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Electrospun Nonwoven Mats from Polymeric Association with Natural Rubber and Functionalization with Propolis for Biomedical Applications

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Tese submetida ao Programa de Pós-graduação em Engenharia Química da Universidade Federal de Santa Catarina para a obtenção do título de Doutor em Engenharia Química.

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O presente trabalho em nível de Doutorado foi avaliado e aprovado, em 14 de outubro de 2022, pela banca examinadora composta pelos seguintes membros:

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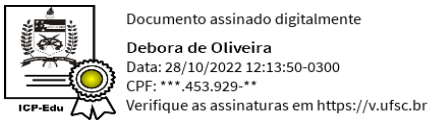
Certificamos que esta é a **versão original e final** do trabalho de conclusão que foi julgado adequado para obtenção do título de Doutor em Engenharia Química.



Coordenação do Programa de Pós-Graduação

Prof. Ricardo Antonio Francisco Machado, Dr.
Orientador

Florianópolis, 2022.

For all the love, affection, and companionship, I dedicate this work to my family and friends who have always supported and encouraged me during this journey, allowing me to advance even during the most difficult times.

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“Só sei que nada sei” (Sócrates).

ABSTRACT

Although there is a great diversity of skin dressings on the market, using natural biopolymers in developing these biomedical devices has received attention due to their biocompatibility, biodegradability, and non-toxicity. Natural rubber (NR) has stood out among biopolymers and has proven to be an excellent material for this purpose. However, NR exhibits hydrophobic characteristics that may hinder its use as a dressing for skin lesions, where hydrophilic properties are desirable. In this sense, the combination of NR with another polymer emerges as an efficient alternative to achieve better performance of this material. Furthermore, combining these materials with the electrowinning technique allows membranes with properties that facilitate cell adhesion and proliferation, which are promising for such applications. In this research, fibers obtained by the electrospinning technique were developed by polymer association from NR. The polymeric associations of NR:Polycaprolactone (NR:PCL) and NR:Polyvinylpyrrolidone (NR:PVP) were tested. After optimizing the electrospinning parameters and identifying the most appropriate polymeric combination for fiber production aimed at biomedical applications, the fibers were functionalized with propolis. The association NR:PCL results showed that the material obtained requires adjustments due to its hydrophobicity. The association of NR:PVP provided the development of fibrous structures with adjustable wettability according to each polymer's proportion, which was proven experimentally and theoretically. FTIR and DSC analyses confirmed the physical mixing of the polymers in the NR:PVP association. The morphological study demonstrated the formation of fibers on the micrometric scale, free of defects and with the presence of crossing points. The addition of PVP in NR caused a decrease in the average diameter of the fibers and, at concentrations ≥ 50%, allowed obtaining a hydrophilic material compatible with applications in skin lesions. The sample with the highest potential application in skin lesions was designated as NR:PVP 50:50 (50NRe-spun). This sample was subjected to the fiber dissolution test and proved to be a promising candidate as a matrix for drug release due to its partial dissolution. Therefore, this sample was functionalized with propolis, and the presence of this bioactive caused a decrease in the average fiber diameter and contact angle values, enhancing the hydrophilic characteristics of the material. Moreover, no significant cytotoxicity was observed for the developed material. It is then concluded that the incorporation of PVP in NR positively affected the surface properties of the biomaterial, exhibiting characteristics that may be of interest in biomedical applications when wettability control is required, such as in skin lesions. It is also worth highlighting the possibility of maintaining and improving the biomaterial's biological properties through propolis's functionalization.

Keywords: Natural rubber; Propolis; Biocompatible fibers; Wound dressing.

