TÜRKİYE CUMHURİYETİ
ADANA ALPARSLAN TÜRKEŞ SCIENCE AND TECHNOLOGY UNIVERSITY

GRADUATE SCHOOL
BIOENGINEERING DEPARTMENT

DEVELOPMENT OF WOUND/BURN DRESSING MATERIAL WITH ASTAXANTHIN-IMPRINTED PHEMA BASED POLYMER

BUKET SABUNCUGİL

M.Sc.

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ADANA, 2024

DECLARATION OF CONFORMITY

In this thesis study, which was prepared following the thesis writing rules of Adana Alparslan Türkeş Science and Technology University Institute of Graduate School, I declare that I provide all the information, documents, evaluations and results in accordance with scientific ethics and moral codes without resorting to any means or assistance that would be contrary to scientific ethics and traditions. I also declare that I refer to all of the articles I used in this study with appropriate references and accept all moral and legal consequences if a situation is found contrary to my statement regarding my work.

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[Signature]

Buket SABUNCUGİL

ÖZET

ASTAKSANTİN BASKILANMIŞ PHEMA BAZLI POLİMER İLE YARA/YANIK ÖRTÜ MALZEMESİNİN GELİŞTİRİLMESİ

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Astaksantin, bir karotenoid pigmentidir ve doğada genellikle yosunlar, mantarlar, bakteriler, algler ve bazı deniz canlıları gibi organizmalarda bulunur. Yüksek antioksidan özelliklere sahip olan astaksantin, özellikle algi, kril, karides ve somon gibi deniz ürünlerinde yüksek miktarlarda bulunabilir. Astaksantin, karotenoid ailesine aittir ve özellikle kırmızı-pembe renk tonlarına sahiptir. Astaksantinin insan sağlığı üzerinde antioksidan ve anti-inflamatuar etkileri olduğu araştırılmış ve yara ve yanıklarla ilgili olarak, astaksantinin özellikle cilt sağlığına olan potansiyel faydaları bilinmektedir. Antioksidan ve anti-inflamatuar özellikleri, ciltteki serbest radikallerle savaşarak ve iltihaplanmayı azaltarak iyileşmeyi destekleyebilir. Bu çalışmada Astaksantin baskılanmış HEMA bazlı polimerler sentezlenmiş ve farklı miktarlarda Astaksantin içeren bu polimerler kullanılarak kriyojeller sentezlenmiştir. Hidroksietil metakrilat (HEMA) bazlı kriyojeller, şişme testleri, taramalı elektron mikroskobu ile karakterize edilmiştir. Kriyojellerin içerisine gömülen Asx-MIP miktarlarına bağlı olarak salım kinetiği incelenmiş; Asthaxthinin fare embriyonik fibroblast (MEF, (CF-1) (ATCC® SCRC-1040™)) hücre hattı üzerindeki etkisini inceleyebilmek için ise MTT assay uygulanmıştır. Sonucunda kriyojellerde bulunan astaksantinin hücre çoğalmasını artırıcı etkiye sahip olduğu görülmüş ve astaksantin içeren MIP kriyojellerin yara iyileşmesini kolaylaştırma potansiyeline sahip olduğu ve yara/yanık pansuman malzemesi olarak kullanabileceği kanıtlanmıştır.

Anahtar Kelimeler: Astaksantin, Moleküler baskılanmış polimer, Kriyojel

ABSTRACT

DEVELOPMENT OF WOUND/BURN DRESSING MATERIAL WITH ASTAXANTHIN-IMPRINTED PHEMA BASED POLYMER

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Astaxanthin is a carotenoid pigment and is commonly found in nature in organisms such as algae, fungi, bacteria, algae and some marine creatures. Astaxanthin, which has high antioxidant properties, can be found in high amounts in seafood, especially algae, krill, shrimp and salmon. Astaxanthin belongs to the carotenoid family and has particularly red-pink hues. It has been researched that astaxanthin has antioxidant and anti-inflammatory effects on human health, and its potential benefits are known, especially for skin health, regarding wounds and burns. Its antioxidant and anti-inflammatory properties can promote healing by fighting free radicals in the skin and reducing inflammation. In this study, Astaxanthin imprinted HEMA based polymers were synthesized and cryogels were synthesized using these polymers containing different amounts of Astaxanthin. Hydroxyethyl methacrylate (HEMA)-based cryogels were characterized by swelling tests, scanning electron microscopy. Release kinetics were examined depending on the amount of Asx-MIP embedded into the cryogels; MTT assay was applied to examine the effect of astaxanthin on mouse embryonic fibroblast (MEF, (CF-1) (ATCC® SCRC-1040™)) cell line. As a result, it has been shown that astaxanthin contained in cryogels has a cell proliferation-enhancing effect, and it has been proven that MIP cryogels containing astaxanthin have the potential to facilitate wound healing and can be used as wound/burn dressing material.

Keywords: Astaxanthin, Molecularly imprinted polymer, Cryogel

Dedication

(I dedicate this thesis to my late mother, father and brother, who always supported me.)

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LIST OF ABBREVIATIONS

Asx	: Astaxanthin
TEM	: transmission electron microscopy
SEM	: Scanning electronic microscopy
VEGFA	: Vascular endothelial growth factor A
WHO	: World Health Organization
NETs	: neutrophil extracellular traps formation
ECM	: extracellular matrix
MMPs	: Matrix metalloproteinases
HIF-1α	: hypoxia-inducible factor 1-alpha
CMC	: carboxymethyl cellulose
MIMO	: molecularly imprinted mesoporous organosilica
MIPN	: molecularly imprinted polymer nanoparticles
PVA/GEL	: polyvinyl alcohol/gelatin nanofiber
SA	: sodium alginate
CaAlg	: calcium alginate
KH-570	: β-methoxyethylene triethyoxysilane
KH-550	: γ-amidopropyl triethyoxysilane
MIPs	: Molecularly imprinted polymers
MAA	: Methacrylic acid

EGDMA	: Ethylene Dimethacrylate
TEMED	: N,N,N',N'-Tetramethyl ethylenediamine
APS	: Ammonium persulfate
HEMA	: 2-hydroxyethyl methacrylate
MEF	: mouse embryonic fibroblast
DMEM	: Dulbecco's Modified Eagle's medium
FBS	: fetal bovine serum

LIST OF SYMBOLS

Sr: Swelling Ratio

Ws: Swollen weight of polymer

Wd: Dry weight of polymer

Wt: Overall monomer mass in polymer

Py: Polymerization yield

1.INTRODUCTION

A naturally occurring xanthophyll carotenoid, astaxanthin can be found in a variety of foods and environments, including complex plants, fungi, seafood, and byproducts from crustaceans and microalgae. The two main sources of astaxanthin are the red yeast *Phaffia rhodozyma* and the green algae Haematococcus pluvialis. Astaxanthin can be obtained from these sources through solvent-based extraction or chemical synthesis. Additionally, genetically modified yeasts like *Kluyveromyces marxianus, Yarrowia lipolytica*, and *Saccharomyces cerevisiae* can produce it. The extraction of astaxanthin from microalgae involves various methods including organic solvents, breakdown pretreatment processes, enzyme lysis, and mechanical disruption. The production of astaxanthin from *H. pluvialis* involves several steps such as dissolution, saponification, collection, cleaning, filtration, concentration, ethanol extraction, and freeze-drying. The esterification of Astaxanthin affects its absorption, with esterified astaxanthin being the predominant form in *Haematococcus algae*, while non-esterified astaxanthin is found in Phaffia yeast. The biosynthesis of astaxanthin in *H. pluvialis* involves the identification of novel cDNA and functional genes, which contributes to its commercial value. Furthermore, one important technique for industrial and medicinal applications is the optimization of nitrogen sources for Phaffia rhodozyma's fermentation-based astaxanthin synthesis. Astaxanthin is known for its unique chemical structure and high antioxidant properties. Its molecular formula is $C_{40}H_{52}O_4$, and it has a molar mass of 596.84 g/mol. Two 6C-cycles with a carbonyl and hydroxy group make up Astaxanthin's chemical structure. They are divided by an unsaturated chain that has eleven carbon-carbon double bonds.

Chronic wounds are classified into four types by the Wound Healing Society: venous ulcers, pressure ulcers, arterial insufficient ulcers, and diabetic ulcers. These classifications help in understanding the different characteristics and treatment approaches for each type of chronic wound. Additionally, the presence of biofilms in wounds has been identified as a complicating factor in wound healing. Biofilms are microbial communities that form on the surface of wounds, and their presence can hinder the healing process. Therefore, it is important to study the microbial composition and distribution in wounds to better understand and manage chronic wounds.

The process of wound healing consists of several overlapping phases, including inflammation, proliferation, and remodeling. Inflammation is a critical component of wound healing as it helps in clearing the wound of potential pathogens and prepares the wound for subsequent healing phases. Proper regulation of hemostasis, the process of controlling bleeding, is crucial for creating a conducive environment for wound healing. Researchers have explored different approaches to modulate hemostasis and enhance wound repair, such as the development of biomimetic glycopolypeptide hydrogels and shape-recoverable hyaluronic acid-waterborne polyurethane hybrid cryogels. These innovative biomaterials have shown promising results in promoting effective hemostatic responses and tissue repair.

During the proliferation phase of wound healing, fibroblast migration and proliferation within the wound site are essential for wound granulation. Fibroblasts play a crucial role in replacing damaged cells by synthesizing collagen proteins. They are also important in restoring the number of cells for wound closure. Furthermore, angiogenesis, or the formation of new blood vessels, is an important step in wound healing. Inadequate angiogenesis can result in impaired wound healing and the formation of chronic wounds. Vascular endothelial growth factor A (VEGFA) promotes the migration and proliferation of wound healing cell types such as keratinocytes, fibroblasts, and myofibroblasts. The decline in neovascularization, which is the formation of new blood vessels, can be attributed to decreased proliferation and migration of endothelial cells in the wound bed, highlighting the significance of angiogenesis in the proliferation phase of wound healing.

A wound dressing is a medical device that is used to cover and protect a wound, creating an optimal environment for the healing process. Wound dressings serve various purposes, including promoting wound healing, preventing infection, and managing the exudate (fluid) that is produced by the wound. They are specifically designed to create and maintain a moist environment, which aids wound healing by increasing the rate of epithelialization (the formation of new skin cells) and angiogenesis (the formation of new blood vessels) (Seshadri et al.).

In addition to promoting wound healing, wound dressings can also control the biochemical states of a wound and aid in its healing process. They can exert biomechanical force on the wound, which helps in promoting wound closure (Li et al., 2020). The selection of the appropriate wound dressing is influenced by several factors, including the type of wound, its

specific requirements, and the need for protection from environmental irritants. Advanced wound dressings have been developed to improve specific wound characteristics and bring them as close to the "ideal" state as possible (Sood et al., 2014). These advanced dressings facilitate wound bed preparation, support healthy granulation tissue (newly formed tissue), and promote subsequent epithelial growth, ultimately leading to wound closure (Vowden, 2017).

Furthermore, wound dressings possess antibacterial properties, which are significant in preventing infection and promoting wound healing. They play a crucial role in wound management by providing an optimal environment for healing, promoting wound closure, and preventing infection. The selection of appropriate wound dressings is crucial for optimizing wound healing outcomes and promoting effective tissue repair. Traditional dressings like cotton bandages and gauze have limitations, such as absorbing a large amount of the wound's moisture, resulting in decreased healing rates and pain during dressing changes (Ghomi et al., 2019). On the other hand, advanced wound dressings, such as hydrogels, offer advantages over traditional dressings. They provide improved moisture retention, pain relief, and enhanced wound healing (Wu & Li, 2021). Moreover, traditional dressings may cause wound dehydration, pain, and restlessness when directly applied to the wound. In contrast, modern wound dressings, including hydrogels, alginate dressings, and bioactive wound dressings, have been developed to address the limitations of traditional dressings. These modern dressings offer improved moisture management, antibacterial effects, and enhanced wound healing (Stoica et al., 2020; Powers et al., 2013; Gore et al., 2021).

