DEVELOPMENT OF CELLULOSE AEROGELS AND COMPOSITES FOR MEDICAL TEXTILES

by

Umaima Saleem Memon

A Dissertation Submitted to the
Graduate School of Sciences and Engineering
in Partial Fulfillment of the Requirements for
the Degree of

Doctor of Philosophy

in

Chemical and Biological Engineering

KOÇ ÜNİVERSİTESİ

February 2021

DEVELOPMENT OF CELLULOSE AEROGELS AND COMPOSITES FOR MEDICAL TEXTILES

Koç University

Graduate School of Sciences and Engineering

This is to certify that I have examined this copy of a doctoral dissertation by

Umaima Saleem Memon

and have found that it is complete and satisfactory in all respects,

and that any and all revisions required by the final

examining committee have been made.

Committee Members:

Prof. Dr. Can Erkey (Advisor)

Assoc. Prof. Dr. Seda kızılel

Asst. Prof. Dr. Zeynep Ülker

Asst. Prof. Dr. Yaprak Özbakır

Asst. Prof. Dr. Arbab Muhammad Toufiq

Date: ________________________________

To my Advisor who never gave up on me

ABSTRACT

DEVELOPMENT OF CELLULOSE AEROGELS AND COMPOSITES FOR MEDICAL TEXTILES

Umaima Saleem Memon
Doctor of Philosophy in Chemical and Biological Engineering
January 2021

Aerogels are a peculiar category of nanomaterials that own some fascinating properties like porous structure, low thermal conductivity, high specific area and, low density. From years, aerogels are being widely been explored in wound dressing applications and currently, aerogels are considered the most propitious material for numerous biomedical applications. It is intriguing that cellulose based aerogels own nanosized structure, biodegradability, sustainability, renewability, and biocompatibility and also have fascinating properties such as low density, high specific surface area and high porosity. These qualitative characteristics enable cellulose aerogel based dressings to be utilized in many wound dressing applications. In this study, pure aerogels were developed using the sol-gel and freeze-thaw method. Moreover, novel cellulose aerogel based drug delivery systems and nonwoven fibrous based composites were synthesized. These cellulose-based aerogels and composites are remarkable materials and can be chosen for innovative medical textile applications. Addition of the drug in any of the steps before gelation is one of the previous methods used to load drugs into cellulose aerogels, but this technique has some disadvantages like low solubility of drugs in supercritical carbondioxide (scCO_2) and possible reactions of pharmaceutical agents with other reactants in gel formation. An alternative technique to load drugs is by contacting it with the drug solution after gelation and allow the drug to diffuse into the pores of gel. ScCO_2 drying method is used in this study and it has an advanatge of not only removing the solvent from the gel pores but also causes the drug precipitation into the aerogel pores. Paracetamol was used as a model drug loaded in to cellulose aerogel matrix using the same technique.

Another promising method to load drugs in to the aerogel matrix is by supercritical deposition. Supercritical carbondioxide is one of the widely used corresponding fluid, because of having low critical pressure and temperature. ScCO_2 is thought to be inert, non-flammable and can be a good solvent for dissolving pharmaceutical compounds. ScCO$_2$ medium is an appropriate replacement for water-insoluble drugs and is applicable to compounds with higher solubility in scCO$_2$. For instance, camphor was used as a model drug because of its high solubility and is incorporated in to cellulose aerogel matrix using supercritical deposition method. The process starts with the solubilization of drug in scCO$_2$, and is exposed to cellulose aerogel followed by depressurization and removal of scCO$_2$. Thus, the scCO$_2$ leaves the cellulose aerogel matrix with camphor inside.

The SEM and IR results indicated the presence of paracetamol and camphor in the aerogel. The paracetamol release from loaded cellulose aerogels in PBS solution was investigated, displaying the possible use of these materials to act as drug delivery carriers. The investigation also yielded results that show that these materials can be suitable in being able to achieve a retarded release profile up to 13 hours. ScCO$_2$ deposition technique produced camphor loaded cellulose aerogels with high loadings up to 50%, making them suitable drug carrier material in wound dressings.

Composite materials of cellulose aerogel with polyester and cotton nonwoven were also synthesized using the sol-gel method. Polyester and cotton nonwovens were soaked in the cellulose gel solution and kept at 50^{o}C for 2 hours, causing the formation of cellulose gel inside the nonwoven sheets. After the solvent exchange process, the gels were then subjected to scCO$_2$ drying to attain cellulose aerogel nonwoven composites. SEM and IR results indicated the presence of cellulose aerogel inside the cotton nonwoven sheet. A wound exudate absorbency test was also carried out for cellulose aerogel cotton nonwoven composites to determine their performance as a wound dressing material. The cellulose aerogel cotton nonwoven exhibited high wound exudate absorbencies as compared to pure cotton nonwoven. The resulting composite material has high porosity, with an average pore diameter of 25nm. Furthermore, silver was loaded to these cellulose aerogel cotton nonwoven composites by soaking it in 0.01M solution of silver nitrate after solvent exchange to achieve antimicrobial properties.

ÖZET

Aerojeller gözenekli yapıları, yüksek yüzey alanları, düşük özkütleleri ve düşük ısı iletim katsayıları gibi kendine has özellikleri olan ayrı bir nanomalzeme türüdür. Uzun yıllardır, aerojellerin yara pansuman malzemesi olarak kullanımındaki rolü genişçe incelenmiştir ve günümüzde aerojeller bir çok sayıda biyomedikal uygulama için en çok umut vaad eden malzemeler olarak değerlendirilmektedir. Selüloz bazlı aerojellerin nano yapıda olması, biyoçözünürlükleri, sürdürülebilirlekleri, yenilenebilirlikleri, biyouyumlulukları, ve ayrıca yüksek spesifik yüzey alanı, düşük özkütle ve yüksek gözeneklilik gibi etkileyici özellikleri olması merak uyandırıcıdır. Bu nitelikli karaktersitik özellikler selüloz aerojel bazlı sargıları çeşitli yara pansuman malzeme uygulamalarında kullanımını sağlar. Bu çalışmada selüloz aerojeller sol-jel ve donma-çözme yöntemleriyle sentezlenmiştir. Sonrasında, ilaç salınım sistemleri ve dokumasız elyaf kompozit tabanlı yenilikçi selüloz aerojeller ilk defa sentezlenmiştir. Selüloz bazlı aerojeller ve kompozitleri çok yenilikçi medikal tekstil uygulamalarında kullanım için oldukça yenilikçi ve elverişlilerdir. İlaçların jelleşme öncesi herhangi bir basamakta eklenmesi ilaçları selüloz aerojellere yüklemek için daha önceden uygulanan yöntemlerden birisidir, fakat bu yöntemin ilaçların süperkritik karbondioksitte (scCO_2) düşük çözünürlüğü ve farmasötik ajanların jel oluşturan diğer reaktantlar ile tepkimeye girmesi gibi çeşitli dezavantajları vardır. İlaç yüklemede alternatif bir yöntem, jelleşmeden sonra ilaç solüsyonu ile ilaçları etkileşime geçirip ilaçların jelin gözeneklerinin içine difüze olmasını sağlamaktır. Bu ilaç yüklenmiş jeller scCO_2'ya maruz kaldığı zaman, bu yöntem hem çözücüyü gözeneklerden atar hem de ilaçların gözeneklerin içine çökmesini sağlar. Parasetamol selüloz aerojel matriksine yüklenmiş model ilaç olarak kullanılmıştır.

İlaçları aerojel matriksine yüklemek için bir diğer umut vaat eden yöntem süperkritik deposizyondur. Superkritik karbondioksit düşük kritik basıncı ve sıcaklığı sebebiyle en yaygın kullanılan akışkanlardan biridir. ScCO_2 reaksiyona girmeyen, yanıcı olmayan ve farmasötik malzemeler için iyi bir çözücü olarak bilinir. ScCO_2 suda çözünmeyen ilaçlar için uygun bir alternatiftir ve scCO_2'da yüksek çözünürlüğü olan maddeler için kullanılabilir. Örnek olarak, kamfor model bir ilaç olarak yüksek çözünürlüğü saysesinde bu yöntemle selüloz aerojel matriksine yüklenmiştir. Yöntem ilacın scCO_2'da çözünmesi ile başlar ve selüloz aerojele maruz kalması sonrası basınç azaltma ve scCO_2'in atılması ile devam eder. Böylece scCO_2 selüloz aerojelden içeride kamforu bırakarak ayrılır. SEM ve IR sonuçları aerojel içinde parasetamol ve kamfor varlığını göstermektedir. İlaç salınımı uyglamalarında potansiyel malzemeler olduğunu göstermek üzere PBS solüsyonunda ilaç yüklenmiş selüloz aerojellerden parasetamol çıkışı incelenmiştir. İncelemeler bu malzemelerin 13 saate kadar geciktirilmiş salınımı elde ederek uygunluğunu açığa çıkartmıştır. $ScCO_2$ deposizyon tekniği ile, kamforun selüloz aerojellere %50’ye kadar yüksek oranda yüklemesi elde edilmiştir ve bu sayede bu malzemeler yara pansuman uygulamalarında ilaç taşıma için uygun hale gelmiştir.

Ayrıca selüloz aerojellerin polyester ve pamuk dokumasız kumaşlarla kompozitleri sol-jel yöntemi ile hazırlanmıştır. Polyester ve pamuk dokumasız kumaşlar selüloz aerojel solüsyonuna batırılmış ve 50^{o}C’de 2 saat boyunca tutulmuştur, böylece selüloz aerojelerin dokumasız kumaş içerisinde oluşumu sağlanmıştır. Etanol ile çözücü değişimi sonrası, selüloz aerojel ve dokumasız kumaş kompozitleri oluşumu için jeller $scCO_2$’ye maruz bırakılmıştır. SEM ve IR sonuçları dokumasız kumaş kağıtları içinde selüloz aerojel varlığını göstermiştir. Bir yara sızması emilme testi, aerojel ve pamuklu dokumasız kumaş kompozitlerinin yara pansuman malzemesi olarak performansını belirlemek için yapılmıştır. Yalın pamuklu kumaşa göre selüloz aerojel kompozit malzemeleri yüksek yara sızması emme performansı göstermiştir. Elde edilen kompozit malzeme yüksek gözenekli yapıdadır ve ortalama gözenek çapı 25 nm’dir. Ayrıca, malzemeye antimikrobiyal özellik katmak için gümüş, selüloz aerojel - pamuklu dokumasız kumaş kompozitlerinin çözücü değişimi sonrası 0.01 M gümüş nitrat solüsyonuna batırılması sonucu, yüklenmiştir.

ACKNOWLEDGMENTS

First, I owe a great debt to my advisor Prof. Dr. Can Erkey for his words of advice and the longtime and tremendous effort to offer every possible help throughout my journey of PhD studies. He has made a positive impact on my life and is an inspiration to.

I am deeply grateful and would like to acknowledge my thesis monitoring committee members, Assoc. Prof. Dr. Seda kızılel and Asst. Prof. Dr. Zeynep Ülker Demir for their cooperation and guidance.

I am grateful to my beloved parents Dr. Saleem Raza and Shabana Memon for nurturing my learning and supporting my dreams. My thankfulness is also to my siblings, Murk, Aslam, Arham and Swaliha for their immense love and prayers. A special thanks to my husband Nahyan Akhter and daughter Enaaya who have kept me a float when times were hard.

I also would like to thank my all colleagues and lab mates. A special thanks to Dr. Yaprak Ozbakir and Dr. İbrahim Şahin for their motivation, guidance and support.

I would like to thank Koç University Turkey and Higher Education Commision (HEC) Pakistan for their technical and financial assistance.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1

INTRODUCTION

1.1 Wounds Dressings

Skin is the largest human organ that act as a protective barrier against external aggressions. Any physical, chemical or thermal damage in the skin epithelial lining continuity is defined as wound. In case of an injury/wound skin has the ability to self-regenerate which generally is slow pace unless a specific environment with the help of an external support is provided. Thus, it still needs external support to augment the wound healing [1]. To this end, wound dressings are a commonly used external support used to generate an ideal environment to hasten the healing process in an optimum way. They are an integral part and an important sector of pharmaceutical and medical wound care market worldwide [2]. They are developed from a variety of natural and synthetic materials. An ideal wound dressing material should have sufficient mechanical stability, wound healing mediators according to wound requirement, engineered structure, absorb wound exudate, porosity, allow moist environment, adequate breathability, comfort, prevent contamination and cost effective [3]. Generally, wounds can be categorized as Penetrating wounds (Stab, Skin cuts, surgical, and gunshot), Non-penetrating (Abrasions, contusions, and skin tear), and Miscellaneous wounds (electrical, thermal, chemical, and bites and stings).

Traditionally wound dressings have been developed having origins from plant herbs, honey and animal fat, spider web and others [2]. Such dressings are non-occlusive as they dry out faster and then adhere to the wounded area, causing bleeding and pain to the patient [42]. In 1980, moist wound healing process were introduced that took a new direction in medical [5]. The choice of wound care material is very complicated and must be specific considering the wound, patient and their multiple needs [6]. Similarly, the concept of moisture assisted wound healing has been introduced for the last three decades. However, even today it is not used in common practice [7]. These dressings play a significant part in; creating moist environment at the wound site, soothing of nerve endings, eliminating or minimizing pain, with less scarring and natural healing of the wound [8, 9].

The modern wound healing dressings started in the beginning of 20th century. Currently more than 5000 wound care products are available. Most modern dressings include materials with higher absorbent power, for example Cellulose. A plethora of products was followed keeping in view the concept of moist dressings which include hydrocolloids [10-13], foams [14-22], aerogels [23, 24] and hydrogels [25-30].

1.2 Cellulose based Aerogels for wound dressing

Natural polymers have attracted tremendous attraction because of their remarkable properties and having unique structures specially in the biomedical area. Such materials have good mechanical properties, biocompatibility, biodegradability and non-toxicity.

Aerogels are the promising materials for the wound dressing products [31, 32]. It is very light in weight composed of 3-dimensional structured polymeric material. The aerogel porous structure makes it the perfect material for wound healing matric [33]. Aerogels have high absorbing power, that can readily absorb external fluid at a very high rate [34] and displays remarkable characteristics due to its porous structure [35].

Biopolymer is one of the suitable materials for manufacturing aerogels because of its biocompatibility, biodegradability, renewable source, abundance and low toxicity, keeping in account the requirements of wound dresser [36-39]. Various natural biopolymers based on plants and animals have been used to prepare aerogels including cellulose, chitosan, collagen, alginate etc.

One of the most abundant products are Cellulose based materials that have high potential. These materials have quite a good scope to be used in biomedical and biotechnology applications [40]. Cellulose is one of the main biopolymer having fascinating properties like biocompatibility, sustainability and biodegradability and is thought as alternative to petroleum based polymers to run in to outstanding market [41]. Being entirely compostable and biocompatible, cellulose derivatives (cellulose hydrogels and aerogels, cellulose fibers, cellulose based films, and cellulose composites) hold excessive properties when compared to synthesized polymers [42]. It is one of the important natural polymers available and a vital sustainable raw material source of renewable materials prepared on an industrial scale nowadays [43-48].

Cellulose aerogels pose great potential in biomedical regenerative medicine field, as they contain properties like their inorganic counterparts along with characteristics of regrowing biopolymer and additional advantages. It is intriguing that cellulose based materials owns nanosized structure, biodegradability, sustainability, renewability, and biocompatibility, but also comprise remarkable properties like high specific area, low density and an upsurge in porosity. These characteristics enable cellulose aerogel dressings to be utilized in many wound dressing applications.