RESUMO

Embora exista uma grande diversidade de curativos cutâneos no mercado, a utilização de biopolímeros naturais no desenvolvimento desses dispositivos biomédicos tem recebido atenção devido à sua biocompatibilidade, biodegradabilidade e não toxicidade. A borracha natural (NR) tem se destacado entre os biopolímeros e demonstrado ser um excelente material para esta finalidade. Contudo, a NR exibe características hidrofóbicas que podem dificultar o seu uso como curativo de lesões de pele, onde propriedades hidrofílicas são desejáveis. Nesse sentido, a combinação de NR com outro polímero surge como alternativa eficiente para alcançar melhores desempenhos desse material. Ainda, a combinação desses materiais com a técnica de eletrofiação permite produzir membranas com propriedades que facilitam a adesão e proliferação celular, que são promissoras para tal aplicação. Nesta pesquisa, fibras obtidas pela técnica de eletrofiação foram desenvolvidas mediante associação polimérica a partir de NR. Foram testadas as associações poliméricas de NR:Policaprolactona (NR:PCL) e NR:Polivinilpirrolidona (NR:PVP). Após otimização dos parâmetros de eletrofiação e identificação da combinação polimérica mais apropriada para produção de fibras visando a aplicação biomédica em questão, foi realizada a funcionalização das fibras com própolis. Os resultados obtidos mediante associação NR:PCL mostraram que o material obtido exige adequações, devido a sua hidrofobicidade. A associação de NR:PVP proporcionou o desenvolvimento de estruturas fibrosas com molhabilidade ajustável de acordo com a proporção de cada polímero, sendo isto comprovado experimentalmente e teoricamente. Análises de FTIR e DSC provaram a mistura física dos polímeros na associação NR:PVP. A análise morfológica demonstrou a formação de fibras na escala micrométrica, livres de defeitos e com a presença de pontos de cruzamento. A adição de PVP em NR causou uma diminuição do diâmetro médio das fibras e, em concentrações ≥ 50%, permitiu a obtenção de um material hidrofílico, compatível com as aplicações em lesões cutâneas. A amostra com maior potencial de aplicação em lesões de pele foi designada como sendo NR:PVP 50:50 ($50NR^{e\text{-}spun}$). Esta amostra foi submetida ao teste de dissolução de fibras e demonstrou ser um candidato promissor como matriz para liberação de medicamentos devido a sua dissolução parcial. Visto isso, esta amostra foi funcionalizada com própolis e a presença desse bioativo ocasionou a diminuição do diâmetro médio das fibras e dos valores de ângulo de contato, enaltecendo as características hidrofílicas do material. Além disso, não foi observada citotoxicidade significativa para o material desenvolvido. Conclui-se então que a incorporação de PVP em NR afetou positivamente as propriedades de superfície do biomaterial, exibindo características que podem ser de interesse em aplicações biomédicas quando o controle da molhabilidade é necessário, como em lesões cutâneas. Vale destacar ainda a possibilidade de manter e melhorar as propriedades biológicas do biomaterial através da funcionalização com própolis.

Palavras-chave: Borracha natural; Própolis; Fibras biocompatíveis; Curativo para lesões.

RESUMO EXPANDIDO

TECIDOS FIBROSOS ELETROFIADOS A PARTIR DA ASSOCIAÇÃO POLIMÉRICA COM BORRACHA NATURAL E FUNCIONALIZAÇÃO COM PRÓPOLIS PARA APLICAÇÕES BIOMÉDICAS

Introdução

Atualmente, a eletrofiação tornou-se uma das técnicas mais versáteis, fáceis e econômicas para a engenharia de materiais avançados, denotando uso em diversas aplicações, principalmente na área biomédica. Essa técnica simples e de baixo custo fornece materiais eletrofiados da ordem de micro e nanômetros, que imitam o ambiente biológico e por isso podem ser aplicados em sistemas de liberação de medicamentos, na engenharia de tecidos e em curativos de lesões de pele, dentre outros.

Com auxílio desta técnica, polímeros naturais e sintéticos podem formar estruturas fibrosas com elevada potencialidade de uso em aplicações biomédicas. Um polímero natural que merece destaque especial é a borracha natural (NR), extraído do látex de borracha natural (NRL) da *Hevea brasiliensis.* A NR é um polímero biocompatível e biodegradável, detentor de propriedades biológicas que auxiliam a angiogênese e promoção de cicatrização, podendo ser utilizado em processos de regeneração celular e óssea e liberação de medicamentos. Ainda, polímeros sintéticos como a policaprolactona (PCL) e a polivinilpirrolidona (PVP) vem sendo muito utilizados pelo setor biomédico devido à adequação para modificação, biodegradabilidade e biocompatibilidade, dentre outras características.