Synthetic receptors known as molecularly imprinted polymers (MIPs) are engineered to contain particular target molecule cavities, enabling targeted recognition and binding. The preparation of MIPs involves the synthesis of three-dimensional crosslinked polymers with selective recognition sites for the target molecule. Various techniques such as scanning electron microscopy and analysis can be used to characterize the MIPs. MIPs have also been combined with biotechnology to create bifunctional nanoparticles that can enrich and degrade template molecules. They have been applied as selective sorbents in solid-phase extraction techniques and have shown high selectivity for molecular recognition in the separation of compounds in complex matrices.

The synthesis of MIPs involves different methods such as precipitation polymerization, sol-gel process, and atom transfer radical polymerization. These methods allow for the preparation of

MIPs with specific molecular recognition sites for target molecules. The resulting MIPs possess specific recognition ability, low cost, reusability, high mechanical strength, stability in harsh environments, and are easy to prepare. Moreover, they have been employed as dispersive solid phase extraction materials to enrich, separate, and identify particular compounds in a range of samples. Covalent imprinting is a technique that has gained significant attention in recent years. It involves covalently binding the template molecules to the functional monomers during the polymerization process, resulting in the formation of highly selective recognition sites within the polymer matrix.

Covalent imprinting has been shown to enhance the specificity and stability of MIPs, making them suitable for various applications such as biomolecule recognition and environmental remediation. It improves the homogeneity and selectivity of molecular cavities within the polymer matrix, leading to enhanced recognition of target molecules. This technique has been applied to develop highly selective and homogeneous molecular cavities in MIPs, particularly through the combination of surface imprinting and semi-covalent imprinting. This approach has demonstrated the potential for the development of MIPs with enhanced binding affinity and selectivity, particularly in the fields of catalysis and chemosensing.

Molecularly imprinted polymers are materials obtained by polymerization of molecules with a specific shape or structure. These polymers may have a variety of applications, particularly in healthcare fields such as wound dressings. In a study, Koudehi and Zibaseresht synthesized molecularly imprinted polymer nanoparticles (MIPN) containing an antibiotic called gentamicin and used them as a polyvinyl alcohol/gelatin nanofiber (PVA/GEL)-based wound dressing for wound healing (Koudehi and Zibaseresht, 2019). As a result, it has been proven that MIPNs provide selective and controlled release of gentamicin and improve the biocompatibility, antibacterial and cellular properties of PVA/GEL nanofibers. In another study, Kurczewska et al (2017) synthesized molecularly imprinted polymers (MIPs) as drug delivery carriers in alginate dressings. The use of MIPs in combination with alginate dressings has provided efficiency and effectiveness in wound treatment, making it a promising approach to improve drug delivery (Kurczewska et al., 2017). In another study, sodium alginate (SA) in CaCl solution was cross-linked to form (CaAlg) hydrogel membranes. The molecularly imprinted polysiloxane (MIP) membrane was characterized. Cell culture data of fibronectin (FN) imprinted polysiloxane showed better performance than NIP in terms of its ability to promote cell adhesion (Liu et al., 2018). In this study, Asthaxthin imprinted HEMA based

polymers were synthesized and cryogels were synthesized using these polymers containing different amounts of Asthaxthin to develop a new wound/burn dressing material.

2. THEORATICAL FOUNDATIONS AND LITERATURE REVIEW

2.1. Astaxanthin

2.1.2. Biosynthesis of Astaxanthin

Astaxanthin (Asx), a xanthophyll carotenoid, is naturally found in various sources such as microalgae, fungi, complex plants, seafood, and crustacean byproducts Higuera-Ciapara et al., 2006; Fassett & Coombes, 2011). The two main natural sources of Asx are the red yeast Phaffia rhodozyma and the green algae Haematococcus pluvialis. (Fassett & Coombes, 2011; Higuera-Ciapara et al., 2006). Asx is obtained from these sources through solvent-based extraction or chemical synthesis (Ma et al., 2015). Furthermore, genetically modified yeasts like Saccharomyces cerevisiae, Yarrowia lipolytica, and Kluyveromyces marxianus can produce Asx. (Zhou et al., 2022). The extraction of Asx from microalgae involves various methods such as organic solvents, breakdown pretreatment processes, enzyme lysis, and mechanical disruption (Cuéllar-Bermúdez et al., 2014). Furthermore, the production of Asx from H. pluvialis involves several steps including dissolution, saponification, collection, cleaning, filtration, concentration, ethanol extraction, and freeze-drying to obtain Asx crystals (Zhang et al., 2022).

The esterification of Asx influences its absorption, with esterified Asx being the predominant form in *Haematococcus algae*, while non-esterified Asx is found in Phaffia yeast (Aoi et al., 2018; Kajiwara et al., 1995). Moreover, the biosynthesis of Asx in H. pluvialis involves the identification of novel cDNA and functional genes, contributing to its commercial value (Kajiwara et al., 1995). Additionally, the primary technique for industrial and pharmaceutical applications is the optimization of nitrogen sources for *Phaffia rhodozyma's* Asx production through fermentation. (Ni et al., 2007).

Natural sources of Asx include microalgae, yeast, and crustacean byproducts, with Haematococcus pluvialis and Phaffia rhodozyma being the primary sources. The extraction and purification of Asx involve various methods such as solvent-based extraction, chemical synthesis, and fermentation. The esterification of Asx influences its bioavailability, and the biosynthesis of Asx involves genetic and fermentation processes.

2.1.3. Chemical Structure of Astaxanthin

Asx, a xanthophyll carotenoid, is known for its unique chemical structure and high antioxidant properties. Its molecular formula is $C_{40}H_{52}O_4$, and its molar mass is 596.84 g/mol Ambati et al. (2014). Two 6C-cycles with a carbonyl and a hydroxy group make up Asx's chemical structure. They are divided by an unsaturated chain that has eleven carbon-carbon double bonds (Zhang et al., 2022). This unique molecular structure contributes to its strong antioxidant, anti-inflammatory, and antiapoptotic activities, making it a potential neuroprotective agent for neurological diseases (Wu et al., 2015). Additionally, the crystal structure of Asx from Haematococcus pluvialis has been identified as 3,3-dihydroxy-4,4-dione-β,β-carotene, further elucidating its chemical properties (Wang et al., 2022). Furthermore, all-trans Asx has been found to exhibit simultaneous inhibitory effects on acetylcholinesterase and oxidative stress due to its unique chemical structure.

Asx's unique molecular structure, with its hydroxyl and keto moieties on each ionone ring, contributes to its high antioxidant properties (Zhang et al., 2022). This molecular structure also influences its bioavailability and biological activity, making it a promising compound for various applications, including potential therapeutic use in neurological diseases and as an antioxidant (Wu et al., 2015). Therefore, the chemical structure of Asx plays a crucial role in determining its biological activities and potential therapeutic applications.

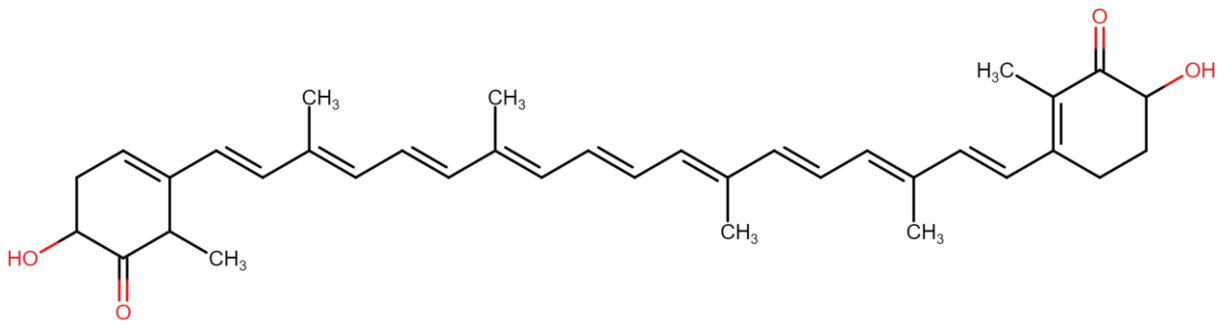

Figure 2.1. Chemical Structure of Asx.

The chemical structure of Asx, characterized by its unique molecular formula and arrangement of functional groups, underpins its potent antioxidant properties and potential therapeutic benefits, making it a subject of significant interest for various biomedical and pharmaceutical applications.

2.1.4. Clinical significance

It has gained attention due to its potent antioxidant, anti-inflammatory, and immune-modulating properties, making it a potential therapeutic agent for various diseases, including cardiovascular diseases, inflammatory responses, neuroprotective effects, and ocular diseases (Chang & Xiong, 2020; Kishimoto et al., 2016; Giannaccare et al., 2020; Wu et al., 2015). Asx has been shown to possess strong antioxidant activity, inhibiting lipid peroxidation more effectively than vitamin E, and has potential in preventing and reversing diet-induced insulin resistance and steatohepatitis (Ota et al., 2015). Additionally, it has been suggested that Asx may have a protective role in COVID-19 due to its antioxidant and anti-inflammatory properties (Ahmadi & Ayazi-Nasrabadi, 2021). Furthermore, Asx has demonstrated potential in ameliorating features of metabolic syndrome and has been associated with neuroprotective effects, particularly in traumatic brain injury (Hussein et al., 2007; Zhang et al., 2021).

Asx has also shown promise in cardiovascular health, with experimental studies indicating its beneficial effects and supporting the need for clinical trials to further explore its potential therapeutic applications (Fassett & Coombes, 2012). Moreover, Asx has been investigated for its inhibitory effects on the proliferation of human gastric cancer cell lines, suggesting potential applications in cancer treatment (Kim et al., 2016). The stability and color change of Asx during processing have also been studied, highlighting its medicinal properties in preventing cardiovascular diseases and cataracts, and acting as an immune booster (Koomyart et al., 2017). Furthermore, Asx has been recognized for its antihypertensive potential and mechanism of action, demonstrating antioxidant and histopathological effects in spontaneously hypertensive rats (Hussein et al., 2006).

2.2. Wound and Wound Dressings

2.2.1. Wound

Wounds are injuries that cause a break in the skin or other body tissues, often resulting from physical trauma or surgical incisions. They are divided into two categories: acute and chronic wounds. Acute wounds are typically caused by sudden injury or trauma, such as cuts, lacerations, or surgical incisions. On the other hand, chronic wounds are long-lasting and often related to underlying health conditions, such as diabetic foot ulcers, venous leg ulcers, and

pressure ulcers (FrykbergRobert, 2015; Wong et al., 2015). The distinction between acute and chronic wounds is crucial as it influences the approach to wound management and treatment.

Furthermore, wounds can be categorized based on various criteria, including etiology, level of microbial infection, morphology, and location. Chronic wounds are classified into four types by the Wound Healing Society: diabetic ulcers, pressure ulcers, arterial insufficient ulcers and venous ulcers (Tsegay et al., 2022). This classification aids in tailoring treatment strategies and understanding the underlying pathophysiology of different wound types. The characteristics of a wound, such as its size, depth, and level of microbial infection, play a significant role in predicting wound outcomes and guiding treatment decisions (Schaarup et al., 2020). Additionally, the presence of biofilms in wounds has been identified as a complicating factor in wound healing, emphasizing the importance of understanding the microbial composition and distribution in wounds (Borges et al., 2022).