1.3 Preparation Methods for developing Cellulose Aerogels

1.3.1 Source Materials for developing cellulose aerogels

Cellulose can be categorized based on its source including the plant, different parts of plants and plant waste. Cellulose aerogels can be classified on the basis on the raw materials as natural cellulose (bacterial cellulose and nanocellulose), renewed or regenerated cellulose and cellulose derivative aerogels.

Natural Cellulose recognized as (cotton) is a pure wound dressing material but it is rarely used because of presence of impurities like wax, lignin, hemicellulose, and pectin and due to high production cost. Viscose fibers are form of cellulosic fibers used as woven or nonwoven textiles and commonly used as base materials for wound dressings. Natural Cellulose is further categorized as BC and nano cellulose. BC is produced via static (bacterial) cultures and contains I_∞ structure and natural 3D network gel [49]. Nanocellulose is further categorized in to two types on the basis of separation methods: (i) cellulose nanocrystals (CNC) (cellulose whiskers), and (ii) cellulose nanofibers (CNF), typically recognized as micro fibrillated cellulose (MFC) or also known as nanofibrillar cellulose (NFC). Similarly, in Klemm’s review a comprehensive detail about different nanocellulose types can be obtained [50].

In general, cellulose chemical processing is a complex procedure because cellulose is insoluble in usual solvents and is not meltable, due complex hydrogen bonds and intermolecular network [51]. The production method of regenerated cellulose is originated from viscose fibers which is a 100-year-old technology. Table 13.1. presents a summary of source materials for preparing cellulose aerogels

Table 1.3.1 Precursor for some cellulosic aerogels based on natural and regenerated cellulosic materials

Source	Application	Properties	Reference
Renewable corn straw	Spillage oil capture	Low cost, ultra-light absorbent	[52]
Lupin hull	Tissue engineering scaffolds and food packaging that are environmental friendly	Highly porous (96.6 to 99.4%), light weight (0.009 to 0.05 g/cm^3), high crystallinity and thermal stability.	[53]
Nano fibrillated	Super absorbents	Water and oil	[54]

cellulose from wood or agricultural byproducts (bagasse)		absorption capacity	
Wood	Templates for green, functional nanocomposites and tissue engineering scaffold synthesis	Ultralight and highly flexible aerogels	[55]
Wheat straw	Thermal insulation	Improved textural properties. Surface area ($120m^2g^{-1}$), bulk density ($0.15\ gcm^{-3}$) and thermal conductivity ($50\ mWm^{-1}K^{-1}$)	[56]
Potato tubers	Environmental friendly filler	Improved mechanical properties and water absorption properties	[57]
Cannabis	Microcrystalline cellulose prepared with improved properties	Improved chemical and physical properties	[58]
Paper waste	Oil absorption	Super hydrophobic property over 5 months. Oil absorption approximately 40 to 90 times of its original weight	[59]
Cotton	Pharmaceutical and biomedical	Highly porous and ultra-light weight	[60]
Pine needles	Thermoplastic composites	Ultrafine, highly flexible and hydrophobic	[62]
Jute fibers	Pharmaceutical, catalyst, tissue engineering scaffolds, liquid filtration and bio-nanocomposites	Diameter from 3-20nm, controllably hierarchical 3D porous structure	[62]
Rice straw	Super absorbents	Ultra-light (1.7 to 8.1 $mg\ cm^{-3}$) and porous (99.5 to 99.9%)	[63]

Cellulose derivative aerogels or functionalized cellulose aerogels are prepared by change in chemical and physical properties of normal cellulose. Some cellulose derivative aerogels like hydroxypropyl methylcellulose (HPMC) and CMC are soluble in water. Table 1.3.2 comprises a detailed summary of modification of some cellulosic materials for achieving enhanced properties. Currently, the cellulose derivative aerogel's most commonly produced types are nanocellulose aerogels oxidized with 2,2,6,6-tetramethylpiperidine-1-oxyl radicals (TEMPO) and aerogel functionalized surface particularly including maleic acid-grafted CNF (CNF-MA) [91], cross-linked carboxymethyl chitosan (CMCT), and bifunctional (aldehyde and carboxyl) nanocellulose (BMCC) [64].

Table 1.3.2. Overview of the functionalization/treatment of some cellulosic materials for wound dressing application

Material	Properties	Functionalization/Treatment	Reference
Viscose Rayon	Increased absorption	Crosslinking co-polymerization	[65]
Polyaniline coated conductive cotton textile	Induced wettability	Doping/Dedoping	[66]
Cellulose acetate (CA)	Enhanced hemostasis	Deposition	[67]
Cellulosic fibers	Alkaline treatment or bleaching	Chemical treatment	[68-70]
Polysaccharide	Controlling bacterial and fungal growth	Biologically encapsulated active polymers or silver (Ag) nanoparticles	[71, 72]
Oxidized regenerated cellulose/collagen	Accelerate wound repair	Addition of antimicrobial compounds	[73]
Nonwoven fabrics	Increased antibacterial efficacy	Chitosan modification	[74]
Chitosan/Polyethylene oxide	Enhanced inactivation of bacteria	Chemical reduction of Ag ions	[75]
Chitin scaffold	Bactericidal and good blood clotting ability	Composite with nano Ag	[76]

Chitosan whiskers in alginate fibers	Increased antibacterial activity	Wet-spun	[77]
Chitosan and cellulose blends	Reduced water vapor transpiration rate, effective antimicrobial capability	Blending	[78]
CA	Wound healing, antimicrobial, anti-inflammatory, antitumor and antioxidant	Binding hydroxynaphthoquinones on polymer surface	[79]
Cotton gauze	Bacterial barrier dressing, protect against wound infections	Chemical modification of the polymer (cationic polymeric biocide) polydiallyldimethylammonium chloride	[80]
Viscose fabrics	Improve adsorption of chitosan yielding increased antimicrobial activity	Oxygen plasma treatment	[81]
CA	Bacterial cell destruction	Amino functionalized surface	[82]
Natural cellulose	Multi drug resistant wound pathogen termination	Copper (Cu) based nanostructured coatings	[83]

1.3.2 Synthesis Pathways of Cellulosic Aerogels

The synthesis of Cellulose aerogels involves three steps (i) first step includes dissolution or dispersion cellulose derivatives or cellulose itself (ii) second step involves gel formation via sol-gel or freeze thaw (FT) method and (iii) and third one is about drying gels retaining the 3D porous structure.

1.3.2.1 Sol-Gel Process

This conventional method known as wet chemical synthesis approach is most frequently used for preparation of aerogels of almost all different kinds including hybrid, organic and inorganic aerogels. The main steps of precursor mixing, hydrolysis, polycondensation, gelation, solvent exchange or ageing and drying are chiefly involved in this whole process. The aerogels produced by mechanism of sol-gel possess a monolith structure, while it can be produced with specific shapes depending upon the required application. The processing steps that involve cellulose aerogels fabrication is replica that of silica aerogel. These steps are as follows: (i) a hydrogel created from an aqueous sol (ii) the water in the hydrogel network is exchanged with an alcohol or acetone and (iii) drying of wet gel.

Usually, cellulose dissolution is a complex process to be achieved and number of available solvents for dissolution process are usually limited. In (Figure 1.3.1) schematic representation of cellulose dissolution via using NaOH is demonstrated. The cellulose nature with different source defines the solvent and gelling methods.

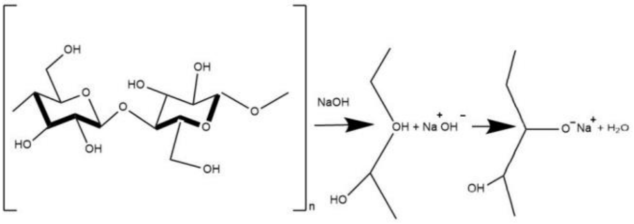


Figure 1.3.1. Schematic representation of cellulose reaction with NaOH

1.3.2.2 Freeze Thaw Method

This method has some advantages over other drying methods like being quite experimentally simple and no requirement of any extra chemical crosslinking agents. FT mechanism involves a phase separation mechanism which occurs upon freezing of solution and in this process the polymer is rejected as the ice crystals grow, and can be refined upon repeated cycling step. The gel structure is reinforced by physical crosslinks (hydrogen bonds and crystalline polymeric regions).

1.3.3 Drying methods

‘Aerogel’ is prepared when the solvent in the gel is replaced by air. There are generally three ways to dry the cellulose hydrogels. (Figure 1.3.2) represents the schematic representation of preparations methods of cellulose aerogels using different synthesis techniques and drying methods.

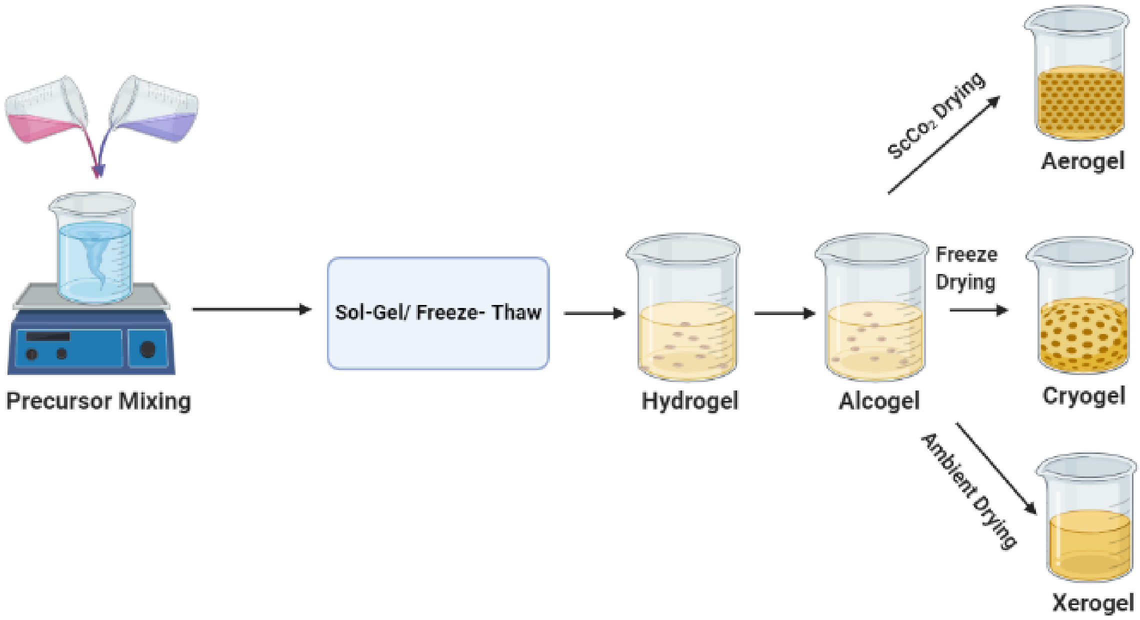


Figure 1.3.2. Schematic representation of cellulose aerogels synthesis pathways

For simplicity they are termed as aerogels, cryogels and xerogels obtained from supercritical CO_2 ($ScCO_2$) drying, ambient pressure or vacuum drying, and freeze drying respectively as shown in (Figure 1.3.3).

Figure 1.3.3. Examples of cellulose gels after drying with different methods (Reprinted with permission from Springer Nature, Copyright 2020.) [84]

Removing unwanted solvent and preserving porosity of the material at the same time are the utmost requirements in drying of most aerogels. In that case ScCO$_2$ drying is the most suitable as it extracts the unwanted solvent from the alcogels as well as retain the porous structure of the resulting aerogel. CO$_2$ has a suitable critical point (304K, 7.4MPa) (31.1^{o}C, 1071psi) having additional advantages of being non-toxic, nonflammable, environmental friendly and leaving no residue in the matrix, it is the most commonly fluid used for ScCO$_2$ drying of cellulose aerogel. The cellulose aerogel produced by this drying method has density in the range of (10-60 kg/m^3) and yielding surface area of (200-310 m^2/g) [85]. The materials used to prepare cellulose aerogels using ScCO$_2$ drying method are summarized in Table 1.3.3.

Freeze drying method is also a commonly used process to obtain dry gels termed as cryogels, while keeping the gel structure intact. This drying method yields cellulose cryogels with sheet like network having large and interconnected pores of several micrometers in diameter. The cryogels produced by this method yields surface area of 160 m^2/g. This drying procedure forms large channels and pores from several microns to tens of microns [86-88]. Freeze drying process involves sublimation of solid from the pores of a wet precursor and is likely to preserve the cellulose wet gel’s porosity. There are many studies on producing cellulose aerogels using the freeze dry method. Precursor materials for developing cellulose aerogels using freeze drying method are summarized in Table 1.3.3.

Ambient drying is a process that evolves drying at optimum pressure and room. This method is useful in case of materials or composites that cannot survive supercritical conditions. In this drying method cellulose hydrogels or alcogels are vacuum dried at room temperature in a standard oven for 48 h producing cellulose xerogels. This process gradually progresses and strong capillary pressure on gel’s pore wall. In case of cellulose, it happens because of the surface tension of water as cellulose is hydrophilic in nature.

Additionally, along with capillary stresses, densification also occurs because of the hydrogen bonds formed between hydroxyl groups that are present in cellulose chain. Consequently, a drawback of high-volume shrinkage in xerogels takes place. It is mainly dependent on the cellulose concentration, as the content of cellulose increases it will have a stronger network so that the pore walls will resist the capillary stress better. Cellulose xerogels are relatively dense to aerogels and cryogels and also their porosity is approximate to zero due to strong contraction of pores during drying. As a consequence, this drying technique cannot be used to prepare porous non-modified cellulose materials. Table 1.3.3. summarizes the current studies on cellulose gels dried with vacuum drying method.

Table 1.3.3. Current studies related to cellulose aerogels, cryogels and xerogels and different drying methods used.

Materials	Drying method	Reference
Wood pulp	$ScCO_2$	[89, 90]
MCC/lignin	$ScCO_2$	[91]
MCC	$ScCO_2$	[92, 93]
Cotton linter	$ScCO_2$	[94]
Cellulose powder	$ScCO_2$	[95]
Paper pulp	$ScCO_2$	[96, 97]
Wood	$ScCO_2$	[98-100]
Cellulose	$ScCO_2$	[101]
Cellulose SiO_2	$ScCO_2$	[102-104]
cellulose: lignin/xylan	$ScCO_2$	[105]
cellulose triacetate aerogels (TAC)	$ScCO_2$	[106]
cellulose acetate (CA)	$ScCO_2$	[107, 108]
Cellulose whiskers/clay/PVA	Freeze drying	[109]
CNC	Freeze drying	[110, 111]
NCF	Freeze drying	[112, 113-116]
NCF/kymene	Freeze drying	[117]

BC/graphene oxide (GO)	Freeze drying	[118]
TEMPO based	Freeze drying	[119, 120, 121, 122, 123]
HPMC	Freeze drying	[124]
BC/silica	Freeze drying	[125]
BC	Freeze drying	[126]
waste newspaper	Freeze drying	[127, 128]
CMC	Freeze drying	[129]
CMC/CNF	Freeze drying	[130]
recycled cellulose	Freeze drying	[131, 132]
MCC	Freeze drying	[133,134]
cotton linter	Freeze drying	[135-136]
cellulose powder	Freeze drying	[137]
cellulose powder/GO	Freeze drying	[138]
CNF membranes	Ambient or Vacuum	[139]
CNF aerogel with inclusion of functional polymers	Ambient or Vacuum	[140]
Cellulose bio composites aerogels	Ambient or Vacuum	[141]
Cellulose aerogel obtained from alkali hydroxide-urea solution	Ambient or Vacuum	[142]
Ice templated CNF aerogels	Ambient or Vacuum	[143]
Chemically crosslinked cellulose aerogels	Ambient or Vacuum	[144]
CNF aerogel microspheres	Ambient or Vacuum	[145]
cellulose-SiO_2 composite	Ambient or Vacuum	[146]

1.4 Cellulose Aerogel based composites for drug delivery and wound dressing

Superior sorption capability, decent infection control, ease of application and minimal side effects are the key demands for developing efficient wound healing dressings. Currently, numerous wound healing dressings are available to treat wounds but either they are ineffective or get easily contaminated. However, Cellulose based aerogels being natural materials possess significant antibacterial properties which makes them a perfect material for wound dressing applications.