Além de possuírem interessantes características biológicas, esses materiais ainda podem servir de matriz para outras substâncias, melhorando ou adquirindo novas propriedades. Numerosas estratégias já foram desenvolvidas com intuito de melhorar a cicatrização e combater infecções de lesões, por exemplo, e é nesse sentido que a incorporação de agentes bioativos ganha destaque. Dentre tais agentes, a própolis é amplamente estudada por apresentar atividade antibacteriana, antiviral, fungicida, anti-inflamatória, imunizante e estimuladora de cicatrização, denotando assim uma ampla variedade de aplicações na área biomédica.

Objetivos

O objetivo desta tese foi desenvolver fibras biocompatíveis a partir de mistura polimérica com NR pela técnica de eletrofiação, funcionalizadas com própolis, para aplicação

biomédica. Neste contexto inclui-se a determinação do melhor polímero para a associação, bem como a identificação dos melhores parâmetros de processamento das fibras. Além disso, buscou-se verificar a amostra mais adequada para funcionalização com própolis, identificar o melhor solvente para a extração desse agente bioativo e avaliar a citotoxicidade do material final obtido.

Metodologia

Para o desenvolvimento das fibras, a NR foi utilizada como material base. Para a mistura polimérica, o PCL (80,000 $g.mol^{-1}$, Sigma Aldrich) e o PVP (K120, 1300 kDa - Sigma Aldrich) foram escolhidos. O solvente foi o clorofórmio (≥ 99.8% de pureza - Dinâmica Química Contemporânea LTDA).

Na primeira etapa da pesquisa foi testada a eletrofiação de NR (50 $mg.mL^{-1}$ - NR-50) e PCL (100 e 120 $mg.mL^{-1}$ - NR:PCL-100 e NR:PCL-120, respectivamente), bem como a associação dessas soluções na proporção 30:70 (NR:PCL). Foram utilizados os seguintes parâmetros de eletrofiação: voltagem de 16 kV, distância entre coletor e agulha de 9 cm e vazão de 0,83 $mL.h^{-1}$, com coletor estático. Uma membrana de NRL *in natura* foi produzida pela técnica de casting para comparação de dados. Análises de espectroscopia no infravermelho por transformada de Fourier (FTIR), microscopia eletrônica de varredura (MEV) e ângulo de contato foram realizadas para caracterização preliminar dos materiais obtidos.

A segunda etapa contemplou a execução de testes de eletrofiação da NR em diferentes concentrações (30, 20 e 15 mg. mL^{-1}), utilizando-se uma voltagem de 9 kV, 14 cm entre coletor e agulha e vazão de 0,40 $mL.h^{-1}$, para identificação da solução e o coletor mais adequado para o processo. Produziu-se uma solução de PVP a 100 mg. mL^{-1} que foi utilizada para eletrofiação individual e para a combinação com a melhor solução de NR identificada na etapa anterior. A eletrofiação da associação polimérica de NR:PVP foi realizada nas proporções 10:90, 25:75, 40:60, 50:50 e 75:25, nos mesmos parâmetros de eletrofiação citados anteriormente, com coletor giratório. As amostras obtidas foram analisadas por MEV e ângulo de contato. Ainda, soluções de PVP em diferentes concentrações (150 e 200 mg. mL^{-1}) foram eletrofiadas e analisadas por MEV e ângulo de contato. Nessa etapa, foram identificadas as melhores condições de produção de fibras a partir da associação NR:PVP.

Na etapa seguinte, fibras de NR (15 $mg.mL^{-1}$) e PVP (200 mg. mL^{-1}) e associações poliméricas de NR:PVP (25:75, 50:50 e 75:25% em relação a massa dos polímeros) foram desenvolvidas mediante voltagem de 9 kV, 14 cm entre coletor e agulha e vazão de 0,40

$mL.h^{-1}$. Membranas desenvolvidas via casting foram produzidas para comparativo em algumas caracterizações. Realizaram-se medições reológicas nas soluções produzidas e as amostras eletrofiadas foram investigadas por MEV, FTIR, calorimetria de varredura diferencial (DSC), microscopia de força atômica (AFM) e teste de dissolução das fibras. A molhabilidade das superfícies foi avaliada por meio de goniômetro e modelagem teórica.