Wounds encompass a broad spectrum of injuries, ranging from acute traumatic wounds to chronic wounds associated with underlying health conditions. The classification of wounds based on various criteria is essential for guiding treatment strategies, predicting outcomes, and understanding the complex pathophysiology of different wound types.

2.2.2. Wound healing process

The wound healing process is a complex and dynamic physiological response involving a series of coordinated events aimed at restoring tissue integrity and function following injury. The process of wound healing can be broadly categorized into several overlapping phases, including inflammation, proliferation, and remodeling (Guo & DiPietro, 2010; Koh & DiPietro, 2011). During the inflammatory phase, the body initiates a response to injury, involving hemostasis, inflammation, and the removal of debris and pathogens from the wound site (Guo & DiPietro, 2010; Koh & DiPietro, 2011). Inflammation is a critical component of the wound healing process, as it helps to clear the wound of potential pathogens and sets the stage for subsequent healing phases (Koh & DiPietro, 2011). As important immune cells, macrophages are essential for coordinating the inflammatory stage and the subsequent tissue repair process (Koh & DiPietro, 2011).The proliferation phase involves the formation of new tissue to fill the wound gap, primarily through the processes of angiogenesis, granulation tissue formation, and re-epithelialization (Tsuda et al., 2010). The remodeling phase, also known as the maturation

phase, involves the reorganization and remodeling of the newly formed tissue, aiming to restore its strength and functionality (Gnyawali et al., 2012).

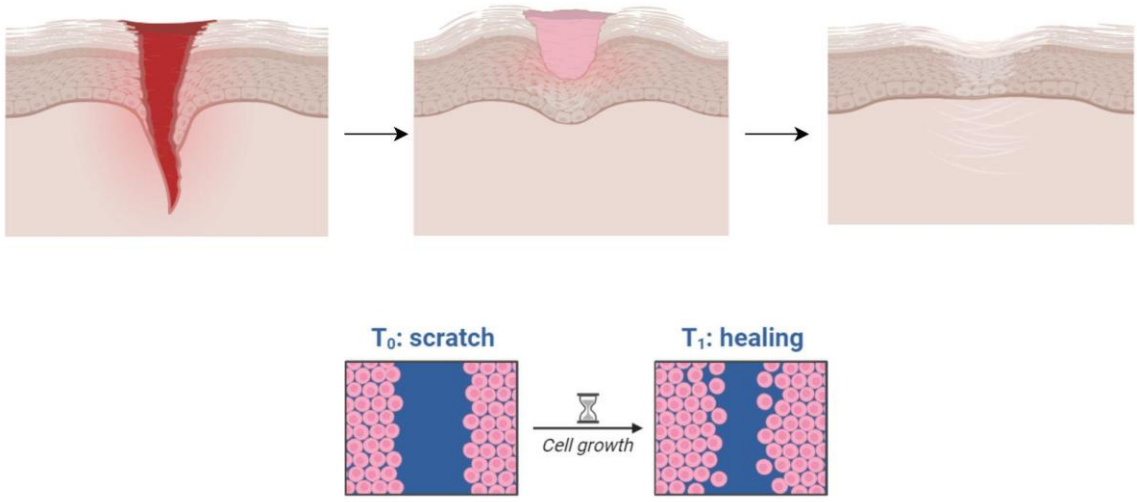

Figure 2.2. Wound Healing Process.

2.2.2.1. Hemostasis

Hemostasis, the first stage of wound healing, is a critical mechanism that aims to stop bleeding and begin the repair of damaged blood vessels and tissues. This process involves a series of intricate events, including vasoconstriction, platelet aggregation, and the formation of a fibrin clot, which collectively contribute to the cessation of bleeding and the establishment of a provisional matrix for subsequent tissue repair Lin et al. (2022). The activation of platelets and the coagulation cascade are central to the hemostatic response, leading to the formation of a stable blood clot at the site of injury (Jansen et al., 2021).

In the context of wound healing, the regulation of hemostasis is essential for ensuring the timely and effective control of bleeding, thereby creating a conducive environment for subsequent healing processes. Numerous strategies to improve wound healing and regulate hemostasis have been investigated in studies. One such strategy is the creation of biomimetic glycopolypeptide hydrogels with microporous structure and tunable adhesion for quick hemostasis (Teng et al., 2021). Additionally, the use of shape-recoverable hyaluronic acid–waterborne polyurethane hybrid cryogels has been investigated for their potential to accelerate hemostasis and wound

healing, highlighting the importance of innovative biomaterials in promoting effective hemostatic responses and tissue repair (Wang et al., 2022).

2.2.2.2. Inflammation

In the wound healing process, inflammation plays a crucial role in orchestrating the initial response to tissue injury and setting the stage for subsequent healing phases. The inflammatory phase involves a complex interplay of immune cells, cytokines, and signaling pathways, aiming to clear the wound of pathogens and debris, and initiate the repair process. Macrophages, as key immune cells, are central to the inflammatory phase and play a pivotal role in coordinating the immune response and tissue repair. While the macrophage is beneficial to the repair of normally healing wounds, this pleiotropic cell type may promote excessive inflammation and/or fibrosis in certain circumstances (Koh & DiPietro, 2011).

Neutrophils, another essential component of the inflammatory response, have been implicated in wound healing through neutrophil extracellular traps formation (NETs), which contribute to the regulation of inflammation and the clearance of pathogens. Disruption of the appropriate inflammatory response can result in delayed healing or lack of healing, highlighting the delicate balance required for effective wound healing.

2.2.2.3. Proliferation

During the proliferation phase of wound healing, fibroblast migration to and proliferation within the wound site are prerequisites for wound granulation Cheng et al. (2019). Fibroblasts play a crucial role in the replacement of damaged cells by synthesizing collagen proteins, making them important in the general wound healing process (Kil et al., 2015). The stimulation of fibroblast migration has been shown to hasten wound healing. (Yu et al., 2015). Additionally, fibroblasts are involved in the replacement of damaged cells by synthesizing collagen proteins, highlighting their significance in wound healing (Öztürk et al., 2006). Furthermore, fibroblasts are essential in restoring the number of cells for wound closure, emphasizing their role in the proliferation phase of wound healing (Choy et al., 2014).

The development of new blood vessels, or angiogenesis, is an essential stage in the processes involved in healing wounds. Inadequate angiogenesis can lead to chronic wound formation and poor wound healing. (Kwon et al., 2017). Vascular endothelial growth factor A (VEGFA) can stimulate the migration and proliferation of various cell types, including keratinocytes,

fibroblasts, and myofibroblasts, which are important components of wound healing (Jeon et al., 2018). Moreover, the decline in neovascularization has been attributed to decreased proliferation and migration of endothelial cells in the wound bed, underscoring the importance of angiogenesis in the proliferation phase of wound healing (Huang et al., 2017).

2.2.2.4. Remodeling

A crucial stage in the healing process, remodeling involves the restructuring and maturation of the newly formed tissue, aiming to restore its strength and functionality. This phase is characterized by the reorganization and realignment of collagen fibers, as well as the resolution of inflammation, ultimately leading to the restoration of tissue integrity (Armstrong & Jude, 2002). The extracellular matrix (ECM) plays a pivotal role in tissue remodeling, and its continuous turnover and remodeling are essential for the restoration of tissue architecture and function (Petri et al., 1997). Matrix metalloproteinases (MMPs) have been extensively studied in normal and abnormal wound healing, highlighting their involvement in ECM degradation and tissue remodeling processes (Armstrong & Jude, 2002). Mast cells have also been identified as significant contributors to the remodeling stage of wound healing, participating in the transformation of fibroblasts into myofibroblasts to promote wound closure (Zgheib et al., 2014).

In addition to ECM remodeling, the regulation of inflammatory mediators and cytokines is crucial for orchestrating the tissue remodeling phase of wound healing. Plasminogen, for example, has been identified as a key proinflammatory regulator that accelerates the healing of acute and diabetic wounds, emphasizing its role in the tissue remodeling process (Shen et al., 2012). Furthermore, the modulation of the inflammatory microenvironment has been recognized as a critical factor in promoting effective tissue remodeling during wound healing (Wang et al., 2022). The reduction in inflammatory molecules has been associated with scarless healing, highlighting the importance of inflammation in tissue remodeling and scar formation (Lang et al., 2017).

Moreover, research on wound healing has focused on the function of growth factors and signaling pathways in tissue remodeling. Insulin-containing wound dressings have been shown to promote diabetic wound healing through the stabilization of hypoxia-inducible factor 1-alpha (HIF-1α), a central regulator of wound healing processes, including tissue remodeling (Yang et al., 2020). MicroRNAs, such as miR-149, have also been implicated in scarless wound healing

by attenuating the inflammatory response, further emphasizing the regulatory role of inflammation in tissue remodeling and scar formation (Lang et al., 2017).

2.3. Factors affecting wound healing

Factors affecting wound healing are multifaceted and encompass a wide range of intrinsic and extrinsic elements. These factors can significantly influence the wound healing process, including its duration and outcomes. Several studies have investigated the impact of various factors on wound healing, shedding light on their diverse roles and implications.

Inflammation, a fundamental component of the wound healing process, has been recognized as a critical factor affecting wound healing outcomes. Exacerbated and prolonged inflammation has been shown to impair wound healing and increase scarring, emphasizing the importance of balanced and regulated inflammatory responses in the healing process Qian et al. (2016). Bacteria have also been identified as influential factors in the immuno-regulation of wound healing, affecting all processes from inflammation to remodeling and being present in the surface and deep tissues of all wounds (Jones et al., 2004).

Growth factors have been extensively studied in relation to wound healing, and they are known to be important players in various stages of the healing process (Yu et al., 1994). Additionally, the expression of growth factors in early wound healing has been investigated, highlighting their significance in the initial stages of the healing process (Yu et al., 1994). Moreover, the modulation of growth factors has been identified as a potential strategy to promote wound healing and tissue regeneration (Almadani et al., 2021).

The influence of environmental factors on wound healing has also been explored, with a variety of intrinsic and extrinsic factors being recognized as potential influencers of the healing process (Pollack, 1979). Furthermore, due to its constant fluctuation during the healing process, the pH has been found to be a significant factor influencing wound healing. (Kruse et al., 2017).

Apart from these variables, the impact of specific medical conditions on wound healing has been a subject of interest. For instance, the impairment of wound healing in the diabetic foot has been extensively studied, shedding light on the challenges and complexities associated with wound healing in diabetic individuals (Falanga, 2005). The factors affecting wound healing are diverse and encompass various biological, environmental, and medical elements.

Understanding the complex interplay of these factors is crucial for optimizing wound healing outcomes and developing targeted interventions to promote effective tissue repair.

2.4. Wound / Burn Dressings

A wound dressing is a medical device used to cover and protect a wound, providing an optimal environment for healing. Wound dressings serve multiple purposes, including promoting wound healing, preventing infection, and managing exudate. They are designed to create and maintain a moist environment, which is conducive to wound healing by increasing the rate of epithelialization and angiogenesis Seshadri et al. (2022). Furthermore, by using biomechanical force to promote wound closure, wound dressings can help regulate the biochemical states of a wound and facilitate its healing process. (Li et al., 2020).

The selection of wound dressings is influenced by various factors, including the type of wound, its specific requirements, and the need for protection from environmental irritants. Advanced wound dressings are designed to improve specific wound characteristics and bring them as close to "ideal" as possible (Sood et al., 2014). By facilitating the preparation of the wound bed, maintaining healthy granulation tissue, and encouraging subsequent epithelial growth that leads to wound closure, they can start and encourage an efficient wound healing response (Vowden, 2017).

