirilmesi ve Uygulamaları, Yüksek Lisans Tezi, Yıldız Teknik Üniversitesi Fen Bilimleri Enstitüsü, İstanbul, Türkiye, 3-11.

[7]: Qiu, Y., Park K. (2012) Environment-sensitive Hydrogels for Drug Delivery. Advanced Drug Delivery Reviews, 64, 49-60.

[8]: Aruntaş, M.S. (2007) Polielektrolit-Protein Kompleksleri. Yüksek Lisans Tezi, Yıldız Teknik Üniversitesi Fen Bilimleri Enstitüsü, İstanbul, Türkiye, 1-5.

[9]: Lin, J., Tang, Q., Hu, D., Sun, X., Li, Q., Wu, J. (2009) Electric Field Sensitivity of Conducting Hydrogels with Interpenetrating Polymer Network Structure. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 346, 177-183.

[10]: Klotz, B.J., Gawlitta, D., Rosenberg, A.J.W.P., Malda, J., Melchels, F.P.W. (2016) Gelatin- Methacryloyl Hydrogels: Towards Biofabrication-Based Tissue Repair. Trends in Biotechnology, 34(5), 394-407.

[11]: Rogina, A., Ressler, A., Matic, I., Ferrer, G.G., Marijanovic, I., Ivankovic, M., Ivankovic, H. (2017) Cellular Hydrogels Based on pH-Responsive Chitosan-Hydroxyapatite System. Carbonhydrate Polymers, 166, 173-182.

[12]: Naahadi, S., Jafari, M., Logan, M., Wang, Y., Yuan, Y., Bae, H., Dixon, B., Chen, P. (2017) Biocompatibility of Hydrogel-Based Scaffolds for Tissue Engineering Applications. Biotechnology Advances, 35(5), 530-544.

[13]: Vedadghavami, A., Minooei, F., Mohammadi, M.H., Khetani, S., Kolahchi, A.R., Mashayekhan, S., Nezhad, A.S. (2017) Manufacturing of Hydrogel Biomaterials with Controlled Mechanical Properties of Tissue Engineering Applications. Acta Biomaterialia, 62, 42-63.

[14]: Dwivedi, R., Singh, A.K., Dhillon, A. (2017) pH-Responsive Drug Release from Dependal-M loaded Polyacrylamide Hydrogels. Journal of Science: Advanced Materials and Devices, 2(1), 45-50.

[15]: Barış, S.M. (2011) Antikolinesteraz İlaç Piridostigmin Bromürün Kitosan/ Sodyum Aljinat Emulsiyon Çapraz Bağlı ve Kitosan/Metil Selüloz İç İçe Geçmiş Ağ Yapılı Mikrokürelerden Salımı, Yüksek Lisans Tezi, Gazi Üniversitesi Fen Bilimleri Enstitüsü, Ankara, Türkiye, 8-10.

[16]: McNeel, K.E., Siraj, N., Negulescu, I., Warner, I.M. (2017) Sodium deoxycholate/TRIS-Based Hydrogels for Multipurpose Solute Delivery Vehicles: Ambient Release, Drug Release, and Enantiopreferential Release. Talanta, 1-8.

[17]: Öncel, P. (2013) İlaç Salımı için Moleküler Baskılanmış Kriyojel Membranlar. Yüksek Lisans Tezi, Hacettepe Üniversitesi Fen Bilimleri Enstitüsü, Ankara, Türkiye, 4-6.

[18]: Xu, X., Xu, Z.K., Yang, X.F., He, Y.H., Lin, R. (2017) Construction and Characterization of a Pure Protein Hydrogel for Drug Delivery Application. International Journal of Biological Macromolecules, 95, 294-298.

[19]: Farhat, W., Venditti, R., Mignanrd, N., Taha, M., Becquart, F., Ayoub., A. (2017) Polysaccharides and Lignin Based Hydrogels with Potential Pharmaceutical Use as a Drug Delivery System Produced by a Reactive Extrusion Process. International Journal of Biological Macromolecules, 104, 564-575.

[20]: Neufeld, L., Peled, H.B. (2017) Pectin–Chitosan Physical Hydrogels as Potential Drug Delivery Vehicles. International Journal of Biological Macromolecules, 101, 852-861.