Com os resultados obtidos, foi possível realizar a identificação das melhores condições experimentais para obtenção de fibras com potencial para aplicação em lesões de pele. Com isso, iniciou-se a etapa de funcionalização das fibras com própolis. Extratos de própolis foram produzidos em diferentes solventes (clorofórmio, tolueno, tetrahidrofurano e etanol), seguida da determinação do conteúdo de flavonoides destes extratos, visando a identificação da melhor extração. A incorporação de 5% de própolis (em relação a massa dos polímeros) foi realizada na solução submetida a eletrofiação mediante os parâmetros: 9 kV de voltagem, 14 cm de entre coletor e agulha e 0,42 $mL.h^{-1}$ de vazão. A amostra produzida foi avaliada por MEV, FTIR, DSC, ângulo de contato e citotoxicidade, sendo esta última comparada com a amostra sem funcionalização com de própolis.

Resultados e discussão

A solução inicial de NR (50 $mg.mL^{-1}$) não demonstrou viabilidade para a produção de fibras. As soluções de PCL-100, NR:PCL-100 e NR:PCL-120 mostraram características semelhantes que permitiram a formação de uma membrana fibrosa fina, maleável e esbranquiçada. Por meio de análise de FTIR foi confirmada a obtenção de uma mistura física de NR e PCL na formação de NR/PCL-100. Os diâmetros das fibras eletrofiadas a partir de NR:PCL-100 variavam de 0,440 a 1 μm, enquanto que nas fibras NR:PCL-120 estes valores variavam de 0,344 a 0,925 μm, sendo identificada a presença de defeitos para esta amostra. As fibras desenvolvidas mostraram-se hidrofóbicas e pode-se afirmar que a adição de PCL à NR causou o aumento da tendência não molhante da superfície, exibindo relação com o aumento da concentração de PCL.

Ao analisar diferentes concentrações de NR para eletrofiação, foi possível verificar que as soluções de NR em concentrações de 30 e 20 $mg.\ mL^{-1}$ não eram adequadas para obter superfícies fibrosas homogêneas. As fibras formadas apresentavam grandes diâmetros, que podiam ser visualmente identificados, além disso, formavam aglomerados que se deslocavam para fora do plano do coletor. A solução de NR com concentração de 15 $mg.mL^{-1}$ revelou-se a mais adequada em coletor rotativo, permitindo a formação de uma superfície fibrosa mais

homogênea, sendo assim demonstrado que esses foram os melhores parâmetros para o desenvolvimento de fibras com associação de PVP.

As amostras eletrofiadas a partir de NR (15 $mg.mL^{-1}$) e PVP (100 $mg.mL^{-1}$) e suas associações (NR:PVP 10:90, 25:75, 40:60 e 50:50) exibiram baixa produção de fibras, defeitos e presença de solvente. As fibras de NR e NR:PVP 75:25 forneceram uma maior quantidade de fibras formadas, maior alinhamento, presença de pontos de cruzamento e isentas de defeitos. Por meio de análise de ângulo de contato foi constatado que a NR é responsável por tornar as propriedades da superfície mais propícias à hidrofobicidade, bem como que a incorporação de PVP proporcionou diminuição dos valores do ângulo de contato, mostrando uma relação linear com a diminuição da proporção de NR adicionada à mistura. Referente ao teste de eletrofiação com soluções de PVP em diferentes concentrações (150 e 200 $mg.mL^{-1}$), ainda foi observada a formação de defeitos, mas em uma proporção menor, sendo mais evidente nas fibras com menor concentração de PVP (150 $mg.mL^{-1}$), bem como os pontos de cruzamento. Assim, a solução de PVP com concentração de 200 $mg.mL^{-1}$ provou ser a mais adequada para produzir fibras em associação com NR.

A análise reológica das soluções de NR (15 $mg.mL^{-1}$), PVP (200 $mg.mL^{-1}$) e associações poliméricas de NR:PVP mostrou que soluções com maior concentração de NR apresentam maior viscosidade (170,4 ± 8,7 $mPa.s^{-1}$) levando a formação de diâmetros médios de fibras mais altos (3,8 ± 0,8 μm) e maiores ângulos de contato (120,1° ± 6,4). As análises de FTIR e DSC demonstraram a mistura física dos polímeros para as amostras associadas de NR:PVP. As imagens de MEV e AFM mostraram a separação de fases apenas para as membranas via *casting* e a rugosidade mudou de forma não linear com a proporção polimérica. Foi verificado que a molhabilidade das superfícies diminui com concentrações mais elevadas de NR, quando comparados com os resultados das membranas produzidas via *casting*. Além disso, foi demonstrado que a molhabilidade pode ser alterada de acordo com a proporção de polímeros nas misturas, uma vez que maiores concentrações de PVP promoveram superfícies mais hidrofílicas, sendo isto comprovado em medições experimentais e por modelagem teórica. O teste de dissolução da amostra NR:PVP 50:50 em água mostrou uma dissolução parcial sugerindo um candidato promissor para aplicação biomédica.