A moist environment can be created, maintained, and controlled with the help of wound dressings and they exhibit various fluid handling mechanisms, such as absorption, gelling, retention, and moisture vapor transmission, which are essential for effective wound management (Rodrigues & Thilagavati, 2021). Furthermore, the antibacterial properties of wound dressings are significant, as they can help prevent infection and promote wound healing. Wound dressings play a crucial role in wound management by providing an optimal environment for healing, promoting wound closure, and preventing infection. The selection of appropriate wound dressings is essential for optimizing wound healing outcomes and promoting effective tissue repair.

2.4.1. Traditional Wound Dressings

Traditional wound dressing materials such as gauze, lint, plasters, bandages, and cotton wool are commonly used for protecting wounds from contamination. However, these traditional

dressings have drawbacks such as being impermeable to water vapor, difficult to remove, and having poor absorption capacity (Thangaraj et al., 2015; Tottoli et al., 2020). Additionally, traditional dressings like cotton bandages and gauze can absorb a large part of the wound's moisture, leading to decreased healing rates and pain during dressing changes (Ghomi et al., 2019). On the other hand, advanced wound dressings, such as hydrogels, offer advantages over traditional dressings, including improved moisture retention, pain relief, and enhanced wound healing (Wu & Li, 2021). Furthermore, traditional dressings may cause wound dehydration, pain, and restlessness when attached directly to the wound (Yahia et al., 2021; Yahia et al., 2021).

In contrast, modern wound dressings, such as hydrogels, alginate dressings, and bioactive wound dressings, have been developed to address the limitations of traditional dressings. These modern dressings offer improved moisture management, antibacterial effects, and enhanced wound healing (Stoica et al., 2020; Powers et al., 2013; Gore et al., 2021). For instance, hydrogel wound dressings have been found to be more cost-effective and beneficial in terms of improved wound healing rates compared to traditional standard care dressings (Zhang et al., 2021; Fournier et al., 2022). Moreover, incorporating materials such as bioglass and silk fibroin into dressings has been shown to improve their mechanical stability, bioactivity, and efficiency in promoting wound healing (Wu & Li, 2021; Wang et al., 2019).

2.4.2. Modern Wound Dressings

Modern wound dressings have revolutionized wound care by offering various advantages over traditional dressings. These advanced dressings, such as hydrogels, bioactive dressings, and electrospun nanofibrous scaffolds, provide a moist wound environment, protect against secondary infections, and promote tissue regeneration (Thangaraj et al., 2015; Tavakoli & Klar, 2020; Shi et al., 2020; Moura et al., 2013; Pilehvar-Soltanahmadi et al., 2018). Additionally, modern wound dressings have been shown to cut down on the length of stay in the hospital, medical expenses, and number of dressing changes, thereby improving patient comfort and quality of life (Tavakoli & Klar, 2020; Brumberg et al., 2021; Rahmawati & Nopitasari, 2021; Jamaludin et al., 2020).

Furthermore, the incorporation of natural substances into modern wound dressings, such as banana leaves and glycyrrhetinic acid-loaded films, has demonstrated biological properties that aid in wound healing (Abruzzo et al., 2021; Guenova et al., 2013). These innovative dressings

not only maintain an optimal moisture level for wound healing but also decrease inflammation in the periwound skin and granulation tissue, contributing to the overall healing process (Yamane et al., 2015).

Moreover, modern wound dressings have been the subject of pharmacoeconomic studies, demonstrating their cost-effectiveness and utility in the management of diabetic foot ulcers (Rahmawati & Nopitasari, 2021). Additionally, meta-analyses and systematic reviews have demonstrated how well advanced wound dressings work to accelerate the healing of chronic wounds (Heyer et al., 2013). Modern wound dressings encompass a wide range of innovative materials and technologies that have significantly improved wound care outcomes, patient comfort, and cost-effectiveness.

2.4.2.1. Hydrogels

While they create a physical barrier and absorb exudate, traditional wound dressings like gauze or adhesive bandages don't really help the healing process. In certain cases, such as when fibers or pieces entangle with the wound tissue and influence the immune response, these dressings may even be detrimental to the wound. This may also result in pain when the dressing is removed, disruption of wound healing, and re-injury. Innovative wound care solutions that enhance the wound healing process or work more intelligently with the wound are required. A number of standards have been proposed for the perfect wound dressing (Stashak et al., 2004). Capable of absorbing fluids, preserving a damp atmosphere, permitting gaseous exchange, providing thermal insulation, protecting against microorganisms, not damaging to the host, and effortlessly removable (Broughton et al., 2006; Opt Veld et al., 2020; Velnar et al., 2009). They arise from the retention of water in a three-dimensional polymer network, either physically or electrostatically (Hoffman, 2002; Pal et al., 2013; Peak et al., 2013). Because hydrogels are inherently abundant in water, this is good for moisturizing the wound but bad for exudate absorbance. Hydrogels are usually used for non-to-low-exuding wounds, although depending on the gel's swelling capacity, they might also be appropriate for moderately-exuding wounds. Hydrogels are frequently used to treat burns and ulcers. They may also aid with difficult-to-debride wounds or reduce the formation of eschar, or dead tissue, which is seen in burn wounds, among other conditions (Dabiri et al., 2016; Opt Veld et al., 2020). The healing process depends greatly on the balance of moisture in the wound, and there are several products available to either raise or lower the hydration level (Okan et al., 2007). Furthermore, hydrogels are

frequently regarded as cooling and calming, which helps the patient feel less pain. Since gel dressings don't stick to the wound bed or have non-adherent fibers, they are frequently simpler to remove and replace. Gaseous exchange, free movement of metabolites, and the provision of a friendly replacement matrix are further advantageous aspects (Opt Veld et al., 2020).

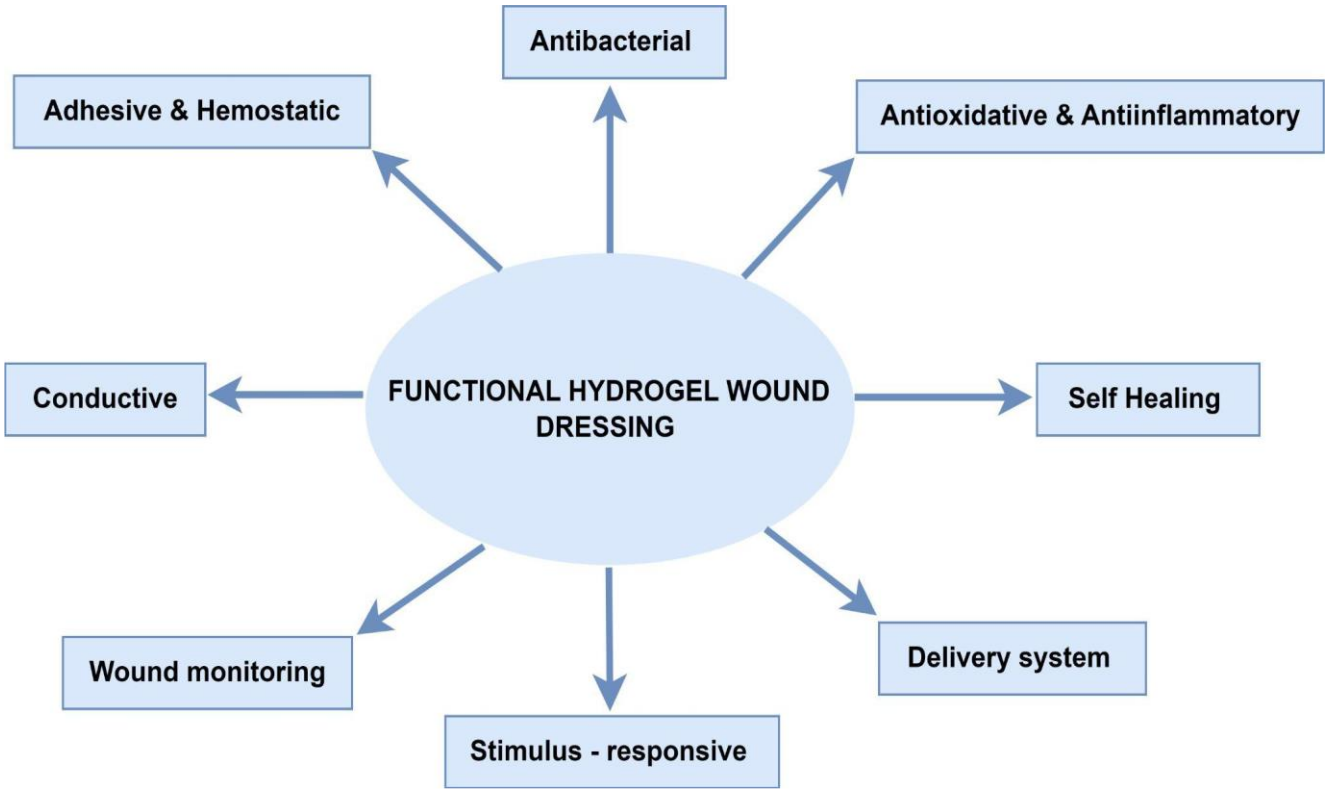

Figure 2.3. Functional hydrogel wound dressing.

2.4.2.2. Hydrocolloids

Originally made in tiny square pieces, a bordered hydrocolloid was released in 1985 and was later followed by several shaped dressings intended for different anatomical locations. In 1989, a "thin" version was created as an alternative to the acrylic-based adhesives more frequently used for film dressings. It comprises a semipermeable membrane coated with a thin coating of hydrocolloid glue. These dressings tend to be less permeable than normal films and have little to no ability to retain fluid on their own. As an alternative to semipermeable polyurethane films, they are utilized as secondary retention products or as postoperative dressings over primary dressings like hydrogels or alginates (Thomas, 2008).

In recent times, the term "hydrocolloid" has been employed to refer to a variety of distinct products, such as an amorphous hydrogel dressing and a fibrous dressing derived from modified carboxymethyl cellulose (CMC). These products differ greatly from the adhesive sheet dressings that were initially described in this manner in terms of both their structure and appearance (Thomas, 2008; Wyatt et al., 1990). Hydrocolloid dressings are most frequently used to treat chronic wounds like leg ulcers and pressure ulcers, but they can also be effectively used to treat a range of acute wounds because of their useful properties, which include facilitating debridement, absorbing excess fluid, and acting as an infection barrier (Thomas, 2008).

Because hydrocolloid dressings stay longer than most other forms of dressings, they require fewer applications. They are available in a range of sizes and shapes to suit various wound types and are simple to apply to the wound. Venous compression can also be employed with hydrocolloid dressing (Koksal and Bozkurt, 2003).

2.4.2.3. Films

It has been widely recognized in recent years that a moist environment accelerates wound healing by stimulating the migration of keratinocytes, which ultimately causes the wound bed to heal quickly (Gomes Neto et al., 2019). The optimal dressing for a wound should be biocompatible, shield the wound bed, keep the site hydrated, permit gas exchange with the surrounding environment, eliminate superfluous exudate, and provide physical protection against bacteria. Additionally, it must possess certain mechanical qualities like resistance and flexibility (Naseri-Nosar & Ziora, 2018). The depth of the wound and the volume of exudate determine which type is best (Koehler et al., 2018). Films can be used to directly administer medication to the wound site because they are impermeable to fluids and bacteria but porous to gases. Films are beneficial because of their flexibility, which makes it easy for them to conform to the patient's body, even in tricky places like joints. They also permit some moisture to evaporate, lessen discomfort, act as a barrier against external contamination, and support examination of the wound bed without removing the dressing (Savencu et al., 2021). Wound dressing films should have a significant capacity to absorb exudates, be easily removed from the packaging, flexible, resistant to breaking, and have adequate adherence and remanence to the wound surface. Ultimately, they ought to be able to release the active principles to the wound site and incorporate them (Savencu et al., 2021).

Their primary drawbacks are that they can be difficult to remove and should only be used to wounds that don't ooze a lot (Gomes Neto et al., 2019; Simões et al., 2018).