[21]: Treesuppharat, W., Rojanapanthu, P., Siangsanoh, C., Manuspiya H., Ummartyotin, S. (2017) Synthesis and Characterization of Bacterial Cellulose and Gelatin-Based Hydrogel Composites for Drug-Delivery Systems. Biotechnology Reports, 15, 84-91.

[22]: Mishra, B., Upadhyay, M., Reddy Adena, S.K., Vasant, B.G., Muthu, M.S. (2017) Hydrogels: An Introduction to a Controlled Drug Delivery Device, Synthesis and Application in Drug Delivery and Tissue Engineering. Austin Journal of Biomedical Engineering, 4(1), 1-13.

[23]: Gupta, P., Vermani, K., Garg, S. (2002) Hydrogels: from Controlled Release to pH-Responsive Drug Delivery. Research Focus, 7(10), 569-579.

[24]: Wang, Y., Wang, J., Yuan, Z., Han, H., Li, T., Li, L. (2017) Chitosan Cross-Linked Poly(acrylic acid) Hydrogels: Drug Release Control and Mechanism. Colloids and Surfaces B:Biointerfaces, 152, 252-259.

[25]: Cao, Y., Kakar, P., Hossen, M.N., Wu, M.X., Chen, X. (2017) Sustained Epidermal Powder Drug Delivery Via Skin Microchannels. Journal of Controlled Release, 249, 94-102.

[26]: Kamble, P., Sadarani, B., Majumdar, A., Bhullar, S. (2017) Nanofiber Based Drug Delivery Systems for Skin: A Promising Therapeutic Approach. Journal of Dug Delivery Science and Technology, 41, 124-133.

[27]: Wong, T.W. (2014) Electrical, Magnetic, Photomechanical and Cavitational Waves to Overcome Skin Barrier for Transdermal Drug Delivery. Journal of Controlled Release, 193, 257-269.

[28]: Akhtar, N., Khan, R.A. (2016) Liposomal Systems as Viable Drug Delivery Technology for Skin Cancer Sites with an Outlook on Lipid-Based Delivery Vehicles and Diagnostic Imaging Inputs for Skin Conditions'. Progress in Lipid Research, 64, 192-230.

[29]: Liuzzi, R., Carciati, A., Guido, S., Caserta, S. (2016) Transport Efficiency in Transdermal Drug Delivery: What is The Role of Fluid Microstructure? Colloids and Surfaces: B Biointerfaces, 139, 294-305.

[30]: Sala, M., Diab, R., Elaissari, E., Fessi, H., Lipid Nanocarriers as Skin Drug Delivery Systems: Properties, Mechanisms of Skin Interactions and Medical Applications. International Journal of Pharmaceuticals, 535(1-2), 1-17.

[31]: Malinovskaja-Gomez, K., Espuelas, S., Gaarrido, M.J., Hirvonen, J., Laaksonen, T. (2017) Comparison of Liposomal Drug Formulations for Transdermal Iontophoretic Drug Delivery. European Journal of Pharmaceutical Sciences, 106, 294-301.

[32]: Chen, Y., Quan, P., Liu, X., Wang, M., Fang, L. (2014) Novel Chemical Permeation Enhancers for Transdermal Drug Delivery. Asian Journal of Pharmaceutical Sciences, 9(2), 51-64.

[33]: Denet, A.R., Vanbever, R., Préat, V. (2004) Skin Electroporation for Transdermal and Topical Delivery. Advanced Drug Delivery Reviews, 56(5), 659-674.

[34]: Denet, A.R., Préat, V. (2003) Transdermal Delivery of Timolol by Electroporation Through Human Skin. Journal of Controlled Release, 88(2), 253-262.

[35]: Indulekha, S., Arunkumar, P., Bahadur, D., Srivastava, R. (2016) Thermoresponsive Polymeric Gel as an On-Demand Transdermal Drug Delivery System for Pain Management. Material Science and Engineering: C, 62, 113-122.

[36]: Zavgorodnya, O., Carmona-Moran, C.A., Kozlovskaya, V., Liu, F., Wick, T.M., Kharlampieva, E. (2017) Temperature-Responsive Nanogel Multilayers of Poly(N-vinylcaprolactam) for Topical Drug Delivery. Journal of Colloid and Interface Science, 506, 589-602.