Para a etapa final que envolveu a funcionalização com própolis em NR:PVP, observou-se que a extração de própolis em clorofórmio forneceu uma maior concentração de quercetina (flavonoide natural detentor de propriedades biológicas). A funcionalização com própolis na solução NR:PVP 50:50 causou uma baixa produção de fibras, o aparecimento de defeitos e maior proeminência dos pontos de cruzamento. As fibras produzidas apresentaram

maior heterogeneidade de diâmetros de fibras e diminuição desses valores. A mistura física de NR e PVP na mistura NR:PVP foi comprovada pela análise de FTIR. A amostra contendo própolis exibiu uma diminuição do valor do ângulo de contato (46,0° ± 3,1) quando comparada com a amostra sem própolis (52,0° ± 1,6), enquanto as amostras obtidas por *casting* exibiram um aumento no valor do ângulo de contato. Mesmo diante disso, manteve-se as propriedades hidrofílicas do material com a adição de própolis. Nenhuma das amostras avaliadas induziu citotoxicidade significativa, uma vez que foram observadas percentagens de viabilidade superiores a 80%. Além disso, não foram observadas diferenças significativas na viabilidade celular ao comparar as amostras testadas.

Considerações finais

Os resultados obtidos demonstram a obtenção de estruturas fibrosas a partir da associação polimérica de NR:PCL pela técnica de eletrofiação. No entanto, a combinação NR:PVP demonstrou ser mais apropriada para aplicações em lesões de pele, além de proporcionar o desenvolvimento de superfícies com molhabilidade ajustável de acordo com a proporção de cada polímero, sendo isto comprovado de forma experimental e teórica. A adição de PVP em NR ocasionou a diminuição dos diâmetros médio das fibras e em concentrações ≥ 50%, permitiu a obtenção de um material hidrofílico, compatível com aplicações em lesões de pele.

O clorofórmio foi o solvente mais eficiente para extração de própolis. A funcionalização de própolis nas fibras interferiu no diâmetro médio das fibras e nas características de molhabilidade, enaltecendo a hidrofilicidade do material. Além disso, não foi observada citotoxicidade significativa nas amostras avaliadas, uma vez que foram observadas percentagens de viabilidade de mais de 80%. Assim, afirma-se que a incorporação de PVP em NR afetou de forma positiva as propriedades superficiais do biocomposto, permitindo a sua utilização em aplicações como lesões de pele e ainda, ressalta-se a possibilidade da manutenção e melhoria das propriedades do biomaterial mediante funcionalização com própolis.

Palavras-chave: Borracha natural; Própolis; Fibras biocompatíveis; Curativo para lesões.

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AFM	Atomic Force Microscopy
DRC	Dry Rubber Content
DSC	Differential Scanning Calorimetry
EQ	Quercetin Equivalent
FTIR	Fourier Transform Infrared Spectroscopy
HEV	Hevein
NR	Natural Rubber
NR^{Cast}	Cast membrane from NR solution
$NR^{e\text{-}spun}$	Electrospun fiber mats from NR solution
NRL	Natural Rubber Latex
NRL membrane	Cast membrane of NRL
NR:PCL-100	Electrospun fiber mats from NR:PCL-100 blend solution: 30:70 wt% of ratio
NR:PCL-120	Electrospun fiber mats from NR:PCL-120 blend solution: 30:70 wt% of ratio
NR:PVP 10:90	Electrospun fiber mats from NR-15:PVP-100 blend solution: 10:90 wt% of ratio
NR:PVP 25:75	Electrospun fiber mats from NR-15:PVP-100 blend solution: 25:75 wt% of ratio
NR:PVP 40:60	Electrospun fiber mats from NR-15:PVP-100 blend solution: 40:60 wt% of ratio
NR:PVP 50:50	Electrospun fiber mats from NR-15:PVP-100 blend solution: 50:50 wt% of ratio
NR:PVP 75:25	Electrospun fiber mats from NR-15:PVP-100 blend solution: 75:25 wt% of ratio
NR-50	Electrospun fiber mats from NR solution: 50 $mg.mL^{-1}$
NR-30	Electrospun fiber mats from NR solution: 30 $mg.mL^{-1}$
NR-20	Electrospun fiber mats from NR solution: 20 $mg.mL^{-1}$
NR-15	Electrospun fiber mats from NR solution: 15 $mg.mL^{-1}$
N/A	Not applicable
PCL	Polycaprolactone