2.4.2.4. Foams

Foam is made of a porous material that, through capillary action, may absorb liquids into areas that are filled with air (Fogh & Nielsen, 2015). Polyurethane foam is the most widely used type. Although silicone foam is commonly placed as an adhesive wound contact layer, it is less commonly employed as the major absorbent in wound dressings. Adhesive or nonadhesive foam treatments come in a range of thicknesses. Typically, the foams are provided with a film backing, which serves as an environmental barrier that is resistant to water and microbes (Naseri-Nosar & Ziora, 2018). The permeability of the film backings varies, which has an impact on the amount of gas exchange and water evaporation.

In wound therapy, other kinds of wound dressings, such as hydroactive polymers and colloids, are also frequently utilized. By expanding when fluids bond to the polymer or colloid, these non-foam materials absorb fluids and form a gel-like solid (Fogh & Nielsen, 2015). The majority of foam dressings absorb exudates vertically, and can observed that the dressing's exudative imprint, which remains consistent with the wound's shape, after absorbing exudates. Additionally, some dressings combine the first two methods; for example, a foam dressing can be separated into layers for contact, absorption, and back layers, among other purposes. Utilizing all of the material's absorption capacity, it absorbs vertically with the wound contact layer and can migrate to the side after entering the absorption layer. The exudate won't overflow because of the locking action of the absorption layer, lowering the chance of impregnation (Sweeney et al., 2012).

2.4.2.5. Alginates

Because of its special qualities such as its non-toxicity, biocompatibility, immunogenicity, affordability, and high absorption capacity, alginate is used in wound dressings (Aderibigbe & Buyana, 2018). However, the poor mechanical characteristics of biopolymers usually provide a limitation. They are customized to change their degradation pattern and mixed with synthetic polymers to improve their mechanical qualities (Ulery et al., 2011; Yadav et al., 2015). Brown seaweed is the natural source of alginate, a naturally occurring anionic biopolymer(Lee & Mooney, 2012). It is non-toxic, easily accessible, and biocompatible. Alginate-based wound

dressings have lower rates of bacterial infections and a moist environment, both of which are critical for wound healing (Lee & Mooney, 2012). Ascophyllum nodosum, Laminaria hyperborea, Laminaria japonica, Macrocystis pyrifera, and Laminaria digitate are among the brown algae (Phaeophyceae) from which alginate is derived (Fertah et al., 2017; Lee & Mooney, 2012). Depending on the source, it has a different ratio of guluronate to mannuronate. Alginate gels can be produced via acid precipitation or ionic crosslinking with cations. Alginate gels because of the cooperative binding of divalent cations and the dimerization of G residues in the polymer's G-block regions (Ching et al., 2017). Trivalent ions, such as Al and Fe, can also cause alginate gels to develop. In contrast to divalent cations, trivalent cations have a more robust binding to alginate, producing a more compact gel network (Ching et al., 2017; Draget & Taylor, 2011; Yang et al., 2013). Alginate dressings have the ability to absorb dry wound fluid and condense it into gels that can limit bacterial infections, give a dry wound a physiologically moist environment, and hasten the process of granulation tissue creation and re-epithelialization (Szekalska et al., 2016).

2.4.2.6. Cryogels

Gels are described as polymer networks that have a fluid expand them across their entire volume. When it comes to hydrogels, water acts as the swelling agent while a hydrophilic polymer makes up the network component (Tofanica et. al., 2022). Cryogel development, however, has become necessary due to their absence of linked macropores and elasticity properties needed for a range of biomedical applications. A kind of hydrogels known as cryogels are created when the solvent's freezing point is reached. A supermacroporous linked structure is produced after a freeze-thaw cycle (Memic et al., 2019). In a scaffold for tissue engineering applications, for example, the homogeneous porosity structure promotes waste exchange and cell proliferation (Bhat & Kumar, 2012). Cryogels have also been used in novel biomedical and biotechnical applications such as wound healing, bioseparation, sensors, controlled drug delivery, and carriers for cell immobilization (Dragan, 2014; Lozinsky et al., 2003; Zhang et al., 2013).

Cryogels are hydrogels that are macroporous and have a huge surface area, high swelling capacity, and interconnected porosity. Numerous final cryogel qualities ultimately depend on the polymer/monomer composition that is selected. The inclusion of fillers or additives, wall thickness, pore size, crosslinking, and other variables all influence the cryogel's characteristics.

The preparation technique can affect the pore size and distribution, wall thickness and density, and pore size of cryogel. For instance, by increasing the freezing rate, smaller pores can be seen (Henderson et al., 2013). The size, thickness, and density of pores have a major impact on the characteristics of cryogels. Higher wall densities and thicker walls often translate into better mechanical qualities; they are determined by the type of crosslinking in the cryogel and the concentration of the monomer or precursors utilized (Plieva et al., 2005). Good mechanical qualities and an innately linked macroporous structure allow cryogels to absorb large volumes of blood from a bleeding location while their form expands (Zhao et al., 2018). Through blood cell and platelet adhesion, enrichment, and activation during blood absorption, these distinctive structures can serve as a filter for blood cells and platelets to aid in blood coagulation (Konovalova et al., 2017). It implies that the use of cryogels in hemostatic applications has enormous potential (Konovalova et al., 2017). Additionally, cryogels can facilitate the migration of cells into the scaffold to enhance wound healing following hemostasis, absorb exudates from the wound area, and offer a moist environment to lower the risk of infection (Zhao et al., 2018).

2.5. Molecularly Imprinted Polymers

Molecularly imprinted polymers (MIPs) are synthetic receptors designed to possess specific cavities for target molecules, allowing for selective recognition and binding (BelBruno, 2018). These polymers have been utilized in various applications such as the determination of organophosphorus pesticides in complex samples (Boulanouar et al., 2018), clearance of MIP-1 by insulin-degrading enzyme (Ren et al., 2010), selective detection of C-reactive protein (Öter, 2023), reduction of cytokine release syndrome (Zhong et al., 2022), selective removal of dibutyl phthalate (Dolai et al., 2019), and detection of nortriptyline (Nezhadali et al., 2019). MIPs have also been employed in the isolation of chelerythrine (Zhong et al., 2018), inhibition of bacterial biofilm formation (Ma et al., 2018), recognition and sustained release of diclofenac (Zheng et al., 2018), and active packaging for beef preservation (Huang et al., 2018).

The preparation of MIPs involves the synthesis of three-dimensional crosslinked polymers with selective recognition sites for the target molecule, which can be characterized using various techniques such as scanning electron microscopy (Öter, 2023). Additionally, MIPs have been combined with biotechnology to obtain bifunctional nanoparticles capable of enriching and degrading template molecules (Zhong et al., 2022). The application of MIPs as selective

sorbents in solid-phase extraction techniques has also been demonstrated (Nezhadali et al., 2019). Furthermore, MIPs have been widely applied in the separation of compounds in complex matrices due to their high selectivity for molecular recognition (Huang et al., 2019).

The synthesis of MIPs involves various methods such as precipitation polymerization, sol-gel process, and atom transfer radical polymerization (Sun et al., 2016; Shin et al., 2013; Duan et al., 2013). These methods allow for the preparation of MIPs with specific molecular recognition sites for certain target molecules (Huang et al., 2017). The resulting MIPs possess specific recognition ability, low cost, reusability, high mechanical strength, good stability in harsh environments, and ease of preparation (He et al., 2016). Moreover, MIPs have been used as dispersive solid phase extraction materials for the enrichment, separation, and detection of specific compounds in various samples (Wang et al., 2013; Wu et al., 2012).

2.5.1. Covalent Imprinting

The synthesis of molecularly imprinted polymers (MIPs) involves various methods, including covalent imprinting, which has gained significant attention in recent years. Covalent imprinting is a technique where the template molecules are covalently bound to the functional monomers during the polymerization process, resulting in the formation of highly selective recognition sites within the polymer matrix Shen & Ren (2014). This approach has been demonstrated to enhance the specificity and stability of MIPs, making them suitable for a wide range of applications, including biomolecule recognition and environmental remediation (Burri, 2015).

In the preparation of MIPs, the use of covalent imprinting has been shown to improve the homogeneity and selectivity of molecular cavities within the polymer matrix, leading to enhanced recognition of target molecules (Dabrowski et al., 2019). This technique involves the formation of covalent bonds between the template molecules and the functional monomers, resulting in the creation of specific binding sites that closely match the shape, size, and functional groups of the target analyte (Dabrowski et al., 2019). Covalent imprinting has been applied in the development of highly selective and homogeneous molecular cavities in MIPs, particularly through the combination of surface imprinting and semi-covalent imprinting (Dabrowski et al., 2019).

Furthermore, the use of covalent imprinting has been explored in the fabrication of molecularly imprinted mesoporous organosilica (MIMO), where the template molecules are covalently

immobilized within the mesoporous structure, leading to the creation of tailored recognition sites for specific analytes (Lofgreen et al., 2011). This approach has demonstrated the potential for the development of MIPs with enhanced binding affinity and selectivity, particularly in the field of catalysis and chemosensing (Lofgreen et al., 2011).

Covalent imprinting has also been utilized in the construction of novel electrochemical sensors based on MIPs for the selective determination of target molecules in real samples (Xu et al., 2017). The modified electrodes are prepared by synthesizing MIPs through a precipitation method and then coating them on a suitable substrate, resulting in the creation of specific recognition sites through covalent or non-covalent interactions between the template and monomer complexes (Xu et al., 2016).

Covalent imprinting represents a promising approach for the synthesis of MIPs with enhanced selectivity and stability. This technique involves the formation of specific recognition sites through covalent interactions between the template molecules and functional monomers, leading to the development of tailored polymers with applications in various fields, including biomolecule recognition, environmental remediation, and sensor technology.

2.5.2. Non- covalent Imprinting

Non-covalent imprinting has emerged as a popular and widely used synthesis strategy for molecularly imprinted polymers (MIPs) due to its experimental simplicity and flexibility in the choice of functional monomers and template molecules (Qi et al., 2014). This approach involves the formation of strong intermolecular non-covalent interactions, such as van der Waals/electrostatic interactions and hydrogen bonding, between the template molecule and the functional monomers (Quint et al., 2015). Non-covalent imprinting has been applied in various fields, including catalysis, solid-phase extraction, and sensor technology, and has demonstrated significant potential in the development of selective recognition materials (Nasir et al., 2014).

The use of non-covalent imprinting has been highlighted in the synthesis of MIPs for the selective extraction of target molecules from complex matrices, such as the preparation of metallic pivot-based imprinted monoliths with a hydrophilic macromonomer for the interaction of template and monomer (Li et al., 2015). Additionally, non-covalent imprinting has been employed in the development of molecularly imprinted polymer nanoparticles (MIP NPs) for

the simultaneous determination of multiple carbamate pesticides from environmental water, demonstrating the versatility and applicability of this approach (Qi et al., 2014).

Furthermore, non-covalent imprinting has been utilized in the preparation of molecularly imprinted polymer inclusion membranes for the determination and quantification of specific compounds in natural waters, showcasing its potential in environmental analysis and monitoring (Vishnuvardhan et al., 2011). This approach has also been employed in the synthesis of MIPs for the selective clean-up of vinblastine from Catharanthus roseus extract, demonstrating its utility in the pharmaceutical and natural product extraction fields (Zhu et al., 2010).

Moreover, non-covalent imprinting has been used in the development of molecularly imprinted polymer membranes and thin films for the separation and sensing of biomacromolecules, opening up new avenues of research and commercial opportunities for MIPs (Boysen et al., 2016). The resulting MIPs from non-covalent imprinting have shown enhanced specific permeabilities and selectivities, making them suitable for various applications, including drug compounding and anti-infective agents (Benito-Peña et al., 2015). Non-covalent imprinting has become a popular and versatile synthesis strategy for the preparation of MIPs, offering simplicity, flexibility, and strong intermolecular interactions for the development of selective recognition materials with diverse applications.