It is vital, that an ideal wound dressing should possess rapid healing and excellent antimicrobial properties [147]. Fortunately, Cellulose aerogel possess all these characteristics and can be safely incorporated with active compounds (drugs).

Another approach for the betterment of drug delivery system is to use a solvent that has little or no affinity for the solute. And this solute will later form a partially miscible solution with the solvent. This technique is known as Gas antisolvent (GAS), where $ScCO_2$ performs as an antisolvent typically reduces the solvent power of solvent, existing in the alcogel pores. In the pores of alcogel, the drug will start to precipitate when CO_2 dissolution in the solvent takes place. This process is maintained until the removal of whole solvent from pores. Subsequently the depressurization of the system is done slowly to attain aerogel with intact structure.

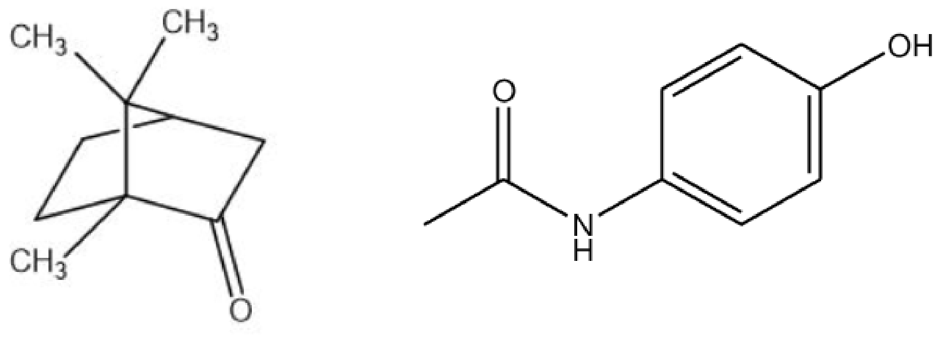
Similarly, supercritical deposition is also an attractive technique for preparing drug loaded aerogels suitable for pharmaceutical applications. This technique is applicable to the compounds with higher soluble in $scCO_2$. The process starts with solubilization of active compound in $scCO_2$, and then this active compound is exposed to polymer followed by depressurization and removal of $scCO_2$. Thus, the $scCO_2$ leaves the polymer matrix quickly with the active compound inside. High biocompatibility, aspect ratio and functionality degree lead to cellulose aerogels antimicrobial application via using different antimicrobial agents.

Cellulose is a “biodegradable and biocompatible” material. Biocompatibility property does not allow it to elicit any systemic or local reaction in the wound. That is why cellulose-based materials are safe. Several studies have supported this finding of cellulose aerogel. According to one study cellulose hydrophilic properties are responsible for blood absorption in hemorrhagic wound treatment induced by gunshot wounds [148]. This study also proposed that cellulose materials are safe to use in hemorrhagic wounds. Additionally, two other studies also supported this finding that cotton aerogel is safe to use as a homeostatic agent as it causes no further complication in patients [149, 150].

Exudate control is a crucial thing in both; surgical and acute wound situations [151]. Cellulose aerogel can absorb higher exudate amounts because of their porous structure and they equally help in preventing infection [152]. Surgical dressings that contain superabsorbent materials or agents promise higher exudate absorbency. Chemical nature of the gel phase and preparation methods highly affects the structural properties of the polysaccharide based aerogels. In this work Microcrytalline cellulose (MCC) was used to produce porous cellulose aerogels, which were loaded with two model drugs namely camphor and paracetamol.Both drugs are incorporated in to the cellulose aerogels by different techniques including GAS and supercritical deposition method. The chemical structure of these model drugs Camphor and Paracetamol is representated in (Figure 1.4.1).

Camphor is made by bark distillation and camphor tree wood. Nowadays camphor is usually produced from turpentine oil. Products made from camphor are generally rubbed on skin (topical) or inhaled. Camphor is applied on skin to relieve the pain and itching. It has also been used to treat cold sores, osteoarthritus, toenail fungus, insect bites, and warts. This drug stimulates the nerve endings that actually helps in relieving symptoms such as itching and pain. It is also very effective for treating the toenails infections due to fungi.

Paracetamol (PC), which is also known as acetaminophen is a common medication used to treat fever and pain. It is side effects free relative to other drugs and lacks significant antiplatelet and gastric irritants.



Camphor

Paracetamol

Figure 1.4.1. Chemical strcture of Camphor and Paracetamol

1.5 Non-woven textiles for wound dressing

Textiles are one of the necessary materials for survival of human life which provides us comfort, cover and protection. Protection from infections and other external factors is vital for wound recovery when it comes to nonwoven based wound dressings. Nonwovens based dressings are known to provide controllable fluid absorption and on the same side are free from chemical contaminants. Wound dressings comprises mainly of an absorbent pad to absorb any fluids (wound exudate) empolyed with nonwoven materials have been commonly used [153, 154], These dressings can be equipped with other agents and materials to improve its properties and makes it an ideal wound dressing. One of the important factor that affects the wound healing process is to provide a moist environment to the wound site so as to expedite the wound healing process. This moist environment can be achieved by maintaining moist environment at the wound site using moisture-vapour-permeable film layers [65, 155–156] or a layer based on gels (hydrogels, hydrofibers, and perforated films [157]. An absorptive nonwoven material can be used to remove the excessive exudate from the wound site and this can be enhanced by adding a diffusion or wicking layer [158] or by paper. Dressing removal is also one of the crucial aspects of wound dressing formations. An ideal wound dressing requires ease of application and removal from the wound site without causing any trauma which can be achieved by using low-adherent materials [159]. In that case biodegradabale materials based wound dressings can relatively reduce the trauma that is caused upon removal by reduction in the need for dressings change.

Fibers are the building materials for textile materials. There are a variety of pure, synthetic fibers and their blends are widely used to manufacture these textile based products. To achieve a require output from specific textile material the most important are its mechanical and physical properties [160]. Textile fibers are converted into a fabric by applying the knitting or weaving [161]. Fabrics that are directly produced fromm fibers are known as nonwoven, which is usually manufactured by airlaid, wetlaid and carding methods and later bonded by chemical, thermal or mechanical bonding (water jet or needles) to structured nonwoven felts [162].

Although silica aerogels are used for many biomedical applications, but the use of oragnic aerogels have found to be superior because of their biocompatibility, nontoxicity, and biodegradability [163], [164], [165]. These aerogels are found to be excellent materials for wound dressings and drug delivery applications [166]–[167].

The need for the wound care products has been increased over the years. The commonly available wound dressings are mostly fabricated in the form of composited which comprises of an outer protective layer to help the wound not get contaminated because of the external factors like water, chemical or any other impurity. This outer layer is usually made up of nonwoven felts and they have some really fascinating properties like being light in weight, being porous, having low density and can easily be fabricated using variety of raw materials.Electrospinning is one of the emerging technique to fabricate these nonwoven webs having diamters ranging from a few nms to several mms by creating an polymer solution or melt electrically charged jet. The nonwoven webs produced using this technique has some remarkable properties such as small pores and high specific surface area which prevents the penetration of bacteria and thus prove to be good candidates for wound dressing materials. A variety of speciality fibers can be spun using this technique because of the flexibility of the process and can be easily converted in to nonwoven fabrics including PET [168].

Polyester is a synthetic polymer which is composed of atleast 85% by weight of an ester of terephthalic acid (p-HOOC-C6H4COOH) and dihydric alcohol (HOROH) [169]. Polyehtylene terephthalate is the widely used linear polymer for the manufacturing of polyester fiber also known as PET. PET based nonwovens have inherently high resilience, high modulus, and compresssion recovery. Polyester wound dressings consist of drylaid mechanically and thermally bonded (90% porous), spunbonded or vapour-permeable meltblown covers.

Chapter 2

MATERIALS AND METHODS

2.1 Preparation of Camphor loaded MCC aerogel by supercritical deposition

Initially, 6g of MCC was mixed with 30gdistilled water and kept at 5^{o}C for 2 hours to allow it to swell. In parallel another solution of 7.6g of NaOH dissolved in 56.4g water was prepared and was cooled at -6^{o}C. These solutions were prepared in a proportion of a total 100g solution. Then these two solutions were mixed together under continuous stirring (1000rpm) for 2 hours at -6^{o}C. Afterwards the solution was transferred in to the molds (the required shape) and heated in an oven at 50^{o}C for 2 hours which causes the gelation of the MCC. The samples were washed several times with distilled water carefully and subjected to a series of solvent exchange steps with ethanol-water solution starting from (10, 30, 50, 70, 90 and 100% ethanol) with a duration of 120 minutes each.

The final step was to dry the cellulose alcogels with scCO$_2$ at 40^{o}C and 90 bar using an scCO$_2$ extractor (Applied Separations Speed SFE) and an extraction vessel of 25ml. The cellulose alcogels were added in to the extraction vessel and filled with ethanol. At first, the excess ethanol inside the extraction vessel was extracted immediately which was then followed by the ethanol removal from the cellulose alcogel pores in order to completely dry it for 6-7 hours and obtain cellulose aerogels. It was made certain that all the ethanol was completely dried and no remains were left inside. Then the sample loaded vessel was slowly depressurized so as to avoid crack formation in the final aerogel samples.

Then these resulting cellulose aerogels were subjected to supercritical depostion (SCD) in cutom-made high pressure staninless stell vessels (57ml) to load Camphor into it. SCD method involves the drug (Camphor) dissolution in a supercritical fluid (CO_2) and the exposure of the cellulose aerogels to this solution. Drugs that have good solubility in supercritical CO_2 can be used for this method of preparation. A schematic of this method is illustrated in (Figure 2.1.1). Cellulose aerogels weighing 0.2mg were placed in SCD vessel with 200mg of Camphor in powder form and separated by a steel mesh in between. The temperature and pressure of the vessel was increased up to 40°C and 2205.03psi respectively, which lies in the range of camphor solubility in supercritical CO_2. These conditions were maintained during 1h, allowing camphor to dissolve and load into the porous cellulose aerogels. The pressure was slowly depressurized at a rate of 0.7Mpa/min at RT till atmospheric pressure was achieved. These experiments were repeated and extended up to 27 hours while keeping the initial drug content same. The resulting aerogels were placed in in sealed containers at RT until characterization.

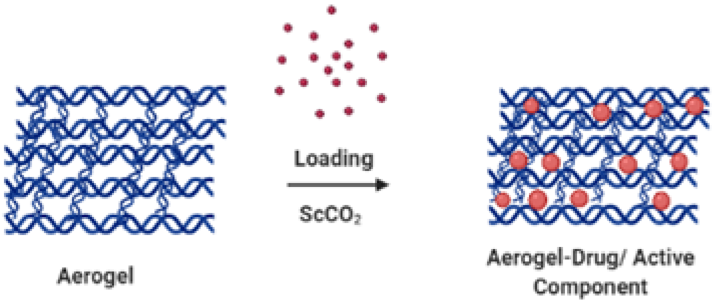


Figure. 2.1.1 Camphor loading in cellulose aerogels

2.1.1 Characterization of Camphor loaded MCC aerogel

To investigate the difference in porous structure of pure cellulose aerogel, pure camphor powder and the resulting camphor loaded cellulose aerogels, the samples were subjected to SEM analysis using field emission scanning electron microscope (zeiss ultra plus) after

4-5nm coating of gold.

ATR spectroscopy was done for the synthesized pure cellulose aerogels, pure camphor and camphor loaded cellulose aerogels using Thermoscientific Nicolet IS10 to check the camphor presence in the loaded samples. The samples were cut in to small dimensions before the measurement as required for the sample size used for IR measurement.

N_2 physiosoption (Micromeritics ASAP 2020) was used to analyze the pore properties of MCC aerogels prepared by sol-gel. Initially, the samples were degassed before measurement for 24 hours at 353K in order to remove any impurities and ethanol remained inside the aerogel pores. The degassed samples were measured for exact weight, analysis was done using the 60 point N_2 adosorption/desorption isotherms with a relative pressure (P/P_o) ranging from (10^{-7} to 1). Also, the pore size distribution was also analyzed for these cellulose aerogels using the Barret, Joyner and Halenda (BJH) method.

Camphor loaded cellulose aerogels were also subjected to effect of time on drug loading. SCD was conducted starting from 1h loading time and extended up to 20 hrs with a subsequent increase of 1h. A constant mass of drug was used to analyze the effect of time on loading. The samples loading % was analyzed on the gravimetrical basis. The initial weight of the cellulose aerogels were measured before and after SCD.

2.2 Preparation of Paracetamol loaded MCC aerogel by Freeze thaw and GAS method

Many trials have been tried so far to dissolve MCC in acqueous NaOH and the following procedure is known to be the optimum one among them. Initially, 2.5g NaOH and 1g MCC is suspended in 26.9ml of distilled water followed by shaking at room temperature so as to dissolved NaOH which results in a suspension of MCC in 8.5% NaOH solution. This suspension is then cooled at -20^{o}C and continued to stay at that temperature until freezed. This frozen mass is then allowed to thaw at RT and transforms in to a gel like mass. The resulting gels were transferred to a regenerating bath where water is used as a coagulation bath liquid. These cellulose hydrogels were then subjected to a solvent exchange process by contacting it with a series of ethanol-water solutions of ethanol concentration starting from 10, 30, 50, 70, 90 to 100% ethanol, with a 120 mins duration each.

The gels were kept in pure ethanol for 72hrs in order to eliminate any impurities or water left in the alcogel pores. Subsequently, these cellulose alcogels were contacted with a PC-ethanol solution. In this study we used an initial concentration of 0.5M PC-ethanol solution. The cellulose alcogels were immersed for 24hrs in this PC-ethanol solution so as to allow the diffusion of PC in ethanol inside the pores of cellulose alcogel.

2.2.1 Supercritical drying coupled with GAS process

Ethanol from PC loaded cellulose alcogels was removed by $scCO_2$ drying. The extraction process was performed at 40^{o}C and 90 bar using an scCO extractor (Applied Separations Speed SFE) system equipped with an extracton vessel of 25ml. The PC loaded cellulose alcogels were added in to the extraction vessel and filled with ethanol. At first, the excess ethanol inside the extraction vessel was extracted immediately which was then followed by the ethanol removal from the cellulose alcogel pores in order to completely dry it for 6-7 hours and obtain PC loaded cellulose aerogels. It was made certain that all the ethanol was completely dried and no remains were left inside. Then the sample loaded vessel was slowly depressurized so as to avoid crack formation in the final PC loaded cellulose aerogel samples.

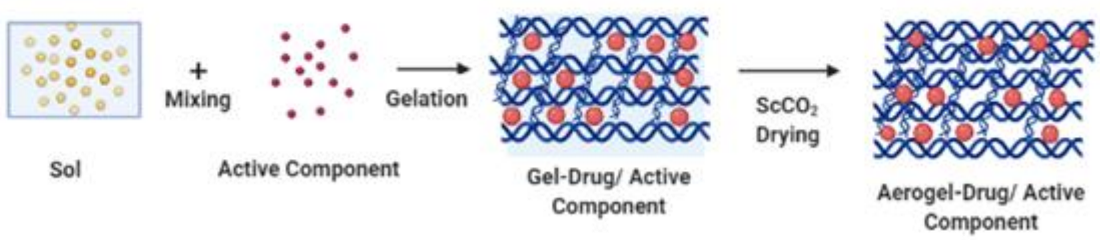


Figure 2.2.1. Loading drug/Active component during solvent exchange Process

2.2.2 Charcterization of Paracetamol loaded MCC aerogel by GAS method

SEM images were taken to investigate the morphology of pure cellulose aerogels prepared by freeze-thaw method, pure PC and PC loaded cellulose aerogels using field emission scnaning electron microscope (zeiss ultra plus) after a gold coating of 2-3nm.