[37]: Craythome, E., Al-Niami, F. (2017) Skin Cancer. Medicine, 45(7), 431-434.

[38]: Linares, M.A., Zakaria, A., Nizran, P. (2015) Skin Cancer. Primary Care: Clinics in Office Practice, 42(4), 645-659.

[39]: Roozeboom, M.H., Arits, A.H.M.M., Mosterd, K., Sommer, A., Essers, B.A.B., Rooij, M.J.M., Quaedvlieg, P.J.F., Steijlen, P.M., Nelemans, P.J., Kelleners-Smeets, N.W.J. (2016) Three-Year Follow-Up Results of Photodynamic Therapy vs. Imiquimod vs. Fluorouracil for Treatment of Superficial Basal Cell Carcinoma: A Single-Blind, Noninferiority, Randomized Controlled Trial. Journal of Investigative Dermotology, 136(8), 1568-1574.

[40]: Hsieh, C.F., Chiang, Y.T., Chiu, H.Y., Huang, W.F. (2016) A Nationwide Cohort Study of Actinic Keratosis in Taiwan. International Journal of Gerontology, 10(4), 218-222.

[41]: Victoria-Martínez, A.M., Martinez-Leborans, L., Salvador, O., Pérez-Ferriols, A. (2017) Treatment of Bowen Disease With Photodynamic Therapy and the Advantages of Sequential Topical Imiquimod. Actas Dermo-Sifiliográficas (English Edition), 108(2), 9-14

[42]: Haque, T., Rahman, K.M., Thurston, D.E., Hadgraft, J., Lane, M.E. (2015) Topical Therapies for Skin cancer and Actinic Keratosis. European Journal of Pharmaceutical Sciences, 77, 279-289.

[43]: Aydın, Z. (2007) İletken Poli(Etilen Teraftalat)/Polipirol Kompozit Liflerinin Kimyasal Polimerizasyonla Hazırlanması ve Karakterizasyonu. Yüksek Lisans Tezi, Ankara Üniversitesi Fen Bilimleri Enstitüsü, Ankara, Türkiye, 7-11.

[44]: Khatoon, H., Ahmad, S. (2017) A review on conducting polymer reinforced polyurethane composites. Journal of Industrial and Engineering Chemistry, 53, 1-22.

[45]: Aydın, Y. (2012) İletken Polimerlerin İçerisinde Enzim Tutuklamasıyla Yapılan Biyosensörler. Yüksek Lisans Tezi, Karamanoğlu Mehmetbey Üniversitesi, Fen Bilimleri Enstitüsü, Karaman, Türkiye, 2-3.

[46]: Hackett, A., Malmström, J., Travas-Sejdic, J. (2017) Functionalization of Conducting Polymers for Biointerface Applications. Progress in Polymer Science, 70, 18-33.

[47]: Naveen, M.H., Gurudatt, N.G., Shim, Y.B. (2017) Applications of Conducting Polymer Composites to Electrochemical Sensors: A Review. Applied Materials Today, 9, 419-433.

[48]: Nakova, A., Illieva, M., Boiadjieva-Scherzer, T., Tsakova, V. (2017) High-Density Pd Nanoparticles Distribution on PEDOT Obtained Through Electroless Metal Deposition on Pre-Reduced Polymer Layers. Electrochimica Acta, 253, 128-133.

[49]: Pisuchpen, T., Keaw-on, N., Kittikulvarakom, K., Kusonsong, S., Sritana-anant, Y., Supaphol, P., Hoven, V.P. (2017) Electrospinning and Solid State Polymerization: A Simple and Versatile Route to Conducting PEDOT Composite Films. European Polymer Journal, 96, 452-462.

[50]: Meng, J., Li, X., Qin, M., Pei, Y., Yang, S., Lan, Y., Wang, R., Chen, G. (2017) Effects of Pore Size of Reverse Opal Structured PEDOT Films on Their Electrochromic Performances. Organic Electronics, 50, 16-24.