2.6. Wound and Burn Dressing Studies with Molecularly Imprinted Polymers

Molecularly imprinted polymers are materials obtained by polymerization of molecules with a specific shape or structure. These polymers may have a variety of applications, particularly in healthcare fields such as wound dressings. For instance, the publication "Synthesis of molecularly imprinted polymer nanoparticles containing gentamicin drug as wound dressing based polyvinyl alcohol/gelatin nanofiber" by Koudehi and Zibaseresht discusses the development of a novel wound dressing material. ‘This publication aims to synthesize molecularly imprinted polymer nanoparticles (MIPN) containing an antibiotic called gentamicin and use them as a wound dressing based on polyvinyl alcohol/gelatin nanofiber (PVA/GEL) for wound healing (Koudehi and Zibaseresht, 2019). The authors prepared the MIPNs by free radical polymerization method and embedded them into PVA/GEL nanofibers

by electro-spinning technique. The authors showed that the MIPNs provided selective and controlled release of gentamicin and improved the biocompatibility, antibacterial and cellular properties of PVA/GEL nanofibers. The authors stated that this study has a potential application in the treatment of chronic and infected wounds (Koudehi and Zibaseresht, 2019).

The article "Molecularly imprinted polymer as drug delivery carrier in alginate dressing by Kurczewska et al. (2017) explores the use of molecularly imprinted polymers (MIPs) as drug delivery carriers in alginate dressings. The study delves into the incorporation of MIPs into alginate dressings to facilitate targeted and controlled drug release for transdermal applications. This research is significant as it potentially contributes to the development of advanced wound dressing materials with enhanced therapeutic capabilities. The utilization of MIPs in conjunction with alginate dressings may offer a promising approach for improving drug delivery efficiency and efficacy in wound management. This article is highly relevant to the topic of using molecularly imprinted polymers in wound dressing materials and drug delivery systems**. (**Kurczewska et al., 2017)

In another study, sodium alginate (SA) in CaCl2 solution was cross-linked to create calcium alginate (CaAlg) hydrogel membranes. (Liu et al., 2018) β-methoxyethylene triethyoxysilane (KH-570) and γ-amidopropyl triethyoxysilane (KH-550) were used as functional monomers to synthesize BSA molecular-imprinted polysiloxane polymer, with BSA serving as the template and CaAlg hydrogel membrane serving as the matrix. Fourier transform infrared spectroscopy (FT-IR), transmission electron microscopy (TEM), and scanning electronic microscopy (SEM) were used to examine the molecularly imprinted polysiloxane (MIP) membrane. The MIP membrane's adsorption and recognition capabilities were assessed. Fibronectin (FN)-imprinted polysiloxane was created by utilizing FN as the template, silanes as functional monomers, and CaAlg hydrogel membrane as the matrix to create a biomaterial that can encourage cell adhesion and proliferation. Cell culture data demonstrated that FN-imprinted polysiloxane outperformed NIP in terms of its ability to promote cell adherence.(Liu et al., 2018).

3. METHODOLOGY

3.1. Materials

Asx, methacrylic acid (MAA), 2-hydroxyethyl methacrylate (HEMA), ethylene dimethacrylate (EGDMA), ammonium persulfate (APS), N,N,N′,N′-tetramethylene diamine (TEMED), dimethyl sulfoxide (DMSO), polyvinyl alcohol (PVA), gelatine, ethanol, sodium hydroxide (NaOH), and all chemicals used in the experiments were sourced from from Sigma-Aldrich (St. Louis, MO, USA). Analytical grade reagents and distilled water (MercAG Millipore Direct-Q 3 UV (Darmstadt, Germany)) were used to prepare the solutions.

3.2. Synthesis of Astaxanthin Imprinted Polymers

Asx was employed as the template molecule for the synthesis of Asx-imprinted polymers (Asx-MIPs). First, pre-complex formation was carried out using Asx and functional monomer MAA at a molar ratio of 1:16 (n_{Asx}:n_{MAA}) (4 hours). The pre-complex was combined with the main monomer HEMA (4.85 mL) and the crosslinking agent EGDMA (2.83 mL). Subsequently, SDS, dissolved in 1.7 mL of distilled water, was introduced into the mixture, and stirring persisted for 10 minutes. Following this, 0.05 g of APS and 25 µL of TEMED were incorporated into the mixture. The entire blend was then loaded into syringes and left to undergo polymerization at -16 ℃ for a duration of 12 hours. The synthesized polymer was subjected to drying in an oven, and the resulting dry polymer was subsequently pulverized into a powder. The powdered polymers underwent a washing process with distilled water at room temperature. Non-imprinted polymers (NIPs) were synthesized using the identical method without using Asx.

3.3. Synthesis of Asx-MIP Embedded Wound Dressing Materials

A 10% (w/v) PVA solution was dissolved in ultrapure water with gentle stirring and heated until the solution turned transparent. Simultaneously, a Gel solution was prepared in ultrapure water, reaching a final concentration of 3% (w/v) at 40 °C using a water bath. The PVA and Gel solutions were then combined in a 1:2 ratio. Powdered Asx-MIPs were incorporated into the PVA-Gel mixture in varying amounts (25 mg, 50 mg, and 100 mg). Subsequently, glutaraldehyde was introduced as a crosslinker to the resultant polymer solution, followed by

vortexing. To serve as a reference, a cryogel without Asx-MIP was synthesized following the same procedure. The mixture was poured into 24-well plates and placed in the freezer at -16°C for 12 hours. Upon completion of the polymerization process, Asx-MIP and NIP loaded cryogels (PVA-Asx-Gel and PVA-Gel, respectively) were extracted from the freezer and allowed to thaw at room temperature, resulting in a highly porous structure. After thawing, the cryogels underwent multiple washes with pure water to eliminate any residual polymer precursors and cross-linkers that did not integrate into the structure.

3.4. Characterization Studies

3.4.1. Swelling tests

To ascertain the swelling ratio (SR) of the synthesized cryogels, both PVA-Asx-Gel and PVA-Gel cryogels underwent swelling in deionized water (DI) and were subsequently lyophilized for 30 minutes at -50°C under a pressure of 0.001 mbar. The weight of the freeze-dried cryogels was then measured. These cryogels were placed in a Falcon tube containing 30 mL of DI water at room temperature for a duration of 2 hours. After removing excess water from the surface of the cryogels using filter paper, the weight of the swollen cryogel samples was determined. The swollen weight (Ws) and dry weight (Wd) were recorded, and the swelling ratio (SR) of the cryogel samples was calculated using Equation (1).

$$SR\ \% = [\ (Ws - Wd) / Wd\ ] \times 100 \qquad \text{Equation (1)}$$

The cryogels were subjected to freeze-drying, and their weight was measured (Wd). The overall monomer mass (Wt) was ascertained, and the polymerization yield (PY) of the cryogels was computed using equation 3.

$$PY\ \% = (Wd / Wt\ ) \times 100 \qquad \text{Equation (2)}$$

3.4.2. SEM Analysis

The morphology of the cryogels was scrutinized through scanning electron microscopy (SEM). For SEM analysis, the cryogels underwent dehydration through a freeze-drying process. Subsequently, a thin coating of gold-palladium was applied to the cryogels, and they were observed using a scanning electron microscope (FEI, Quanta 650 Field Emission SEM). The determination of pore sizes in the cryogels was accomplished by analyzing SEM images through ImageJ software.

3.5 *In vitro* Release Studies

Asx release studies from PVA-Asx-Gels were carried out at room temperature using DMSO. For this purpose, 10 mL DMSO was added to 5 cryogels and samples were taken at different time intervals (0-180 min, and 24-48 h). DMSO was added as much as the volume of the sample taken each time. In order to determine the Asx concentration in the samples taken at different time intervals, absorbance measurements were made using a UV spectrophotometer (Genesys 150, Thermo Scientific, United States) at 492 nm.

3.6. *In Vitro* Cell Studies

3.6.1. Cells and culture conditions

Cell studies were performed using mouse embryonic fibroblast (MEF, (CF-1) (ATCC® SCRC-1040™)) cell line. The cells were cultured in Dulbecco's Modified Eagle's medium (DMEM, Hyclone) supplemented with 10% fetal bovine serum (FBS, South America) and 55 μM β-mercaptoethanol (Merck) specifically for MEF cells. The cells were then incubated in a humidified incubator at 37 °C with 5% CO2. $10x10^4$ cells/well were seeded onto scaffolds. As a control group the same number of cells were seeded as 2D.

3.6.2. Sterilization of Cryogels

Cryogels were subjected to sterilization using 70% ethanol (Merck). They were immersed in 70% ethanol within sterile Petri dishes for a duration of 2 hours. Subsequently, the cryogels underwent two rinses with sterile ultra-pure water and were soaked in ultra-pure water for an additional 2 hours. Following this, the cryogels were introduced into a 24-well plate and exposed to DMEM for 2 hours after being washed twice with culture medium (DMEM). Prior to cell seeding, the DMEM was extracted, and the cryogels were left to air-dry for 1 hour.

3.6.3. MTT Assay

Cell viabilities were evaluated through the MTT (4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide assay, conducted at 24, 48, and 72-hour intervals. At the end of the relevant incubation periods, the medium was removed, and the cells were washed with PBS. Subsequently, MTT reagent (0.25 mg/mL in PBS) was administered to each well and incubated at 37°C for 2 hours.

Following the incubation period, the MTT solution was removed, and DMSO was introduced to wells. Samples were subjected to 30 minutes of shaking in a dark environment. Subsequently, the samples were assessed using a spectrophotometer with readings taken at 570 nm.

The cell viability percentage was calculated considering the control group as 100. The following formula was utilized for the calculation.

Cell viability (%) = (Average of test cells / Average of control cells) ×100 Equation (3)

In the given equation, the term "test cells" refers to the assessment of cell viability for cells cultured on cryogels, whereas the term "control cells" pertains to the evaluation of cell viability for cells cultured on a standard culture plate.

4. ANALYSIS AND DISCUSSION

4.1. Synthesis of Astaxanthin Imprinted Polymers

Asx-MIPs were synthesized in syringes by cryogelation method. As a result of polymerization, a monolith structure was formed and left to dry in an oven. The resulting dry polymer was crushed into powder with the help of a mortar. NIP were synthesized using the same method without the use of Asx. Asx-MIPs and NIPs are shown in Figure 4.1.

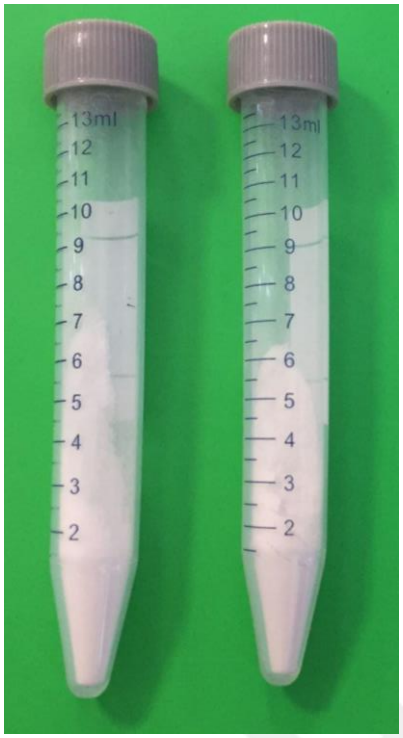

Figure 4.1. Asx-MIPs and NIPs.