ATR spectroscopy was done for the synthesized pure cellulose aerogels, pure PC and PC loaded cellulose aerogels using Thermoscientific Nicolet IS10 to check the PC presence in the loaded samples. The samples were cut in to small dimensions before the measurement as needed for the sample size used for IR measurement.

N_2 physiosoption (Micromeritics ASAP 2020) was used to analyze the pore properties of MCC aerogels prepared by freeze-thaw method. Initially, the samples were degassed before measurement for 24 hours at 353K in order to remove any impurities and ethanol remained inside the aerogel pores. The degassed samples were measured for exact weight, analysis was done using the 60 point N_2 adosorption/desorption isotherms with a relative pressure (P/P_o) ranging from (10^{-7} to 1). Also, the pore size distribution was also analyzed for these cellulose aerogels using the Barret, Joyner and Halenda (BJH) method.

The release profile of cellulose aerogels loaded PC in vitro were determined using PBS

(Poly buffer solution) as the release medium. PC loaded cellulose aerogels were placed in a beaker on a mesh wire to avoid its contact with the magnetic stirrer bar that may possibly hit and damage the aerogels. Fresh PBS was filled in the beaker and used as a release medium for PC. The release experiments of PC loaded cellulose aerogels were performed under constant stirring at 37^{o}C (Pharmacokinetics). At appropriate intervals of 5min to 24h, 1.0ml of the PBS solution (release medium) was collected and make up was done with 1.0ml of fresh PBS so as to keep the initial amount of the release medum same. The release PC amount was determined by comparing with its calibration curve using a Shimadzu UV-2550 spectrophotometer.

2.3 Preparation of MCC aerogel composite with Polyester nonwoven

Initially 5.5g of MCC was mixed with 30gdistilled water and kept at 5^{o}C for 2 hours to allow it to swell. In parallel another solution of 7.6g of NaOH dissolved in 56.9g water was prepared and was cooled at -6^{o}C. These solutions were prepared in a proportion of a total 100g solution. Then these two solutions were mixed together under continuous stirring (1000rpm) for 2 hours at -6^{o}C. Then nonwoven felt (PET) samples were soaked in the prepared MCC solution and kept for 60 mins in order to allow the diffusion of MCC solution in the PET nonwoven felt network. Then the soaked samples were suspended for 30 secs to remove any excess MCC solution and heated in an oven at 50^{o}C for 2 hours which causes the gelation of the MCC in the PET nonwoven felt network. The samples were washed several times with distilled water carefully and subjected to a series of solvent exchange steps with ethanol-water solution starting from (10, 30, 50, 70, 90 and 100% ethanol) with a duration of 120 minutes each.

The final step was to dry these cellulose alcogels inside the PET nonwoven felt with scCO$_2$ at a temperature and pressure of 40^{o}C and 90 bar respectively using an scCO$_2$ extractor (Applied Separations Speed SFE) and an extraction vessel of 25ml. The cellulose alcogels were added in to the extraction vessel and filled with ethanol. At first, the excess ethanol inside the extraction vessel was extracted immediately which was then followed by the ethanol removal from the pores of alcogel and nonwoven network in order to completely dry it for 6-7 hours and obtain cellulose aerogel composite PET nonwoven. It was made certain that all the ethanol was completely dried and no remains were left inside. Then the sample loaded vessel was slowly depressurized so as to avoid crack formation in the final aerogel samples.

Monoliths of pure MCC aerogels were also synthesized as a control sample. Pure MCC solution were transferred to the respective moulds and heated at 50 ºC in oven for 2 hours so as to cause gelation. Subsequently, ageing and $scCO_2$ drying steps were performed as for the composite samples.

2.3.1 Characterization of MCC Aerogel Composite with Polyester Nonwoven

The morphology of MCC aerogel composite with PET nonwoven was analyzed by field emission scanning electron microscope (Zeiss ultra plus). The substrates were coated with a gold layer of 2-4nm thick. The SEM images were taken at different magnifications from the cross-section and surface of fibers.

Attenuated Total Reflectance (ATR) spectroscopy was used to analyze the presence of MCC aerogel presence in the non woven structure using Thermoscientific Nicolet IS10. The substrates for measurement were prepared in to small dimensions before the measurement as needed for the substrate size used for IR measurement.

2.4 Preparation of MCC aerogel Cotton Nonwoven composite

MCC aerogels were prepared following the same method of sol-gel as previously described. Then a cotton nonwoven prepared via needle punched technique and having 350 g/m^2 (areal density) was soaked in the MCC solution for a duration of 30 mins in order to cause the diffusion of MCC solution within the nonwoven felt. Then, this MCC solution loaded cotton nonwoven felt was heated at 50 ºC in oven for 2 hours. The heating process will cause gelation of MCC solution inside the nonwoven felt network. Following gelation process, the composite was washed several times carefully with distilled water carefully and forwarded to a series of ethanol-water solutions of rising ethanol concentration (10, 30, 50, 70, 90 and 100% ethanol) at least for 120 minutes.

The final step was to dry these cellulose alcogels inside the nonwoven felt with $scCO_2$ at a temperature and pressure of 40^oC and 90 bar respectively using an $scCO_2$ extractor (Applied Separations Speed SFE) and an extraction vessel of 25ml. The cellulose alcogels were added in to the extraction vessel and filled with ethanol. At first, the excess ethanol inside the extraction vessel was extracted immediately which was then followed by the ethanol removal from the pores of alcogel and nonwoven network in order to completely dry it for 6-7 hours and obtain cellulose aerogel composite cotton nonwoven. It was made certain that all the ethanol was completely dried as cotton is a hydrophilic fiber and no remains should left inside. Then the sample loaded vessel was slowly depressurized (0.3ml/min) so as to avoid crack formation in the final aerogel samples.

Monoliths of pure MCC aerogels were also synthesized as a control sample. Pure MCC solution were transferred to the respective moulds and heated at 50 ºC in oven for 2 hours so as to cause gelation. Subsequently, ageing and $scCO_2$ drying steps were performed as for the composite samples.

2.4.1 Silver loaded MCC cellulose aerogel cotton nonwoven composite

In order to make these cellulose aerogel cotton nonwovens antibacterial, they were equipped with silver. The synthesis process for loading silver in to these composites is similar until the ageing step as for the cellulose aerogel composite without silver incorporation. When the cellulose gel cotton nonwoven composite is in 100% ethanol solution, a solution of silver nirate (0.01M) was prepared in ethanol and the composite was immersed in it for 24hrs. Drying of composite with $scCO_2$ was done similarly as for the samples without silver. The schematic of process flow of cellulose aerogel cotton nonwoven composite loaded with silver is displayed in (Figure 2.4.1).

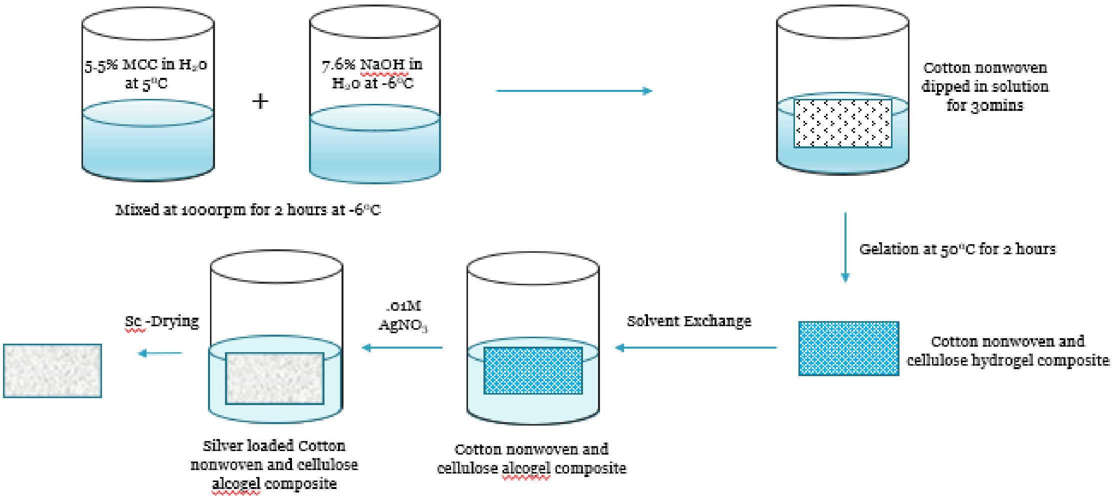


Fig 2.4.1. Schematic of Process flow of silver loaded cellulose aerogel-cotton nonwoven composite

2.4.2 Chacterization of MCC Cellulose aerogel Cotton Nonwoven composite

The morphology and porous structure of pure cellulose aerogel, pure nonwoven and their composite were investigated using field emission scanning electron microscope (Zeis ultra plus).

Attenuated Total Reflectance (ATR) was also determined for the cellulose aerogel cotton nonwoven composites using Thermoscientific Nicolet IS10 to check the cellulose aerogel creation inside the nonwoven cotton felt.

The MCC aerogel cotton nonwoven composite were also characterized for their capacity to absorb wound exudate according to standard test methods EN 13726-1:2002. Iitially

0.368 g calcium chloride dihydrate and 2.298 g and sodium chloride were dissolved in 1 liter distilled water to form a solution. This solution mimics the human serum or wound exudate ionic composition. The cellulose aerogel and composite samples were cut in to dimensions of 5 cm x 5cm and measured their dry weights.

This solution was then heated at a temperature of 37°C. After that the solution was taken equal to 40 times weight of the analyzing sample and was dispersed on these samples in separate beakers. These samples were kept at 37 °C for 30 min. Then these samples were picked from their respective beakers and suspended for 30 sec to drop down excessive solution.

Then the weight of these samples was recorded and fluid absorbency was calculated by following expression:

$$\text{Fluid absorbency (\%)} = \frac{weight\ of\ wet\ sample - weight\ of\ dry\ sample}{weight\ of\ dry\ sample} X100$$

Chapter 3

RESULTS AND DISCUSSIONS

3.1 Camphor loaded Cellulose aerogel

3.1.1 Appearance and Morphology

Cellulose hydrogel and aerogels are indicated in (Figures 3.1.1a and 3.1.1b) respectively. The produced cellulose aerogels were solid, brittle and milky white in colour as shown**.** There were no cracks observed in the cellulose aerogels monolith after supercritical drying step. There was no difference in appearance in the Cellulose aerogel after the Camphor loading.

Figure 3.1.1a. Cellulose Hydrogel

Figure 3.1.1b. Cellulose Aerogels

The SEM images of pure cellulose aerogel and Camphor is indicated in (Figures 3.1.2a, and 3.1.2b) respectively. One can see the porous network of cellulose aerogel which are interconnected. (Figure 3.1.2c) show that the Camphor is clearly incorporated in these cellulose aerogels network.

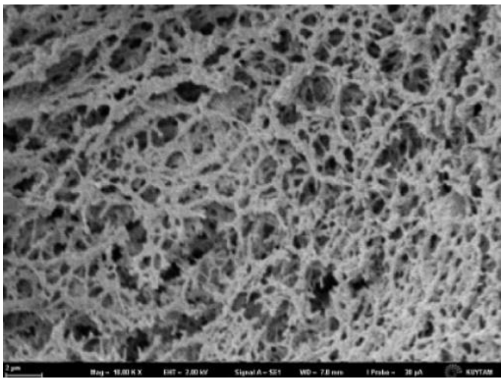


Figure 3.1.2a. Pure Cellulose aerogel

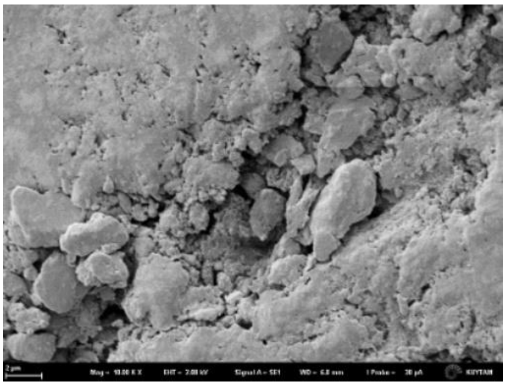


Figure 3.1.2b. Pure Camphor

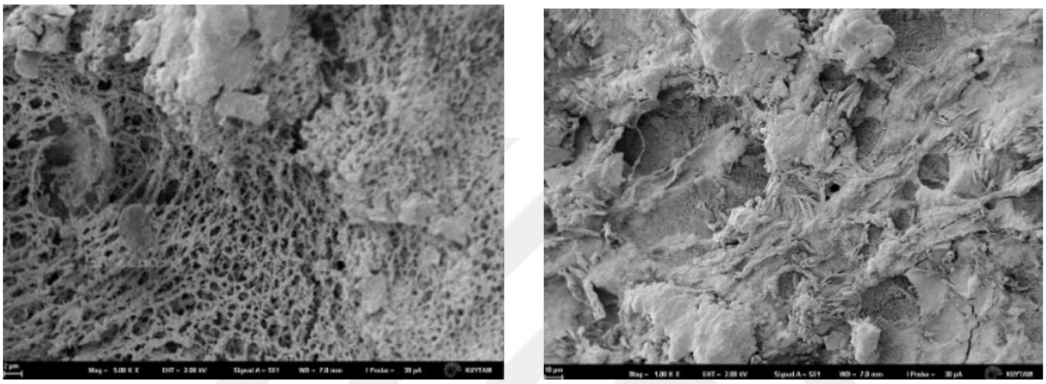


Figure 3.1.2c. Camphor loaded Cellulose aerogel

3.1.2 IR spectra

The IR spectra of pure cellulose aerogel, pure camphor and camphor loaded cellulose aerogels are shown in (Figure 3.1.3). The peaks around 1020cm^{-1} , 2900cm^{-1} and 3300cm^{-1} are attribited to C-O (stretching), C-H (stretching) and O-H respectively. The peak at 1750cm^{-1} is the characteristic peak attributed to C=O stretch in Camphor. As displayed in IR spectra, the camphor loaded cellulose aerogels comprises peaks of both pure camphor and pure cellulose aerogel.

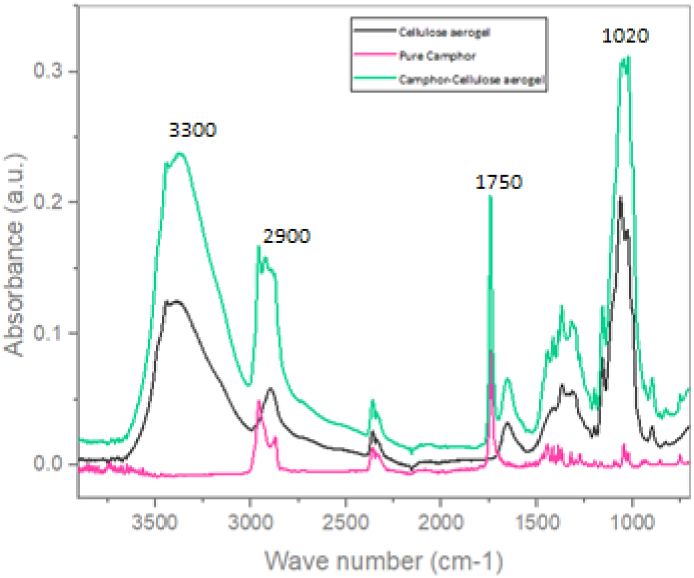


Figure 3.1.3 pure camphor, pure cellulose aerogel and camphor-cellulose aerogel IR spectra

3.1.3 Pore properties (BET)

The N2 adsorption-desorption isotherms at 77K of cellulose aerogel are indicated in (Figure 3.1.4a). The cellulose aerogels prepared using sol-gel method has shown similar profile as of adsorption isotherm (type-IV) according to IUPAC nomenclature, which indicates that the material possess mesoporous structure. (Figure 3.1.4b) represents the cellulose aerogel pore size distribution. The average pore size, BET surface area and pore volume of cellulose aerogels prepared by this method are 30nm, 338 m^2/g and 2.4 cm^3/g respectively.