PVA	Polyvinyl alcohol
PVP	Polyvinylpyrrolidone
PVP^{Cast}	Cast membrane from PVP solution
$PVP^{e\text{-}spun}$	Electrospun fiber mats from PVP solution: 200 $mg.mL^{-1}$
PVP-100	Electrospun fiber mats from PVP solution: 100 $mg.mL^{-1}$
PVP-120	Electrospun fiber mats from PVP solution: 120 $mg.mL^{-1}$
PVP-200	Electrospun fiber mats from PVP solution: 200 $mg.mL^{-1}$
RH	Relative Humidity
RT	Room temperature
SEM	Scanning Electron Microscopy
TDDS	Transdermal Drug Delivery System
$25NR^{Cast}$	Cast membrane from NR:PVP blend solution: 25:75 wt% of ratio
$25NR^{e\text{-}spun}$	Electrospun fiber mats from NR:PVP blend solution: 25:75 wt% of ratio
$50NR^{Cast}$	Cast membrane from NR:PVP blend solution: 50:50 wt% of ratio
$50NR^{Cast+prop}$	Cast membrane from NR:PVP blend solution: 50:50 wt% of ratio, functionalized with propolis
$50NR^{e\text{-}spun}$	Electrospun fiber mats from NR:PVP blend solution: 50:50 wt% of ratio
$50NR^{e\text{-}spun+prop}$	Electrospun fiber mats from NR:PVP blend solution: 50:50 wt% of ratio, functionalized with propolis
$75NR^{Cast}$	Cast membrane from NR:PVP blend solution: 75:25 wt% of ratio
$75NR^{e\text{-}spun}$	Electrospun fiber mats from NR:PVP blend solution: 75:25 wt% of ratio

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1 INTRODUCTION

1.1 MOTIVATION

The constant demand in the medical field for bioalternatives capable of performing vital activities of the organs of the human body has been continuously arousing the interest of researchers in developing new biomaterials. Thus, discovering and developing biomaterials with utility in medical sciences, enabling better performance, increasing or replacing natural functions of a defective organ, and interacting with the biological system, have been challenging tasks of considerable importance nowadays.

Although there is a great diversity of biomaterials in the market, the use of natural polymers in biomedical and biopharmaceutical applications has received research attention mainly due to their biocompatibility, biodegradability, and non-toxicity. Several studies have already proven the power of induction of angiogenesis, tissue repair, and biocompatibility of materials from the NRL and NR of *Hevea brasiliensis*. These studies show that the NRL and NR have several applications in the biomedical area, such as cell and bone regeneration, and drug applications, among others, and are still under full development. Besides representing a promising therapeutic resource, these materials can also serve as a matrix for another bioactive material, improving and/or combining their properties, thus denoting a great and interesting potential for application in drug delivery systems. In this sense, propolis, which presents a therapeutic application in popular medicine since ancient times and, due to its antimicrobial activity, is widely used in dressings, triggering the acceleration of the lesion healing process. It is worth mentioning that these materials are raw materials found abundantly in the Brazilian biodiversity, therefore, they are easily accessible and have low cost.

In addition, the use of polymeric mixtures to obtain electrospun fibers can provide several advantages that are not achieved when polymers are used individually. An example is the improvement and modification of surface properties that can be provided by the presence of an adjuvant, such as polyvinylpyrrolidone (PVP) and polycaprolactone (PCL).

1.2 RESEARCH OBJECTIVES

This work has the general objective of developing biocompatible fibers from polymeric mixtures with NR, by the electrospinning technique, functionalized with propolis, for biomedical application.