4.2. Synthesis of Astaxanthin Imprinted Polymers Embedded Wound Dressing Materials

PVA-Asx-Gel and PVA-Gels were synthesized using powdered Asx-MIP and NIPs, respectively. Polymerization was carried out at -16 °C for 12 hours in a 24 well plate. The cryogels formed after polymerization were allowed to melt at room temperature. Thus, cryogels with a very high porous structure were obtained. Images of cryogels before and after polymerization are given in Figure 4.2.

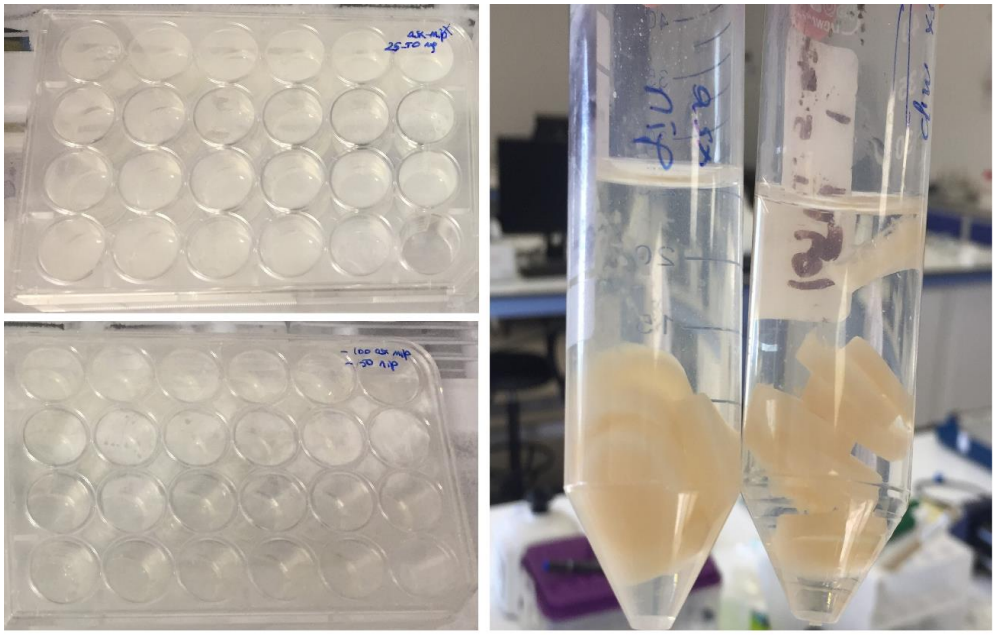

Figure 4.2. Images of PVA-Asx-Gel and PVA-Gel cryogels before and after polymerization.

4.3. Characterization Studies

4.3.1. Swelling tests

Swelling experiments of PVA-Asx-Gel and PVA-Gel were carried out using DI. In swelling experiments, swelling percentages were calculated using the weights of the cryogels dried in the lyophilizer and the weighted weights of these dry gels after they were swollen in DI for 2 hours. During synthesis, gels loaded with different concentrations of Asx-MIP and NIP were divided into 12 wells of 500 µl volume. Polymerization yield was calculated based on total volume. The results obtained are given in Table 4.1. Dry and wet images of the gels are shown in Figure 4.3. As can be seen from table 4.1 the polymerization yields obtained are quiete high and the swelling degree were calculated as around 145%for all polymers.

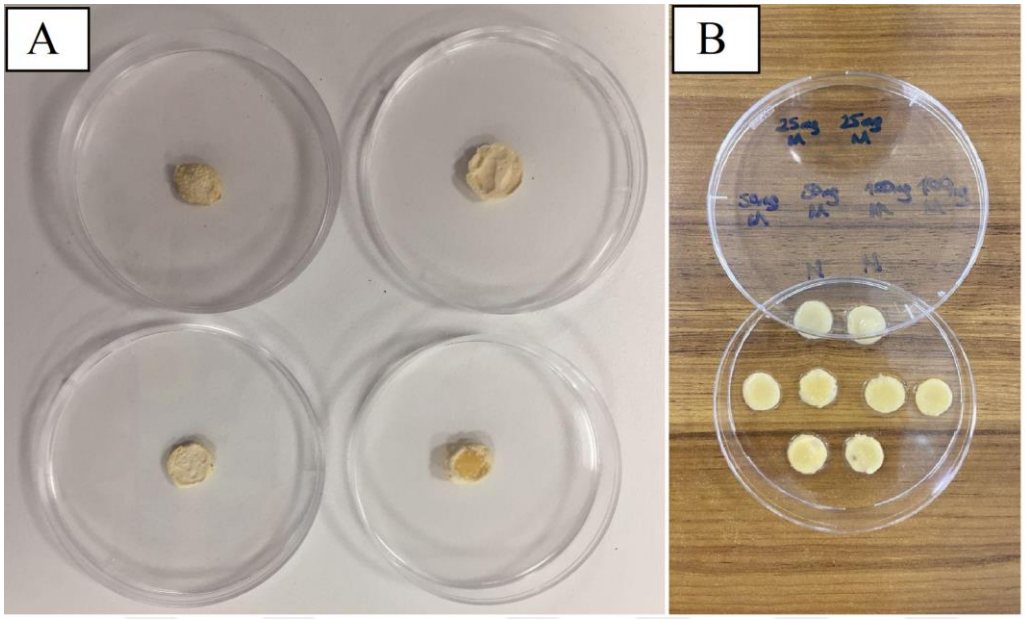

Figure 4.3. A) Dried cryogels and B) swollen cryogels.

Table 4.1. Swelling ratio and polymerization yield of Asx-MIP and NIP embedded cryogels.

Polymer	**Swelling Ratio (%)**	**Polymerization Yield (%)**
50 mg NIP embedded cryogel	144.8	90.6
25 mg Asx-MIP embedded cryogel	143.8	90.5
50 mg Asx-MIP embedded cryogel	145.9	89.6
100 mg Asx-MIP embedded cryogel	148.1	87.9

4.3.2. SEM Analysis

SEM analysis was used to examine the surface morphologies of PVA-Asx-Gel and PVA-Gel cryogels. SEM images taken at different magnifications provide detailed information about the structural properties of cryogels and these images are presented in Figure 4.4. When SEM images are examined, it can be seen that Asx-MIP and NIP polymers are clearly incorporated into the cryogel structure.

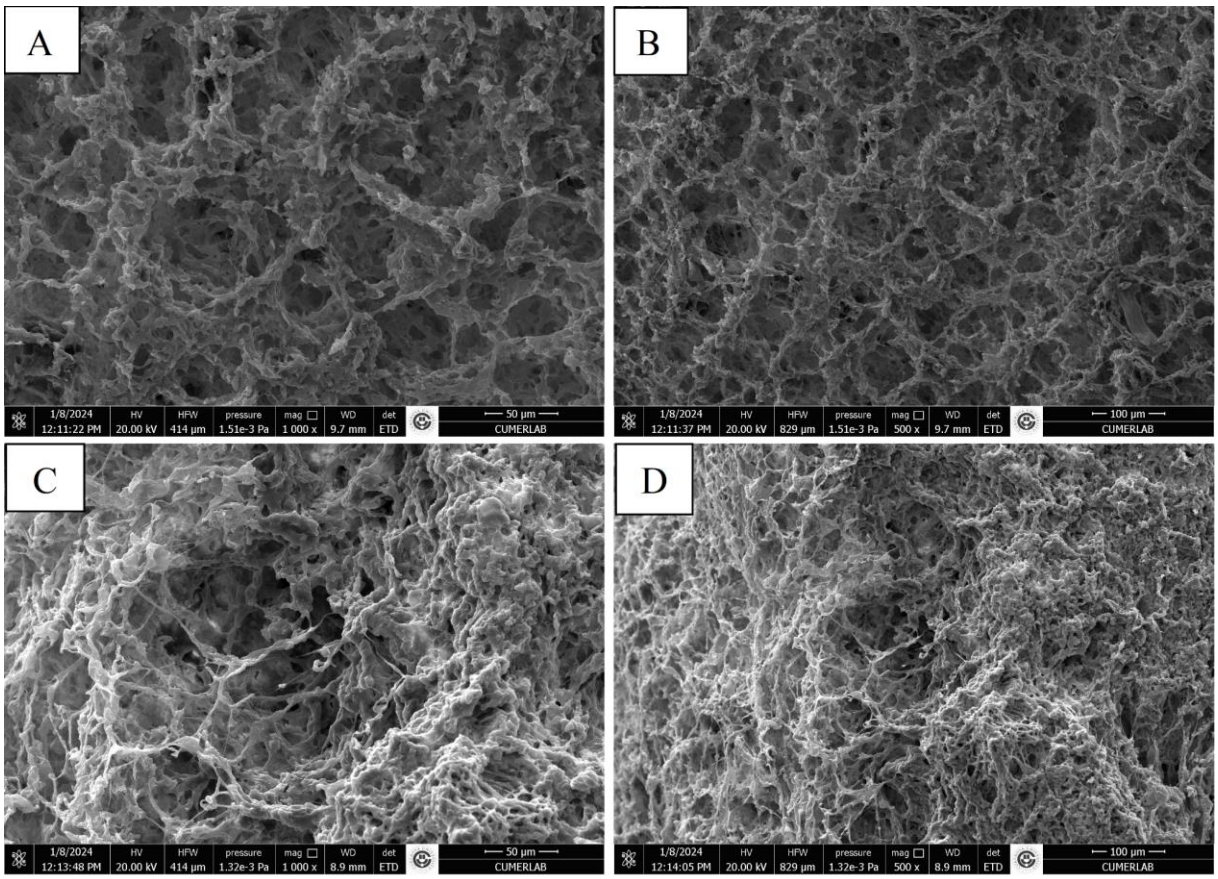

Figure 4.4. Surface morphology images of A-B) PVA-Asx-Gel (1000x-500x) and C-D) PVA-Gel (1000x-500x) taken with SEM.

4.4. *In vitro* Release Studies

The time-release behavior of Asx was investigated using PVA/gels synthesized by incorporating varying amounts of Asx-MIP (25, 50, and 100 mg). Release studies were carried out with DMSO at room temperature and the graph created according to the data obtained is given in Figure 4.5.