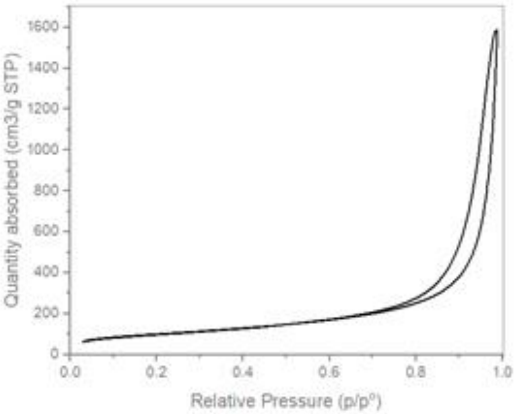


Figure 3.1.4a. N_2 adsorption Isotherm of cellulose aerogel

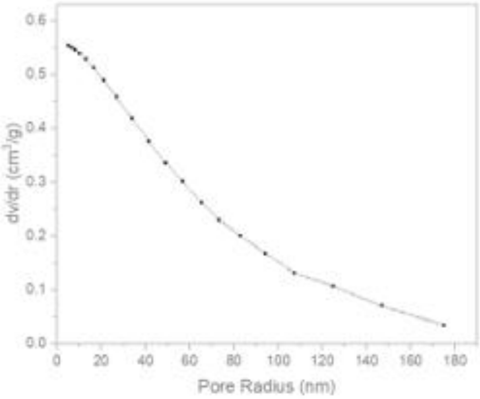


Figure 3.1.4b. Pore size distribution of cellulose aerogel

3.1.4 Effect of time on loading (Absorbate loading Vs time)

During drug loading experiments, initially a burst of 10% camphor loading was observed for the first hour and then it increased lineraly with the increase in time as shown in (Figure 3.1.5). A maximum loading of 50% of the initial mass of cellulose aerogel was observed at 18 hours and it remained constant until 20 hours. However, the integrity of cellulose aerogels remained intact until the end of experiments.

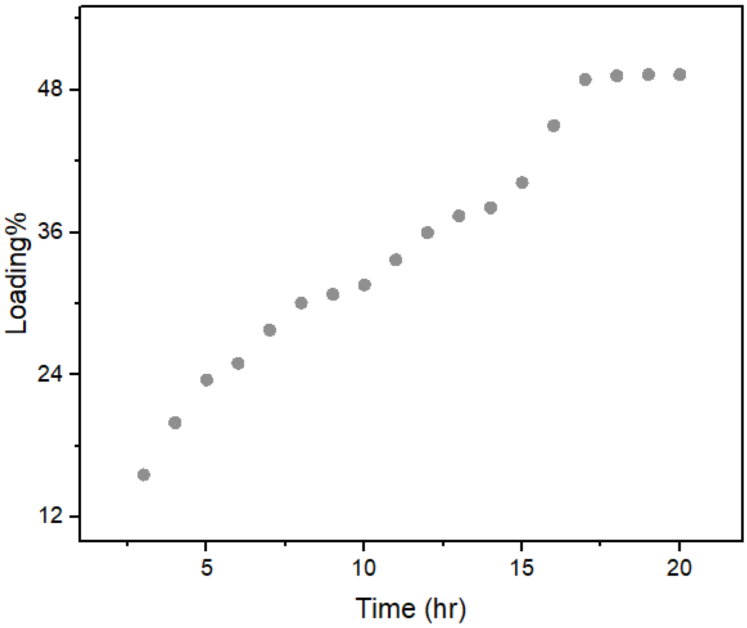


Figure 3.1.5. Effect of time on drug loading

3.2 Paracetamol loaded Cellulose aerogel

Synthesized cellulose aerogels were characterized by various techniques as explained in chapter 2.

3.2.1 Appearance and Morphology

Paracetamol loaded Cellulose aerogels were solid, brittle and milky white in color. There were no cracks observed after supercritical drying step due to slow depressurization of the system. Figure shows the appearance of PC loaded cellulose aerogels after supercritical drying coupled with GAS process.

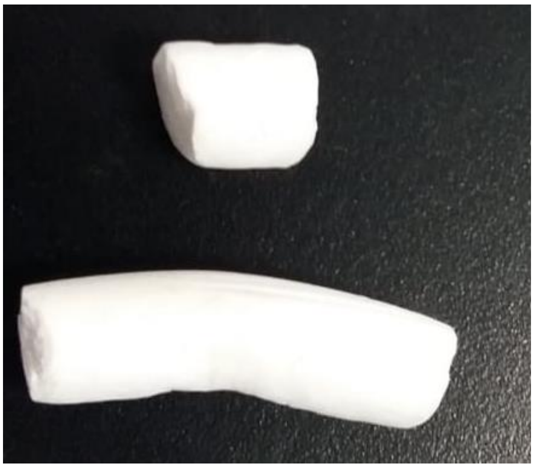


Figure 3.2.1. PC loaded Cellulose aerogels

(Figure 3.2.1) reveals the smooth and regular surface of origional paracetamol having different shapes and size. Cellulose aerogels had wide pore size distribution as seen from the SEM images of pure cellulose aerogels and Paracetamol loaded cellulose aerogels displayed in (Figure 3.2.2 and Figure 3.2.3) respectively. SEM images of pure cellulose aerogel also indicate a fibrous cross-linked structure with different sized pores. The smaller ones are quite sperical while the larger ones are elongated. The incorporation of Paracetamol into the cellulose aerogel network and the retained porous structure of cellulose aerogel is evident in the (Figure 3.2.4). The SEM image of PC loaded cellulose aerogel shows the possible crystallization of PC inside the cellulose aerogel pores during the $scCO_2$ drying step.

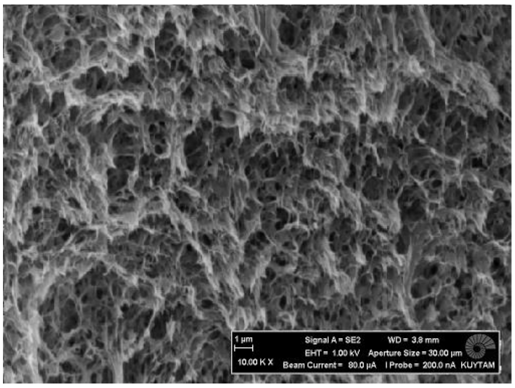


Figure 3.2.2. Pure Cellulose aerogel

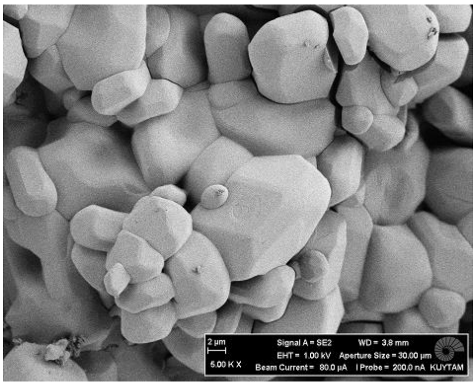


Figure 3.2.3. Pure Paracetamol

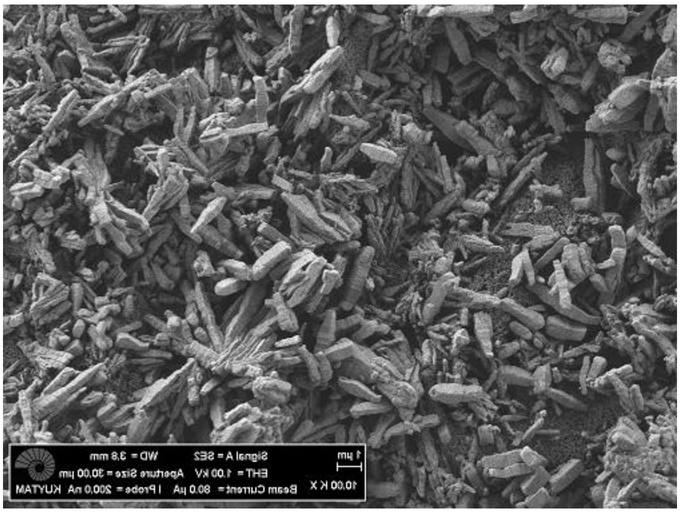


Figure 3.2.4. Paracetamol loaded Cellulose aerogel

3.2.2 IR spectra

Monolithic cellulose aerogels loaded with PC were subjected to IR after $scCO_2$ drying process. The IR spectra of PC, PC loaded cellulose aerogel and pure cellulose aerogel are displayed in (Figure 3.2.5). As indicated in IR spectra, the peaks of pure PC and pure cellulose aerogel were obvious in the PC loaded cellulose aerogels representing the presence of PC in cellulose aerogel matric.

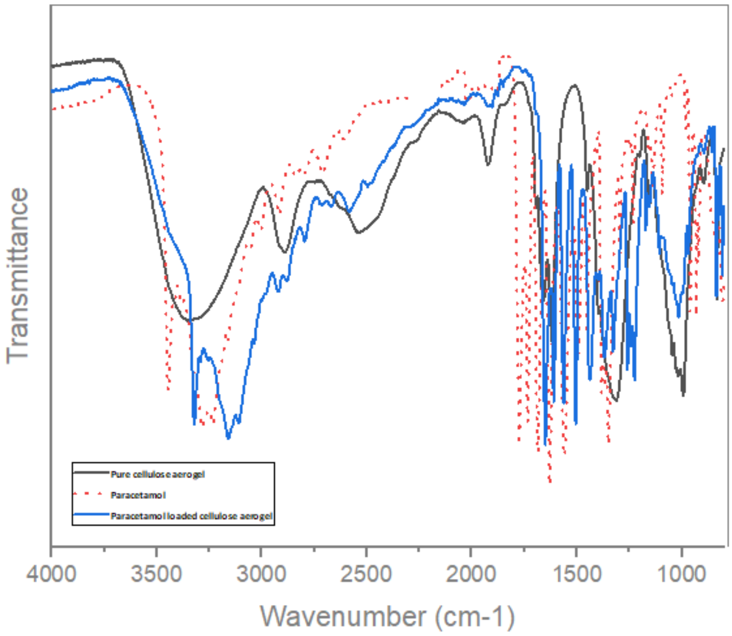


Figure 3.2.5. Pure cellulose aerogel, pure paracetamol and paracetamol loaded cellulose aerogel IR spectra

3.2.3 Pore properties (BET)

The N2 adsorption-desorption isotherms at 77K of cellulose aerogel are indicated in (Figure 3.2.6). The cellulose aerogels prepared using freeze thaw method has shown similar profile as of adsorption isotherm (type-IV) according to IUPAC nomenclature, which indicates that the material possess mesoporous structure. (Figure 3.2.7) displays cellulose aerogel pore size distribution. The BET surface area of cellulose aerogels prepared by freeze-thaw method is found to be 178m^2/g.

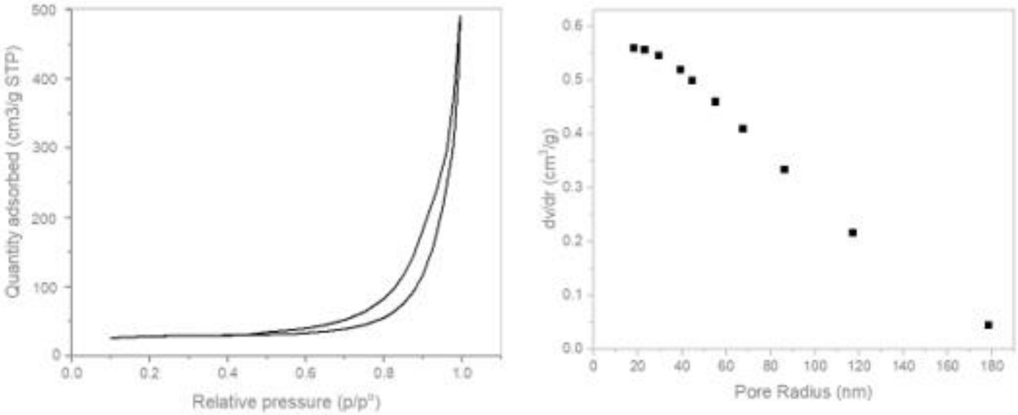


Figure 3.2.6 N_2 adsorption Isotherm of cellulose aerogel (freeze-thaw method), Figure 3.2.7. Pore size distribution of cellulose aerogel (Freeze-thaw method)

3.2.4 In Vitro Paracetamol Release Profiles

The PC release profile is displayed in (Figure 3.2.8). During release experiments, the cellulose aerogels remain integrated and did not collapsed when immersed in the release medium because of the flexibility of the polymer chains. Besides, they primalrily shrank a little and then remained intact until the end of experiment. Initially a burst release was observed until 120 mins followed by a slower drug release rate until 800mins demonstrating that these cellulose aerogels are capable as drug delivery carriers in order to achieve retarded drug release rates.

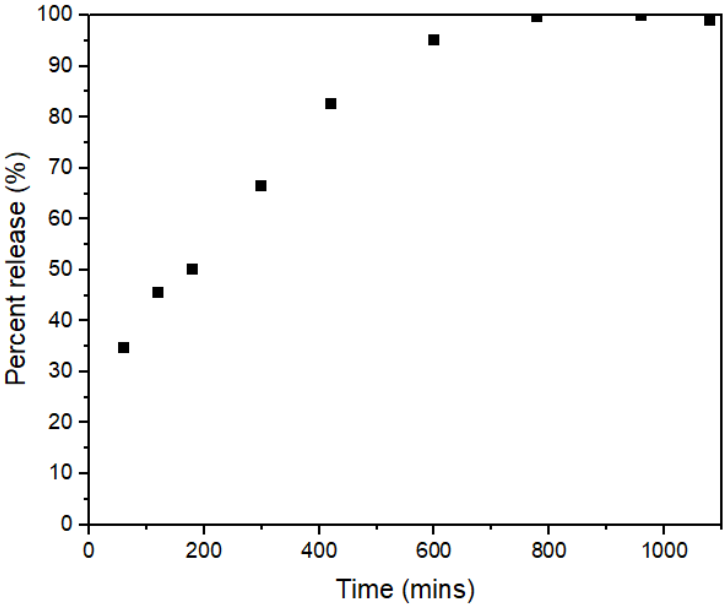


Figure 3.2.8 In-vitro paracetamol release profile

3.3 Cellulose aerogel composite with Polyester nonwoven textiles

The MCC solution diffused easily into the PET nonwoven felt because of the inherent high porosity of nonwovens. The stability and shape of this nonwoven PET felt was well-preserved even by the addition of MCC solution. Gelation of this cellulose solution was caused by applying heat up to 2 hours. The resulting gels was irreversible and remained stable at room temperature.

3.3.1 Morphology

(Figures 3.3.1 & 3.3.2) display the SEM images of pure nonwoven PET and cellulose aerogel-PET nonwoven felt. It is observed from (Figure 3.3.1), that pure PET nonwoven has an interconnected network of fibers. There are no visible pores on PET fiber’s surface itself. (Figure 3.3.3) depicts incorporation of cellulose aerogel on the surfaces and between these PET nonwoven fibers and also confirms the porous structure of cellulose aerogel incorporated in PET nonwoven felt. The PET fibrous form was retained even after the assimilation of cellulose aerogel. The PET nonwoven fibers provided reinforcement to the composite , whereas the cellulose aerogel acts as a resin.