[51]: Wang, F., Zhang, X., Yang, L., Xu, D., Ma, Y., Chen, D., Wang, L., Zhao, C., Yang, W. (2016) A Scalable Route to Prepare Core–Shell Structured ZnO@PEDOT Nanowires and PEDOT Nanotubes and Their Properties as Electrode Materials. Applied Surface Science, 370, 102-110.

[52]: Rajesh, M., Raj, C.J., Manikandan. R., Kim, B.C., Park, S.Y., Yu, K.H. (2017) A High Performance PEDOT/PEDOT Symmetric Supercapacitor by Facile In-Situ Hydrothermal Polymerization of PEDOT Nanostructures on Flexible Carbon Fibre Cloth Electrodes. Material Today Energy, 6, 96-104.

[53]: Guex, A.G., Puetzer, L.P., Armgarth, A., Littmann, E., Stavrinidou, E., Giannelis, E.P., Malliaras, G.G., Stevens, M.M. (2017) Highly Porous Scaffolds of PEDOT:PSS for Bone Tissue Engineering. Acta Biomaterialia, 62, 91-101.

[54]: Vitoratos, E., Sakkopoulos, S., Dalas, E., Paliatsas, N., Karageorgepoulos, D., Petraki, F., Kennou, S., Choulis, S.A. (2009) Thermal Degradation Mechanisms of PEDOT:PSS. Organic Electronics, 10, 61-66.

[55]: Zhou, Y., Liu, G., Liu, J., Wang, Y., Ai, Q., Huang, J., Yuan, Z., Tan, L.., Chen, Y. (2017) Effective Network Formation of PEDOT by in-situ Polymerization Using Novel Organic Template and Nanocomposite Supercapacitor. Electrochemica Acta, 247, 871-879.

[56]: Lin, Y.J., Lee, J.Y., Chen, S.M. (2016) Changing Electrical Properties of PEDOT:PSS by Incorporating with Dimethyl Sulfoxide. Chemical Physics Letters, 664, 213-218.

[57]: Seo, Y.K., Joo, C.W., Lee,J., Han, J.W., Lee, D.J., Entifar, S.A.N, Kim,S., Cho, N.S., Kim, Y.H. (2017) Enhanced Electrical Properties of PEDOT:PSS Films Using Solvent Treatment and Its Application to ITO-Free Organic Light-Emitting Diodes.

[58]: Bai, S., Ma, Y., Jiang, X., Li, Q., Yang, Z., Liu, X., He, D. (2017) Greatly Improved Cyclability for Li-Ion Batteries with a PEDOT–PSS Coated Nanostructured Ge Anode. Surfaces and Interfaces, 8, 214-218.

[59]: Zahid, M., Papadopoulou, E.L., Athanassiou, A., Bayer, I.S. (2017) Strain-Responsive Mercerized Conductive Cotton Fabrics Based on PEDOT:PSS/Graphene. Materials&Design, 135, 213-222.

[60]: Seo, Y.K., Joo, C.W., Lee, J., Han, J.W., Cho, N.S., Lim, K.T., Yu, S., Kang, M.H., Yun, C., Choi, B.H., Kim,Y.H. (2017) Efficient ITO-Free Organic Light-

Emitting Diodes Comprising PEDOT:PSS Transparent Electrodes Optimized with 2-ethoxyethanol and Post Treatment. Organic Electronics, 42, 348-354.

[61]: Lay, M., Pèlach, M.À., Pellicer, N., Tarrés, J.A., Bun, K.N., Vilaseca, F. (2017) Smart Nanopaper Based on Cellulose Nanofibers with Hybrid PEDOT:PSS/Polypyrrole for Energy Storage Devices. Carbonhydrate Polymers, 165, 86-95.

[62]: Yue K, Santiago G.S, Mois M., Tamayol A., Annabi N., Khademhosseini A., (2015) Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels, Biomaterials, 73, 254-271.

[63]: Roy, B.C., Das, C.,Hong, H., Betti M., Bruce, H.L. (2017) Extraction and characterization of gelatin from bovine heart. Food Bioscience, 20,116-124.

[64]: Tan G., Zhou L., Ning, C., Tan, Y., Ni, G., Liao, J., Yu, P., Chen X. (2013) Biomimetically-mineralized composite coatings on titanium functionalized with gelatin methacrylate hydrogels. Applied Surface Science, 279, 293-299.