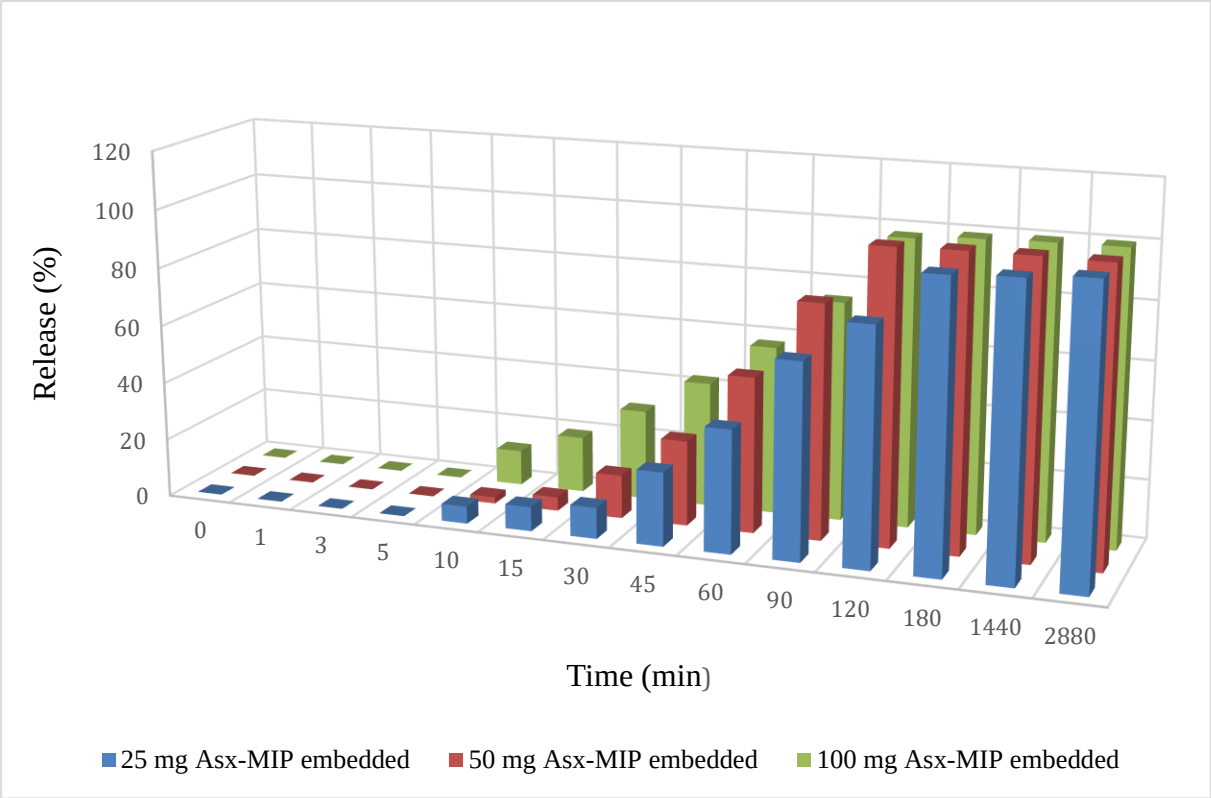

Figure 4.5. Effect of the amount of Asx-MIP embedded on release (%)

The Asx release rate depending on the amount of embedded Asx-MIP polymers shows a positive relationship as shown in Figure 4.5. This expected result can be explained by the higher driving force for diffusion out of the Asx-MIP embedded cryogels caused by the higher Asx content in the polymer system, which shows up as a bigger concentration gradient.

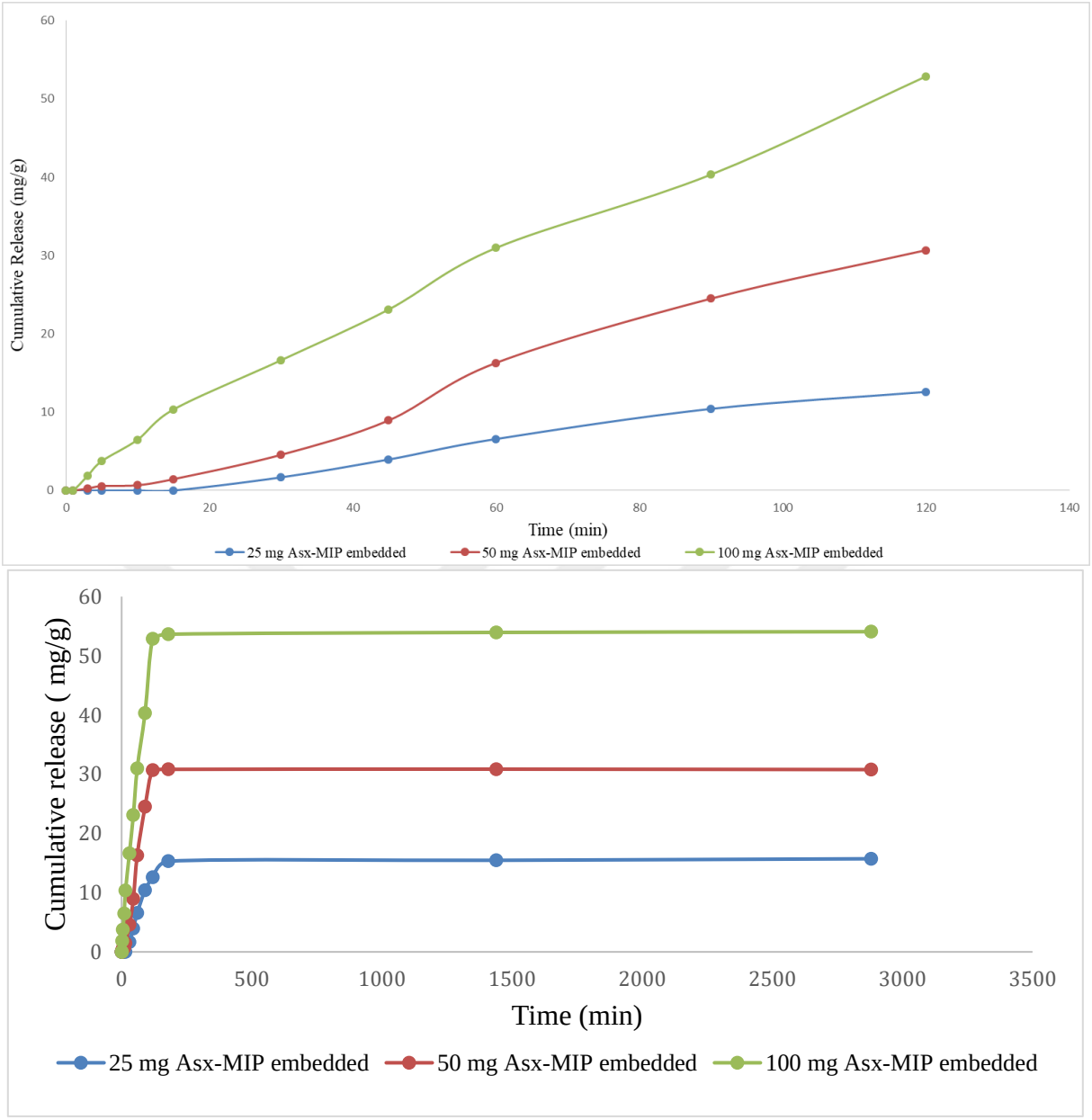

Figure 4.6. Cumulative release amount over time based on the amount of Asx-MIP embedded

The cumulative release graph of cryogels containing different amounts of Asx-MIP polymers is given in Figure 4.6. When the graph was examined, it was seen that Asx was released at a high rate within two hours. Later, according to the samples taken for 2 days, it was shown that the Asx release continued slowly.

4.5. *In vitro* Cell Studies

4.5.1. MTT Assay

MTT assay results revealed that all synthesized cryogels had no cytotoxic effect on MEF cells and were suitable for cell growth (Figure 4.7.). As the incubation time increased, cell proliferation in all three MIP cryogels increased, and it was determined that the viability was higher than the 2D control group. For NIP cryogel, cell viability was surprisingly equal to the 2D control. This is thought to mean that NIP cryogel does not inhibit cell growth but does not have a proliferation-enhancing effect either.

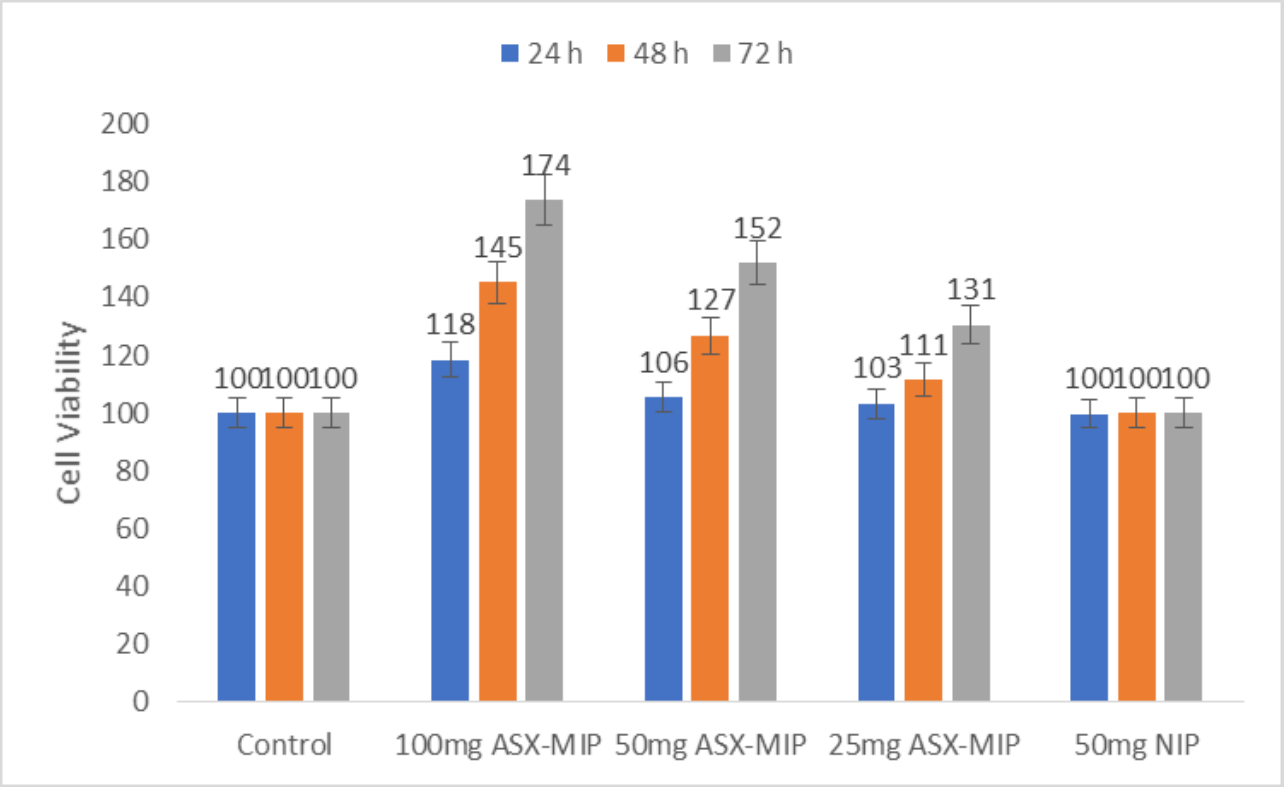

Figure 4.7. The viability of MEF cells cultured on synthesized cryogels.

The cryogels referred to as 25 mg Asx-MIP, 50 mg Asx-MIP and 100 mg Asx-MIP contained $9.16x10^{-4}$ mg/mL, $18.32x10^{-4}$ mg/mL and $36.64x10^{-4}$ mg/mL Asx respectively. When Figure 4.7 is examined, it is noteworthy that as the amount of Asx in the cryogels increases, cell viability increases in all three incubation periods. This suggests that Asx contained in cryogels has a cell proliferation-enhancing effect. Based on this, it is thought that MIP cryogels containing Asx have the potential to facilitate wound healing and are suitable as wound/burn dressing materials.

5. CONCLUSION

In this study, Asx imprinted HEMA based polymers were synthesized and these polymers containing different amounts of Asx were ground and embedded into cryogels. Hydroxyethyl methacrylate (HEMA)-based cryogels were characterized by swelling tests, scanning electron microscopy. As a result of swelling tests, Asx-MIP and NIP embedded cryogels showed high swelling properties of 642 and 645.9 percent, respectively. The surface morphology and bulk structure of Asx-MIP and NIP embedded cryogels were analyzed by scanning electron microscopy (SEM). When SEM photographs were examined, it was seen that Asx-MIP and NIP particles were distributed homogeneously in the polymer matrix and Asx release could occur without any obstacle from cryogel disks with sufficiently large pores. Release kinetics were examined depending on the amount of Asx-MIP embedded in the cryogels and it was determined that a high rate of Asx was released within the first 2 hours. With in vitro study, the effect of Asx on mouse embryonic fibroblast (MEF, (CF-1) (ATCC® SCRC-1040™)) cell line was examined and MTT analysis was performed. As a result of all analyses, it has been shown that astaxanthin contained in cryogels has a cell proliferation-enhancing effect, and it has been proven that MIP cryogels containing Asx have the potential to facilitate wound healing and can be used as wound/burn dressing material.

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