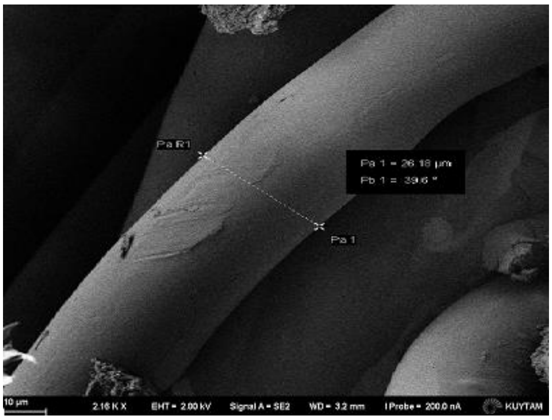


Figure 3.3.1. Polyester nonwoven felt

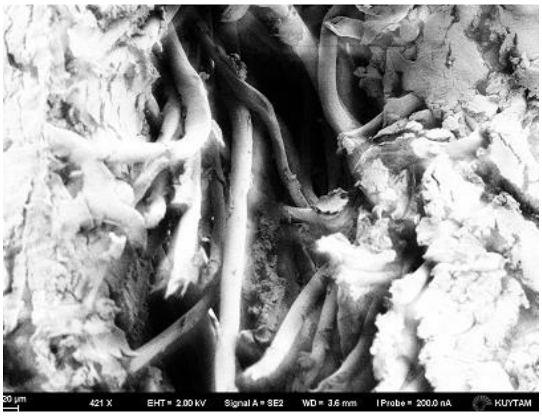


Figure 3.3.2. Cellulose aerogel PET nonwoven composite

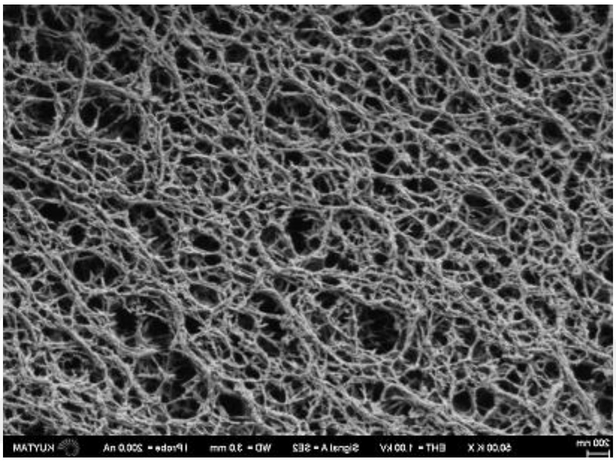


Figure 3.3.3. Porous cellulose aerogel PET nonwoven composite

3.3.2 IR spectra

Polyester nonwoven-cellulose aerogel composite and pure cellulose aerogel IR spectra are given in (Figure 3.3.4). The corresponding peaks at 1712 cm^{-1} and 1408 cm^{-1} corresponds to C=O vibration and aromatic ring respectively, which are the characteristic peaks of pure polyester. The peaks around 1020cm^{-1} , 2900cm^{-1} and 3300cm^{-1} are attribited to C-O (stretching), C-H (stretching) and O-H respectively. It was also pragmatic that the composite spectra comprises peaks from both, the pure cellulose aerogel and pure polyester nonwoven felt.

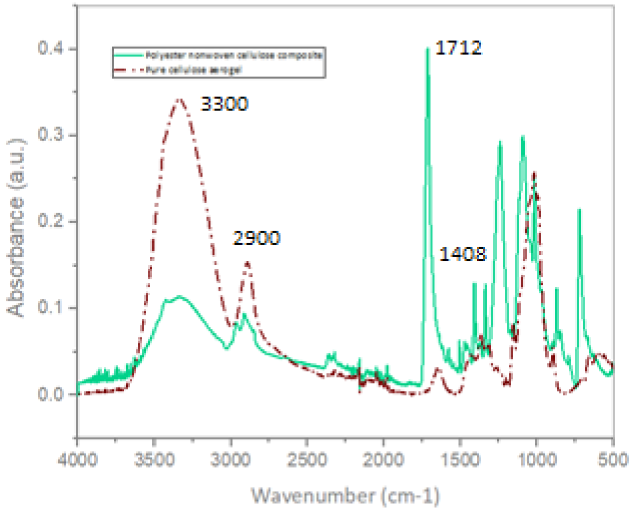


Figure 3.3.4 Pure cellulose aerogel and cellulose aerogel composite with polyester nonwoven IR spectra

3.4 MCC aerogel cotton nonwoven composite

The MCC solution simply diffused into the cotton felt because of the inherent high porosity of nonwovens. The stability and shape of cotton nonwoven felt was well-preserved even with the addition of MCC. Heat was applied for 2 hours (50°C) to cause the gelation of MCC. The resulting gels was irreversible and remained stable at room temperature.

3.4.1 Appearance and Morphology

The images of pure cellulose hydrogel and cellulose hydrogel cotton nonwoven composite are displayed in (Figures 3.4.1a & 3.4.1b) respectively. The texture and surface of cellulose aerogel cotton nonwoven composite is smooth and neat. Some impurities were detected in the composite material that came inherently from the pure cotton nonwoven since cotton is a natural polymer and these impurities are commonly found in cotton nonwoven felts.

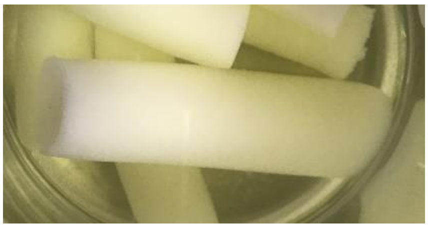


Figure 3.4.1a. Cellulose Hydrogel

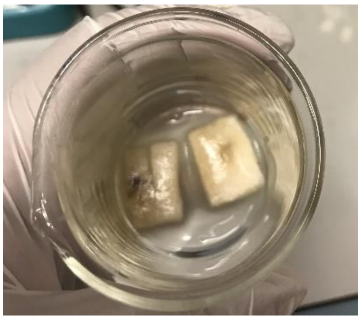


Figure3.4.1b. Cellulose aerogel-cotton nonwoven

The (Figures 3.4.2 and 3.4.3) displays the SEM image of pure cotton nonwoven and cellulose aerogel composite. The fibers (Figure 3.4.2) are found to have random orientation inside the nonwoven network. The cellulose aerogel incorporation is obvious in the form of blocks (Figure 3.4.3) between empty spaces inside the nonwoven network. The fibrous form of cotton is retained even after the assimilation of cellulose aerogel. Nonwoven fibers act as a reinforcement, whereas the cellulose aerogel works as a resin in the resulting material. The cellulose aerogel possess a porous structure inside the cotton nonwoven felt is displayed in (Figure 3.4.4).

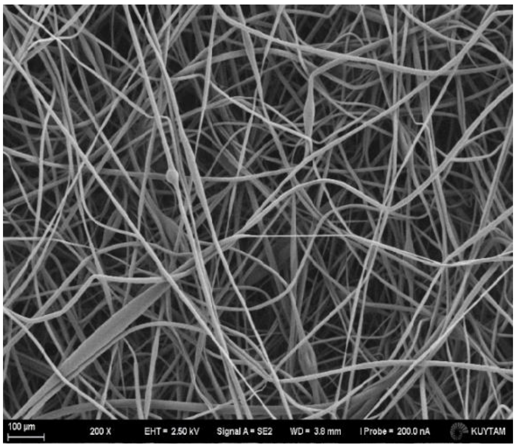


Figure 3.4.2 Pure cotton nonwoven

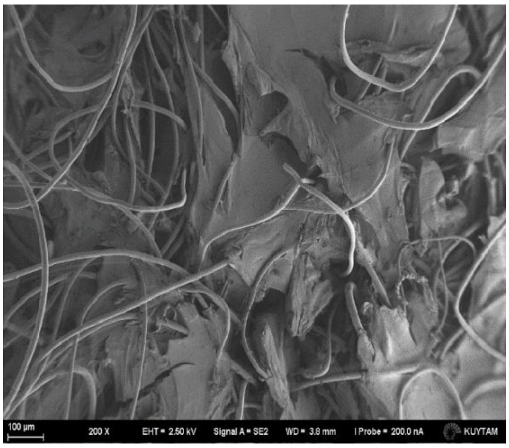


Figure 3.4.3 Cellulose aerogel nonwoven composite

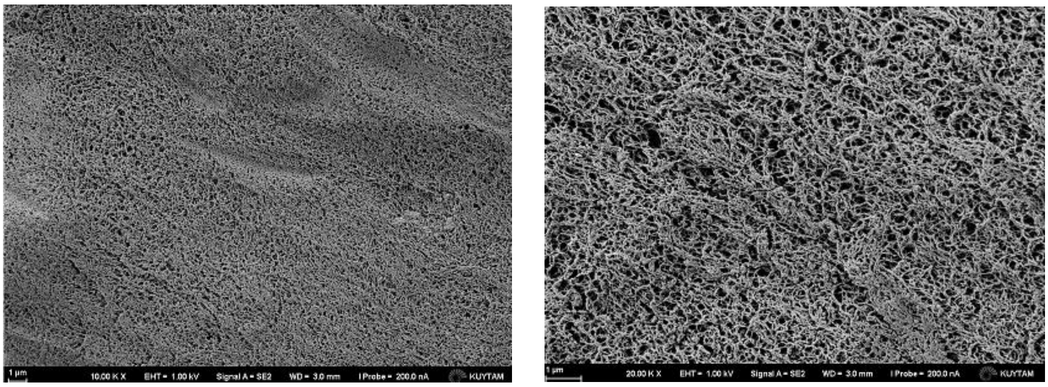


Figure 3.4.4. Cellulose aerogel cotton nonwoven composite

3.4.2 IR spectra

Figure 3.4.5 shows the IR spectra of pure cotton nonwoven , pure cellulose aerogel and their composite. The corresponding peaks at 3300 cm^{-1}, 2900 cm^{-1}, 1650 cm^{-1}, 1370 cm^{-1}, and 1030 cm^{-1} are ascribed to O-H, C-H (stretching), H-O-H, C-H (bending) and C-O (stretching) respectively. The composite IR spectra comprises characteristic peaks of both, the pure cotton nonwoven and pure cellulose aerogel.

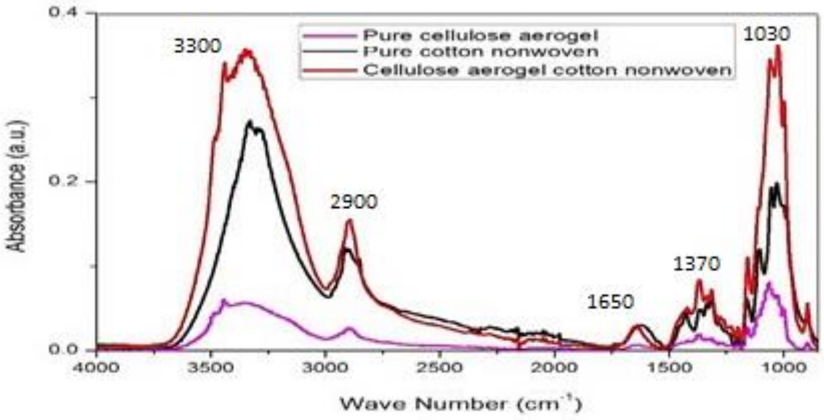


Figure 3.4.5. Pure cotton nonwoven, pure cellulose and cellulose aerogel cotton nonwoven composite IR spectra

3.4.3 Wound Exudate Absorbency

The wound exudate absorbency was determined according to standard test method EN 13726-1:2002. The wound exudate absorbencies of cotton nonwoven and aerogel composite were found to be as 80 % and 350 % respectively. Cotton is a hydrophilic material whereas, the cotton nonwoven textile has a highly porous structure. Which indicates that the arrangement of cotton in the form of nonwoven makes it a highly absorbent material (wound exudate). Moreover, the cellulose aerogel is a superabsorbent material. Cellulose aerogel is incorporated into cotton nonwoven textile in the form of nano porous blocks yielding higher absorbencies. The fluid absorbency of this composite material is approximately four times higher than that of pure cotton nonwoven which is mainly accredited to the cellulose aerogel porous structure.

Chapter 4

CONCLUSION AND FUTURE WORK

Aerogel based textiles have become intriguing materials for the researchers in the field of medical textiles, erosion control, sound absorption, oil/water absorption, and thermal insulation due to their unique and fascinating properties. In this work, aerogel based textile materials were developed in form of aerogels and composites with nonwoven textiles. Novel materials consiting of drugs loaded cellulose aerogels and nonwoven composites were synthesized for the first time. The specific surface area of the produced cellulose aerogels was also determined and was found to be 338 m^2/g and 178 m^2/g for sol-gel and freeze-thaw method respectively. Furthermore, the cellulose aerogels were found to be mesoporous up to 96% porosity.

To analyze the produced cellulose aerogels as drug delivery materials, PC was selected as a model drug because of its high ethanol solubility and limited/no $scCO_2$ solubility. These synthesized alcogels were then successfully contacted with a solution of PC in ethanol for loading purpose. The use of $scCO_2$ drying method caused PC precipitation in the aerogel pores, which is alike GAS process. The monolithic structure and porous characteristic of resulting PC loaded cellulose aerogels were intact according to SEM analysis. This method of loading have certainly a good scope specially for drug delivery systems due to possibility of loading for a variety of pharmaceutical compounds. Furthermore, this technique permits a facile and novel approach for loading drugs into cellulose aerogels which are becoming interestingly significant in various fields. This method has an advantage of combining two processes (drug loading and drying) in a single process thus reducing the cost and time of production.

The research on using cellulose based aerogels as drug delivery carriers is increasing rapidly, thus various loading methods have already been devised with different cellulose aerogel types. In this work, $scCO_2$ deposition method was applied to load drug into cellulose aerogels. $ScCO_2$ can act as a good solvent medium for dissolving pharmaceutical compounds, and also thought to be inert and non-flammable. $ScCO_2$ medium is a good substitute for drugs that are insoluble in water. This technique is applicable to the compounds with higher soluble in $scCO_2$. Camphor was used as a model drug in this study because of its high solubility in $scCO_2$. The process starts with solubilization of drug in $scCO_2$, and is exposed to cellulose aerogel followed by depressurization and removal of $ScCO_2$. Thus, the $scCO_2$ leaves the cellulose aerogel matrix quickly with camphor inside. Loadings as high as 50 wt.% for cellulose aerogels were obtained while keeping the integrity of the cellulose aerogel intact.

The cellulose aerogel composite with cotton nonwoven was synthesized by soaking cotton nonwoven textile in the MCC solution. Heating the composite material causes gelation, which was later subjected to $scCO_2$ drying to attain cellulose aerogel cotton nonwoven composite. The cellulose aerogel was formed inside the cotton nonwoven textile in the form of blocks and also act as a reinforcement to the nonwoven textile network. The synthesized composite was found to be very absorbent to wound exudate (fluid). The absorbency test was carried out using the standard test method of fluid absorbency for wound dressings. Moreover, silver was added into this composite material to achieve antibacterial properties. Different initial concentrations of cellulose, ratios of cellulose aerogel with cotton nonwoven composites and concentrations of silver can be used and investigated to have a better understanding of their effect on the final properties of the composite material.

Overall, this dissertation contributes in understanding the possible usage of cellulose aerogels as drug delivery carriers indicating that cellulose aerogels display a great potential in drug delivery systems. The optimum loading and release profiles of the pharmaceutical compounds can be modified by varying the synthesis conditions. In view of the growing importance of cellulose based aerogels in various applications, their role in medical textiles can be anticipated to raise in the coming years.