[65]: Coimbra, P., Fernandes, D., Ferreira, P., Gil, M.H., Sousa, H.C. (2008) Solubility of Irgacure® 2959 photoinitiator in supercritical carbon dioxide: Experimental determination and correlation. The Journal of Supercritical Fluids, 45(3), 272-281.

[66]: Nickol, J.W.,Koshy, S.T.,Bae, H.,Hwang, C.M.,Yamanlar, S.,Khademhosseini, A. (2010) Cell Laden Microengineered Gelatin Metacrylate Hydrogels. Biomaterials, 31, 5536-5544.

[67]: Qi, Z.; Pickup, P.G. (1998) High performance conducting polymer supported oxygen reduction catalysts. Chem. Commun, 299-2300.

[68]: Ulutürk C., (2016) Synthesis of Chitosan Based Biocompatible Conductive Polymer for Biosensor Applications. Master Thesis, Marmara University, Institute for Graduate Studies in Pure and Applied Sciences, İstanbul, Turkey, 20-21.

[69]: Kim, Y.S.; Cho, K.; Lee, H.J.; Chang, S.; Lee, H.; Kim, J.H.; Koh, W.G. (2016) Highly conductive and hydrated PEG-based hydrogels for the potential application of a tissue engineering scaffold. Reactive and Functional Polymers, 109, 15-22.

[70]: Sahu, P.; Kashaw, S.K.; Jain, S.; Sau, S.; Iyer, A.K. (2017) Assessment of penetration potential of pH responsive double walled biodegradable nanogels coated with eucalyptus oil for the controlled delivery of 5-fluorouracil: In vitro and ex vivo studies Journal of Controlled Release, 253, 122.

[71]: Yue, K., Santiago, G.T., Alvarez, M.M., Tamayol, A., Annabi, N., Khademhosseini, A. (2015) Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. Biomaterials, 73, 254-271.

[72]: Chen, Y., Xu, J., Yang, Y., Zhao, Y., Yang, W., Mao, X., He, X., Li, S. (2016) The preparation and electrochemical properties of PEDOT:PSS/MnO2/ PEDOT ternary film and its application in flexible micro-supercapacitor. Electrochimica Acta, 193, 199-205.

[73]: Kuo, Y.C., Chen, Y.C. (2016) Regeneration of neurite-like cells from induced pluripotent stem cells in self-assembled hyaluronic acid-gelatin microhydrogel. Journal of the Taiwan Institute of Chemical Engineers, 67, 74-87.

[74]: Khan, S., Ul-Islam, M., Ullah, M.W., Israr, M., Jang, J.H., Park, J.K. (2017) Nano-gold assisted highly conducting and biocompatible bacterial cellulose-PEDOT:PSS films for biology-device interface applications. International Journal of Biological Macromolecules, 107, 865-873.

[75]: Sağir, T.; Huysal, M.; Durmus, Z.; Zengin Kurt, B.; Senel, M. Isık, S. (2016) Preparation and in vitro evaluation of 5-flourouracil loaded magnetite– zeolite nanocomposite (5-FU-MZNC) for cancer drug delivery applications. Biomedicine & Pharmacotherapy, 77, 182–190.

[76]: Zahid, M., Papadopoulou, E.L., Athannassiou, A., Bayer, İ.S. (2017) Strain-responsive mercerized conductive cotton fabrics based on PEDOT:PSS/graphene. Materias & Design, 135, 213-222.

[77]: Pal, R.K., Turner, E.E., Chalfant, B.H., Yadavalli, V.K. (2017) Mechanically robust, photopatternable conductive hydrogel composites. Reactive and Functional Polymers, 120, 66-73.

[78]: Li, J., Ma, P. C., Chow, W. S., To, C. K., Tang, B. Z., & Kim, J. K. (2007) Correlations between percolation threshold, dispersion state, and aspect ratio of carbon nanotubes. Advanced Functional Materials, 17(16), 3207–3215.

[79]: Kim, Y.S., Cho, K., Lee, H.Y., Chang, S., Lee, H., Kim, J.H., Koh, W. (2016) Highly conductive and hydrated PEG-based hydrogels for the potential application of a tissue engineering scaffold. Reactive and Functional Polymers, 109, 15-22.