Chapter 5

BIBLIOGRAPHY

1. Robson, S.D.F.M., MC Wound healing: Biological features and approaches to maximize healing trajectories. Curr. Probl. Surg. 38(2): p. 65-140.
2. Szycher, M. and S.J. Lee, Modern wound dressings: a systematic approach to wound healing. Journal of biomaterials applications, 1992. 7(2): p. 142-213.
3. Schreml, S., et al., Oxygen in acute and chronic wound healing. British Journal of Dermatology, 2010. 163(2): p. 257-268.
4. Rajendran, S. and S. Anand, Hi-tech textiles for interactive wound therapies, in Handbook of medical textiles. 2011, Elsevier. p. 38-79.
5. Lazarus, G.S., et al., Definitions and guidelines for assessment of wounds and evaluation of healing. Wound repair and regeneration, 1994. 2(3): p. 165-170.
6. Bischoff, M., L. Kinzl, and A. Schmelz, The complicated wound. Der Unfallchirurg, 1999. 102(10): p. 797-804.
7. Miguel, S.P., et al., Electrospun polymeric nanofibres as wound dressings: A review. Colloids and surfaces B: Biointerfaces, 2018. 169: p. 60-71.
8. Boateng, J.S., et al., Wound healing dressings and drug delivery systems: a review. Journal of pharmaceutical sciences, 2008. 97(8): p. 2892-2923.
9. Zarrintaj, P., et al., Can regenerative medicine and nanotechnology combine to heal wounds? The search for the ideal wound dressing. Nanomedicine, 2017. 12(19): p. 2403-2422.
10. George Broughton, I., J.E. Janis, and C.E. Attinger, A brief history of wound care. Plastic and reconstructive surgery, 2006. 117(7S): p. 6S-11S.
11. Sipos, P., et al., Special wound healing methods used in ancient Egypt and the mythological background. World journal of surgery, 2004. 28(2): p. 211.
12. Rogers, A., et al., Adsorption of serum-derived proteins by primary dressings: implications for dressing adhesion to wounds. Journal of wound care, 1999. 8(8): p. 403-406.

13. Alvarez, O., Moist environment for healing: matching the dressing to the wound. Ostomy/wound management, 1988. 21: p. 64.

14. Reddy, M., et al., Practical treatment of wound pain and trauma: a patient-centered approach. An overview. Ostomy/wound management, 2003. 49(4 Suppl): p. 2-15.

15. Winter, G.D., Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. Nature, 1962. 193(4812): p. 293-294.

16. Eaglstein, W.H., Moist wound healing with occlusive dressings: a clinical focus. Dermatologic surgery, 2001. 27(2): p. 175-182.

17. Foertsch, C., et al., Treatment-resistant pain and distress during pediatric burn-dressing changes. The Journal of burn care & rehabilitation, 1998. 19(3): p. 219-224.

18. Nemeth, A.J., et al., Faster healing and less pain in skin biopsy sites treated with an occlusive dressing. Archives of dermatology, 1991. 127(11): p. 1679-1683.

19. Rubio, P., Use of semiocclusive, transparent film dressings for surgical wound protection: experience in 3637 cases. International surgery, 1991. 76(4): p. 253-254.

20. Eisenberg, M., The effect of occlusive dressing on re-epithelializations of wounds in children with epidermolysis bullosa. Journal of pediatric surgery, 1986. 21(10): p. 892-894.

21. Eaglstein, W., P. Mertz, and V. Falanga, Occlusive dressings. American family physician, 1987. 35(3): p. 211-216.

22. Eaglstein, W.H., Experiences with biosynthetic dressings. Journal of the American Academy of Dermatology, 1985. 12(2): p. 434-440.

23. Ehleben, C.M., S.R. May, and J.M. Still Jr, Pain associated with an adherent polyurethane wound dressing. Burns, 1985. 12(2): p. 122-126.

24. Harding, K., V. Jones, and P. Price, Topical treatment: which dressing to choose. Diabetes/metabolism research and reviews, 2000. 16(S1): p. S47-S50.

25. Campbell, K., et al., A clinical evaluation of 3M no sting barrier film. Ostomy/wound management, 2000. 46(1): p. 24-30.

26. Burge, T., Removing adhesive retention dressings. British journal of plastic surgery, 2004. 57(1): p. 93.

27. Baxter, H., A comparison of two hydrocolloid sheet dressings. British Journal of Community Nursing, 2000. 5(11): p. 572-577.

28. Chang, K., et al., Pressure ulcers--randomised controlled trial comparing hydrocolloid and saline gauze dressings. The Medical Journal of Malaysia, 1998. 53(4):

p. 428-431.

29. Tracy, G., et al., Varihesive sealed dressing for indolent leg ulcers. Medical Journal of Australia, 1977. 1(21): p. 777-780.

30. Friedman, S.J. and W.D. Su, Management of leg ulcers with hydrocolloid occlusive dressing. Archives of dermatology, 1984. 120(10): p. 1329-1336.

31. Heffernan, A. and A. Martin, A comparison of a modified form of Granuflex (Granuflex Extra Thin) and a conventional dressing in the management of lacerations, abrasions and minor operation wounds in an accident and emergency department. Emergency Medicine Journal, 1994. 11(4): p. 227-230.

32. Martini, L., et al., Comparison of two dressings in the management of partial-thickness donor sites. Journal of wound care, 1999. 8(9): p. 457-460.

33. Ashford, R., N. Freear, and J. Shippen, An in-vitro study of the pressure-relieving properties of four wound dressings for foot ulcers. Journal of wound care, 2001. 10(2): p. 34-38.

34. Ballard, K., The Tielle family of dressings: overview of the product range. British Journal of Nursing, 2001. 10(12): p. 808-814.

35. Carter, K., Hydropolymer dressings in the management of wound exudate. British journal of community nursing, 2003. 8(Sup3): p. S10-S16.

36. Fletcher, J., The application of foam dressings. Nursing times, 2003. 99(31): p. 59-59.

37. Kammerlander, G. and T. Eberlein, Use of Allevyn Heel in the management of heel ulcers. Journal of wound care, 2003. 12(8): p. 313-315.

38. Thomas, S., et al., A comparison of two dressings in the management of chronic wounds. Journal of Wound Care, 1997. 6(8): p. 383-386.

39. Ballard, K., Clinical and scientific data of a hydropolymer range of dressings. British journal of nursing, 2002. 11(Sup4): p. S37-S43.

40. Viamontes, L., et al., An evaluation of an adhesive hydrocellular foam dressing and a self-adherent soft silicone foam dressing in a nursing home setting. Ostomy/wound management, 2003. 49(8): p. 48-52, 54.

41. Bale, S., et al., Exploring the use of an alginate dressing for diabetic foot ulcers. Journal of wound care, 2001. 10(3): p. 81-84.

42. PIACQUADIO, D. and D.B. NELSON, Alginates: A “New” Dressing Alternative: A “New” Dressing Alternative. The Journal of dermatologic surgery and oncology, 1992. 18(11): p. 992-995.

43. Whittle, H., et al., Nursing management of pressure ulcers using a hydrogel dressing protocol: four case studies. Rehabilitation Nursing, 1996. 21(5): p. 239-242.

44. Misterka, S., Clinical evaluation of hydrogel-type dressing materials after their 8-year use. Polimery w medycynie, 1991. 21(1-2): p. 23.

45. Sedlarik, K., et al., Modern dressings. Hydrogels. Rozhledy v Chirurgii: Mesicnik Ceskoslovenske Chirurgicke Spolecnosti, 1995. 74(1): p. 3-7.

46. Agren, M., An amorphous hydrogel enhances epithelialisation of wounds. Acta Dermato Venereologica, 1998. 78(2): p. 119-122.

47. Kickhöfen, B., et al., Chemical and physical properties of a hydrogel wound dressing. Biomaterials, 1986. 7(1): p. 67-72.

48. Mandy, S.H., A new primary wound dressing made of polyethylene oxide gel. The Journal of dermatologic surgery and oncology, 1983. 9(2): p. 153-155.

49. Chang, C. and L. Zhang, Cellulose-based hydrogels: Present status and application prospects. Carbohydrate polymers, 2011. 84(1): p. 40-53.

50. Stergar, J. and U. Maver, Review of aerogel-based materials in biomedical applications. Journal of Sol-Gel Science and Technology, 2016. 77(3): p. 738-752.

51. Soorbaghi, F.P., et al., Bioaerogels: Synthesis approaches, cellular uptake, and the biomedical applications. Biomedicine & Pharmacotherapy, 2019. 111: p. 964-975.

52. Pilehvar-Soltanahmadi, Y., et al., An overview on application of natural substances incorporated with electrospun nanofibrous scaffolds to development of innovative wound dressings. Mini reviews in medicinal chemistry, 2018. 18(5): p. 414-427.

53. Hrubesh, L.W., Aerogel applications. Journal of Non-Crystalline Solids, 1998. 225: p. 335-342.

54. Gupta, P., et al., Low density and high strength nanofibrillated cellulose aerogel for thermal insulation application. Materials & Design, 2018. 158: p. 224-236.

55. Ko, E., et al., Morphological study of cellulosic hydrogel nanofiber for biomedical application. Cellulose, 2019. 26(17): p. 9107-9118.

56. Séon-Lutz, M., et al., Electrospinning in water and in situ crosslinking of hyaluronic acid/cyclodextrin nanofibers: Towards wound dressing with controlled drug release. Carbohydrate polymers, 2019. 207: p. 276-287.

57. Long, L.-Y., Y.-X. Weng, and Y.-Z. Wang, Cellulose aerogels: Synthesis, applications, and prospects. Polymers, 2018. 10(6): p. 623.

58. Shera, S.S., N. Kulhar, and R.M. Banik, Silk and silk fibroin-based biopolymeric

composites and their biomedical applications, in Materials for Biomedical Engineering. 2019, Elsevier. p. 339-374.

59. Ioelovich, M., Cellulose as a nanostructured polymer: a short review. BioResources, 2008. 3(4): p. 1403-1418.

60. Wang, S., A. Lu, and L. Zhang, Recent advances in regenerated cellulose materials. Progress in Polymer Science, 2016. 53: p. 169-206.

61. Sharma, R.K., R. Kumar, and A.P. Singh, Metal ions and organic dyes sorption applications of cellulose grafted with binary vinyl monomers. Separation and Purification Technology, 2019. 209: p. 684-697.

62. Marques-Marinho, F., et al., Cellulose—Medical, Pharmaceutical and Electronic Applications. 2013, InTech Open.

63. Wertz, J.-L., O. Bédué, and J.P. Mercier, Cellulose science and technology. 2010: EPFL press.

64. Klemm, D., et al., Cellulose: fascinating biopolymer and sustainable raw material. Angewandte chemie international edition, 2005. 44(22): p. 3358-3393.

65. Klemm, D., et al., Comprehensive cellulose chemistry. Volume 1: Fundamentals and analytical methods. 1998: Wiley-VCH Verlag GmbH.

66. Ummartyotin, S. and H. Manuspiya, A critical review on cellulose: from fundamental to an approach on sensor technology. Renewable and Sustainable Energy Reviews, 2015. 41: p. 402-412.

67. Rehman, N., et al., Ecofriendly Isolation of Cellulose from Eucalyptus lenceolata: A Novel Approach. International Journal of Polymer Science, 2018. 2018.

68. Draman, S.F.S., R. Daik, and N. Mohd, Eco-friendly extraction and characterization of cellulose from lignocellulosoic fiber. ARPN Journal of Engineering and Applied Sciences, 2016. 11(16): p. 9591-9595.

69. Chávez-Guerrero, L., et al., Eco-friendly isolation of cellulose nanoplatelets through oxidation under mild conditions. Carbohydrate polymers, 2018. 181: p. 642-649.

70. Rowe, R.C., P. Sheskey, and M. Quinn, Handbook of pharmaceutical excipients. 2009: Libros Digitales-Pharmaceutical Press.

71. Zugenmaier, P., Conformation and packing of various crystalline cellulose fibers. Progress in polymer science, 2001. 26(9): p. 1341-1417.

72. O'sullivan, A.C., Cellulose: the structure slowly unravels. Cellulose, 1997. 4(3): p. 173-207.

73. de Oliveira Barud, H.G., et al., A multipurpose natural and renewable polymer in

medical applications: Bacterial cellulose. Carbohydrate Polymers, 2016. 153: p. 406-420.

74. Chawla, P.R., et al., Microbial cellulose: fermentative production and applications. Food Technology and Biotechnology, 2009. 47(2): p. 107-124.

75. Sai, H., et al., Flexible aerogels with interpenetrating network structure of bacterial cellulose–silica composite from sodium silicate precursor via freeze drying process. RSC Advances, 2014. 4(57): p. 30453-30461.

76. Klemm, D., et al., Nanocelluloses: a new family of nature-based materials. Angewandte Chemie International Edition, 2011. 50(24): p. 5438-5466.

77. Fu, J., et al., Facilitated fabrication of high strength silica aerogels using cellulose nanofibrils as scaffold. Carbohydrate polymers, 2016. 147: p. 89-96.

78. Lindman, B., G. Karlström, and L. Stigsson, On the mechanism of dissolution of cellulose. Journal of molecular liquids, 2010. 156(1): p. 76-81.

79. Li, Y., et al., Preparation of corn straw based spongy aerogel for spillage oil capture. Korean Journal of Chemical Engineering, 2018. 35(5): p. 1119-1127.

80. Ciftci, D., et al., Lupin hull cellulose nanofiber aerogel preparation by supercritical CO2 and freeze drying. The Journal of Supercritical Fluids, 2017. 127: p. 137-145.

81. Delgado Aguilar, M., et al., Cellulose nanofibers modified with alkyl ketene dimer for oil absorbent aerogels. © Cellulose Chemistry and Technology, 2016, vol. 50, núm. 3-4, p. 369-375, 2016.

82. Chen, W., et al., Ultralight and highly flexible aerogels with long cellulose I nanofibers. Soft matter, 2011. 7(21): p. 10360-10368.

83. Perez-Cantu, L., F. Liebner, and I. Smirnova, Preparation of aerogels from wheat straw lignin by cross-linking with oligo (alkylene glycol)-α, ω-diglycidyl ethers. Microporous and mesoporous materials, 2014. 195: p. 303-310.

84. Dufresne, A., D. Dupeyre, and M.R. Vignon, Cellulose microfibrils from potato tuber cells: processing and characterization of starch–cellulose microfibril composites. Journal of Applied Polymer Science, 2000. 76(14): p. 2080-2092.

85. Virtanen, T., et al., A physico-chemical characterisation of new raw materials for microcrystalline cellulose manufacturing. Cellulose, 2012. 19(1): p. 219-235.

86. Feng, J., et al., Advanced fabrication and oil absorption properties of super-hydrophobic recycled cellulose aerogels. Chemical Engineering Journal, 2015. 270: p. 168-175.

87. Liebner, F., et al., Cellulose aerogels: highly porous, ultra-lightweight materials.

Holzforschung, 2008. 62(2): p. 129-135.

88. Xiao, S., et al., Fabrication and characterization of nanofibrillated cellulose and its aerogels from natural pine needles. Carbohydrate polymers, 2015. 119: p. 202-209.

89. Lin, J., et al., Cellulose nanofibrils aerogels generated from jute fibers. Carbohydrate polymers, 2014. 109: p. 35-43.

90. Jiang, F. and Y.-L. Hsieh, Amphiphilic superabsorbent cellulose nanofibril aerogels. Journal of Materials Chemistry A, 2014. 2(18): p. 6337-6342.

91. Kim, C.H., H.J. Youn, and H.L. Lee, Preparation of cross-linked cellulose nanofibril aerogel with water absorbency and shape recovery. Cellulose, 2015. 22(6): p. 3715-3724.