[80]: Dai, T., Qing, X., Lu, Y., Xia, Y. (2009) Conducting Hydrogels with enhanced mechanical strength. Polymer, 50, 5236-5241.

[81]: Kashi, M., Baghbani, F., Moztarzadeh, F., Mobasheri, H., Kowsari, E. (2018) Green synthesis of degradable conductive thermosensitiveoligopyrrole/chitosan hydrogel intended for cartilage tissue engineering. International Journal of Biological Macromolecules, 107, 1567-1575.

[82]: Bukhari, S.M.H, Khan, S., Rehanullah, M., Ranjha, N.M. (2015) Synthesis and Characterization of Chemically Cross-Linked Acrylic Acid/Gelatin Hydrogels: Effect of pH and Composition on Swelling and Drug Release. Hindawi Publishing Corporation, 1-16.

[83]: Lin, S.B., Yuan, C.H., Ke, A.R., Quan, Z.L. (2008) Electrical response characterization of PVA–P(AA/AMPS) IPN hydrogels in aqueous Na2SO4 solution. Sensors and Actuators B: Chemical, 134, 281-286.

[84]: Murdan, S., (2003) Electro-respunsive drug delivery from hydrogels. Journal of Controlled Release, 92, 1-17.

[85]: Bajpai, A.K., Shukla, S.K., Bhanu, S., Kankane, S. (2008) Responsive polymers in controlled drug delivery. Progress in Polymer Science, 33, 1088-1118.

[86]: Quio, Y., Park, K. (2012). Environment-sensitive hydrogels for drug delivery. Advanced Drug Delivery Reviews. 64, 49-60.

[87]: Wang, Y., Wang, J., Yuan, Z., Han, H., Li, T., Li, L., Guo, X. (2017) Chitosan cross-linked poly(acrylic acid) hydrogels: Drug release control and mechanism, Colloids and Surfaces B: Biointerfaces, 152, 252-259.

[88]: Liu, Y., Servant, A., Guy, O.J., Al-Jamal, K.T., Williams, P.R., Hawkins, K.M., Kostarelos, K. (2012). An electric-field responsive microsystem for controllable miniaturised drug delivery applications. Sensors and Actuators B: Chemical. 175, 100-105.

[89]: Sawahata, K., Hara, M., Yasunaga, H., Osada, Y. (1990) Electrically controlled drug delivery system using polyelectrolyte gels. J. Control. Release, 14, 253–262.

[90]: Amasya, G.; Gumustas, M.; Badilli, U.; Ozkan, S.A.; Tarimci, N. (2018) Development of a HILIC method for the determination of 5-fluorouracil from nano drug delivery systems and rat skin extracts. Journal of Pharmaceutical and Biomedical Analysis, 154, 285-293.

[91]: Dante, M.C.L.; Borgheti-Cardoso, L.N.; Fantini, M.C.A.; Praça, F.S.G.; Medina, W.S.G.; Pierre, M.B.R.; Lara, M.G. (2018) Liquid Crystalline Systems Based on Glyceryl Monooleate and Penetration Enhancers for Skin Delivery of Celecoxib: Characterization, In Vitro Drug Release, and In Vivo Studies. Journal of Pharmaceutical Sciences, 107(3), 870-878.

[92]: Sutani, K., Kaetsu, I., Uchida, K. (2001) The synthesis and the electric-responsiveness of hydrogels entrapping natural polyelectrolyte. Radiat. Phys. Chem., 61, 49–54.

ÖZGEÇMİŞ

Kişisel Bilgiler

Adı Soyadı:	Salise OKTAY
Adres:	Burhaniye Mh. Gürgen Sk. No: 8/1 Üsküdar/İSTANBUL
Doğum Yeri ve Tarihi:	Üsküdar / 18.05.1993
Email:	saliseoktay@hotmail.com

Eğitim Bilgileri

2007-2011	Kazım İşmen Anadolu Lisesi
2011-2016	Marmara Üniversitesi, Mühendislik Fakültesi, Kimya Müh. Bölümü
2016-	Marmara Üniversitesi, Fen Bilimleri Enstitüsü, Kimya Müh. Bölümü