92. Yang, H., A. Sheikhi, and T.G. Van De Ven, Reusable green aerogels from cross-linked hairy nanocrystalline cellulose and modified chitosan for dye removal. Langmuir, 2016. 32(45): p. 11771-11779.

93. Hengstberger, M., O. Kaltenecker, and W. Oppermann, Vliesstoffe mit superabsorbierenden Eigenschaften. Tech Textil, 1999. 42: p. 295-297.

94. JIN, J., et al., DOPING/DEDOPING PROCESS INDUCED WETTABILITY SWITCHING OF POLYANILINE-COATED CONDUCTIVE TEXTILE [J]. Acta Polymerica Sinica, 2010. 2.

95. Hyde, G.K., et al., Atomic layer deposition of titanium dioxide on cellulose acetate for enhanced hemostasis. Biotechnology journal, 2011. 6(2): p. 213-223.

96. Durso, D., CHEMICAL MODIFICATION OF CELLULOSE A HISTORICAL REVIEW, in Modified cellulosics. 1978, Elsevier. p. 23-37.

97. Fengel, D. and G. Wegener, Reactions in alkaline medium. Wood: Chemistry, Ultrastructure, Reaction, Walter de Gruyter, Berlin. New York. pp, 1984: p. 296-318.

98. Freytag, R., Alkali Teatment of Cellulose Fibers. Handbook of Fiber Science and Technology; Vol. I, Chemical Processing of Fibers and Fabrics, Fundamentals and Preparation, Part, 1983. 93.

99. Lewin, M. and S.B. Sello, B leaching of C e llu losic and Syn th e tic Fab rics, in Handbook of Fiber Science and Technology: Volume 1. 2017, Routledge. p. 115-189.

100. Breitwieser, D., et al., Design of simultaneous antimicrobial and anticoagulant surfaces based on nanoparticles and polysaccharides. Journal of Materials Chemistry B, 2013. 1(15): p. 2022-2030.

101. Chekmareva, I., Experimental study of reparative regeneration processes in the wound treated with bioactive dressings. Bulletin of experimental biology and medicine,

2002. 133(2): p. 192-195.

102. Hart, J., et al., The role of oxidised regenerated cellulose/collagen in wound repair: effects in vitro on fibroblast biology and in vivo in a model of compromised healing. The international journal of biochemistry & cell biology, 2002. 34(12): p. 1557-1570.

103. Liu, B., J. Hu, and Q. Meng, Nonwoven supported temperature-sensitive poly (N-isopropylacrylamide)/polyurethane copolymer hydrogel with antibacterial activity. Journal of Biomedical Materials Research Part B: Applied Biomaterials: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials, 2009. 89(1): p. 1-8.

104. An, J., et al., Preparation and antibacterial activity of electrospun chitosan/poly (ethylene oxide) membranes containing silver nanoparticles. Colloid and Polymer Science, 2009. 287(12): p. 1425-1434.

105. Madhumathi, K., et al., Development of novel chitin/nanosilver composite scaffolds for wound dressing applications. Journal of Materials Science: Materials in Medicine, 2010. 21(2): p. 807-813.

106. Watthanaphanit, A., et al., Wet-spun alginate/chitosan whiskers nanocomposite fibers: Preparation, characterization and release characteristic of the whiskers. Carbohydrate Polymers, 2010. 79(3): p. 738-746.

107. Wu, Y.-B., et al., Preparation and characterization on mechanical and antibacterial properties of chitsoan/cellulose blends. Carbohydrate Polymers, 2004. 57(4): p. 435-440.

108. Kontogiannopoulos, K.N., et al., Electrospun fiber mats containing shikonin and derivatives with potential biomedical applications. International journal of pharmaceutics, 2011. 409(1-2): p. 216-228.

109. Mikhaylova, A., et al., Preclinical evaluation of antimicrobial efficacy and biocompatibility of a novel bacterial barrier dressing. Wounds, 2011. 23(2): p. 24.

110. Fras Zemljič, L., Z. Persin, and P. Stenius, Improvement of chitosan adsorption onto cellulosic fabrics by plasma treatment. Biomacromolecules, 2009. 10(5): p. 1181-1187.

111. Reichel, V.E., Functionalization of cellulose acetate surfaces for the removal of endocrine disrupting compounds. 2012: na.

112. Cady, N.C., J.L. Behnke, and A.D. Strickland, Copper-based nanostructured

coatings on natural cellulose: Nanocomposites exhibiting rapid and efficient inhibition of a multi-drug resistant wound pathogen, A. baumannii, and mammalian cell biocompatibility in vitro. Advanced Functional Materials, 2011. 21(13): p. 2506-2514.

113. Hüsing, N. and U. Schubert, Aerogels—airy materials: chemistry, structure, and properties. Angewandte Chemie International Edition, 1998. 37(1-2): p. 22-45.

114. Gesser, H. and P. Goswami, Aerogels and related porous materials. Chemical Reviews, 1989. 89(4): p. 765-788.

115. Gurav, J.L., et al., Silica aerogel: synthesis and applications. Journal of Nanomaterials, 2010. 2010.

116. Yokoyama, F., et al., Morphology and structure of highly elastic poly (vinyl alcohol) hydrogel prepared by repeated freezing-and-melting. Colloid and Polymer Science, 1986. 264(7): p. 595-601.

117. Li, J., et al., Lignocellulose aerogel from wood-ionic liquid solution (1-allyl-3-methylimidazolium chloride) under freezing and thawing conditions. Biomacromolecules, 2011. 12(5): p. 1860-1867.

118. Jiang, F. and Y.-L. Hsieh, Super water absorbing and shape memory nanocellulose aerogels from TEMPO-oxidized cellulose nanofibrils via cyclic freezing–thawing. Journal of Materials Chemistry A, 2014. 2(2): p. 350-359.

119. Li, Y., et al., Construction of functional cellulose aerogels via atmospheric drying chemically cross-linked and solvent exchanged cellulose nanofibrils. Chemical Engineering Journal, 2019. 366: p. 531-538.

120. Wan, C., et al., Preparation, characterization and oil adsorption properties of cellulose aerogels from four kinds of plant materials via a NAOH/PEG aqueous solution. Fibers and Polymers, 2015. 16(2): p. 302-307.

121. Wan, C., et al., Preparation of mechanically strong and lightweight cellulose aerogels from cellulose-NaOH/PEG solution. Journal of Sol-Gel Science and Technology, 2015. 74(1): p. 256-259.

122. Lu, Y., et al., Fabrication of mesoporous lignocellulose aerogels from wood via cyclic liquid nitrogen freezing–thawing in ionic liquid solution. Journal of Materials Chemistry, 2012. 22(27): p. 13548-13557.

123. Jiang, F. and Y.-L. Hsieh, Cellulose nanofibril aerogels: synergistic improvement of hydrophobicity, strength, and thermal stability via cross-linking with diisocyanate. ACS applied materials & interfaces, 2017. 9(3): p. 2825-2834.

124. Wan, C., et al., Preparation, characterization, and antibacterial properties of silver

nanoparticles embedded into cellulose aerogels. Polymer Composites, 2016. 37(4): p. 1137-1142.

125. Wu, T., et al., Dual-porous cellulose nanofibril aerogels via modular drying and cross-linking. Nanoscale, 2020. 12(13): p. 7383-7394.

126. Wan, C. and J. Li, Graphene oxide/cellulose aerogels nanocomposite: Preparation, pyrolysis, and application for electromagnetic interference shielding. Carbohydrate polymers, 2016. 150: p. 172-179.

127. Buchtova, N. and T. Budtova, Cellulose aero-, cryo-and xerogels: Towards understanding of morphology control. Cellulose, 2016. 23(4): p. 2585-2595.

128. Hoepfner, S., L. Ratke, and B. Milow, Synthesis and characterisation of nanofibrillar cellulose aerogels. Cellulose, 2008. 15(1): p. 121-129.

129. García-González, C., M. Alnaief, and I. Smirnova, Polysaccharide-based aerogels—Promising biodegradable carriers for drug delivery systems. Carbohydrate Polymers, 2011. 86(4): p. 1425-1438.

130. Gavillon, R. and T. Budtova, Aerocellulose: new highly porous cellulose prepared from cellulose− NaOH aqueous solutions. Biomacromolecules, 2008. 9(1): p. 269-277.

131. Sescousse, R., R. Gavillon, and T. Budtova, Aerocellulose from cellulose–ionic liquid solutions: preparation, properties and comparison with cellulose–NaOH and cellulose–NMMO routes. Carbohydrate polymers, 2011. 83(4): p. 1766-1774.

132. Fischer, F., et al., Cellulose-based aerogels. Polymer, 2006. 47(22): p. 7636-7645.

133. Yu, M., J. Li, and L. Wang, KOH-activated carbon aerogels derived from sodium carboxymethyl cellulose for high-performance supercapacitors and dye adsorption. Chemical engineering journal, 2017. 310: p. 300-306.

134. Fang, Y., et al., Synthesis and characterization of cellulose triacetate aerogels with ultralow densities. RSC advances, 2016. 6(59): p. 54054-54059.

135. Sehaqui, H., et al., Mechanical performance tailoring of tough ultra-high porosity foams prepared from cellulose I nanofiber suspensions. Soft Matter, 2010. 6(8): p. 1824-1832.

136. Lee, J. and Y. Deng, The morphology and mechanical properties of layer structured cellulose microfibril foams from ice-templating methods. Soft Matter, 2011. 7(13): p. 6034-6040.

137. Zhou, Y., et al., Preparation of aligned porous chitin nanowhisker foams by directional freeze–casting technique. Carbohydrate polymers, 2014. 112: p. 277-283.

138. Simón-Herrero, C., et al., Effects of freeze-drying conditions on aerogel

properties. Journal of Materials Science, 2016. 51(19): p. 8977-8985.

139. Sehaqui, H., Q. Zhou, and L.A. Berglund, High-porosity aerogels of high specific surface area prepared from nanofibrillated cellulose (NFC). Composites science and technology, 2011. 71(13): p. 1593-1599.

140. Jin, H., et al., Nanofibrillar cellulose aerogels. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2004. 240(1-3): p. 63-67.

141. Toivonen, M.S., et al., Ambient-dried cellulose nanofibril aerogel membranes with high tensile strength and their use for aerosol collection and templates for transparent, flexible devices. Advanced Functional Materials, 2015. 25(42): p. 6618-6626.

142. Tsioptsias, C., et al., Development of micro-and nano-porous composite materials by processing cellulose with ionic liquids and supercritical CO 2. Green Chemistry, 2008. 10(9): p. 965-971.

143. Innerlohinger, J., H.K. Weber, and G. Kraft. Aerocellulose: aerogels and aerogel-like materials made from cellulose. in Macromolecular Symposia. 2006. Wiley Online Library.

144. Sescousse, R., A. Smacchia, and T. Budtova, Influence of lignin on cellulose-NaOH-water mixtures properties and on Aerocellulose morphology. Cellulose, 2010. 17(6): p. 1137-1146.

145. Schestakow, M., I. Karadagli, and L. Ratke, Cellulose aerogels prepared from an aqueous zinc chloride salt hydrate melt. Carbohydrate polymers, 2016. 137: p. 642-649.

146. Pircher, N., et al., Impact of selected solvent systems on the pore and solid structure of cellulose aerogels. Cellulose, 2016. 23(3): p. 1949-1966.

147. Karadagli, I., et al., Production of porous cellulose aerogel fibers by an extrusion process. The Journal of Supercritical Fluids, 2015. 106: p. 105-114.

148. Cai, J., et al., Cellulose aerogels from aqueous alkali hydroxide–urea solution. ChemSusChem, 2008. 1(1-2): p. 149-154.

149. Cai, J., et al., Nanoporous cellulose as metal nanoparticles support. Biomacromolecules, 2009. 10(1): p. 87-94.

150. Chen, C. and J. Li. Preparation of lignocellulose aerogel from wood-ionic liquid solution. in Advanced Materials Research. 2011. Trans Tech Publ.

151. Laskowski, J., B. Milow, and L. Ratke, The effect of embedding highly insulating granular aerogel in cellulosic aerogel. The Journal of Supercritical Fluids, 2015. 106: p. 93-99.

152. Cai, J., et al., Cellulose–silica nanocomposite aerogels by in situ formation of silica in cellulose gel. Angewandte Chemie, 2012. 124(9): p. 2118-2121.

153. Demilecamps, A., et al., Cellulose–silica aerogels. Carbohydrate polymers, 2015. 122: p. 293-300.

154. Aaltonen, O. and O. Jauhiainen, The preparation of lignocellulosic aerogels from ionic liquid solutions. Carbohydrate Polymers, 2009. 75(1): p. 125-129.

155. Guilminot, E., et al., Use of cellulose-based carbon aerogels as catalyst support for PEM fuel cell electrodes: Electrochemical characterization. Journal of power sources, 2007. 166(1): p. 104-111.

156. Gawryla, M.D., et al., Clay aerogel/cellulose whisker nanocomposites: a nanoscale wattle and daub. Journal of Materials Chemistry, 2009. 19(15): p. 2118-2124.

157. Shamskar, K.R., H. Heidari, and A. Rashidi, Preparation and evaluation of nanocrystalline cellulose aerogels from raw cotton and cotton stalk. Industrial Crops and Products, 2016. 93: p. 203-211.

158. Pääkkö, M., et al., Long and entangled native cellulose I nanofibers allow flexible aerogels and hierarchically porous templates for functionalities. Soft Matter, 2008. 4(12): p. 2492-2499.

159. Zhang, X., et al., The effect of freezing speed and hydrogel concentration on the microstructure and compressive performance of bamboo-based cellulose aerogel. Journal of wood science, 2015. 61(6): p. 595-601.

160. Jin, H., et al., Superhydrophobic and superoleophobic nanocellulose aerogel membranes as bioinspired cargo carriers on water and oil. Langmuir, 2011. 27(5): p. 1930-1934.

161. Aulin, C., et al., Aerogels from nanofibrillated cellulose with tunable oleophobicity. Soft Matter, 2010. 6(14): p. 3298-3305.

162. Meng, Y., et al., Ultralight carbon aerogel from nanocellulose as a highly selective oil absorption material. Cellulose, 2015. 22(1): p. 435-447.

163. Meng, Y., et al., Optimization of cellulose nanofibrils carbon aerogel fabrication using response surface methodology. European Polymer Journal, 2015. 73: p. 137-148.

164. Cai, H., et al., Aerogel microspheres from natural cellulose nanofibrils and their application as cell culture scaffold. Biomacromolecules, 2014. 15(7): p. 2540-2547.

165. Wang, Y., et al., Ultra-light nanocomposite aerogels of bacterial cellulose and reduced graphene oxide for specific absorption and separation of organic liquids. RSC Advances, 2014. 4(41): p. 21553-21558.

166. Seantier, B., et al., Multi-scale cellulose based new bio-aerogel composites with thermal super-insulating and tunable mechanical properties. Carbohydrate polymers, 2016. 138: p. 335-348.

167. Nemoto, J., T. Saito, and A. Isogai, Simple freeze-drying procedure for producing nanocellulose aerogel-containing, high-performance air filters. ACS applied materials & interfaces, 2015. 7(35): p. 19809-19815.

168. Martins, B.F., P.V. de Toledo, and D.F. Petri, Hydroxypropyl methylcellulose based aerogels: Synthesis, characterization and application as adsorbents for wastewater pollutants. Carbohydrate polymers, 2017. 155: p. 173-181.

169. Wu, Z.Y., et al., Ultralight, flexible, and fire-resistant carbon nanofiber aerogels from bacterial cellulose. Angewandte Chemie, 2013. 125(10): p. 2997-3001.