The specific objectives are:

a) Optimize the best polymer composition for the development of the individual solutions, for subsequent electrospinning;

b) Identify the most appropriate polymer to perform the association with NR;

c) Determine the best parameters of the electrospinning process to obtain fibers from this polymeric association;

d) Characterize chemically, physically, and morphologically the fibers produced;

e) Designate the best sample produced for further functionalization with propolis;

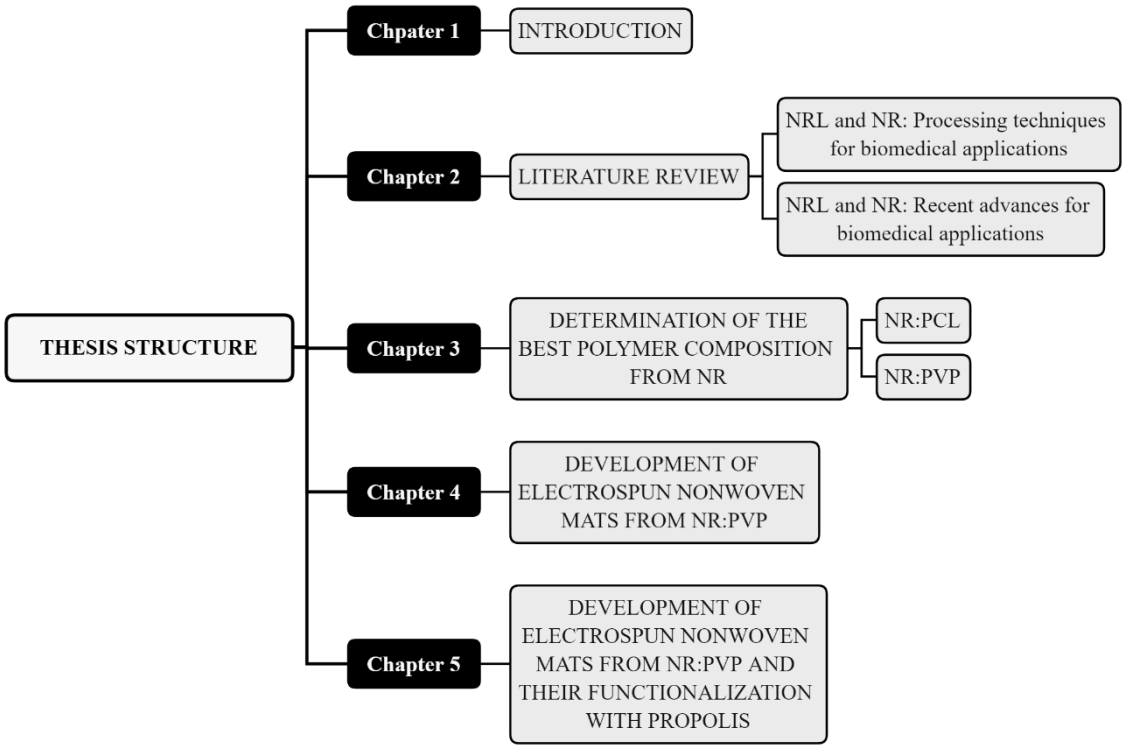
f) Verify the most suitable solvent for extraction of propolis;

g) Investigate the cytotoxicity of the electrospun nonwoven mats with and without propolis functionalization, aiming for the use of the final material for biomedical purposes.

1.3 THESIS STRUCTURE

This thesis is structured into five chapters. Chapter 1 describes the introduction and the objectives of the research (Figure 1). Chapter 2 comprises the literature review, which describes the main techniques used to produce materials from NRL and NR for biomedical purposes, as well as the conformations of the materials produced. Preliminary tests regarding the electrospinning of polymer blends from NR:PCL and NR:PVP are described in Chapter 3. Chapters 4 and 5 refer to the results of the research, reporting the development and characterization of fibers from NR:PVP and the production of these fibers functionalized with propolis, respectively.

Figure 1 - Thesis structure.



2 LITERATURE REVIEW

Chapter 2 aims to provide the reader with an overview of the use of NRL and NR in biomedical applications. Section 2.1 of this chapter corresponds to a review article submitted, which highlights the state of the art of NRL and NR with a focus on processing techniques in biomedical science. Following this, section 2.2, is a review article accepted for publication that describes recent advances in the development of NRL and NR as biomedical materials with potential properties including biocompatibility and biodegradability.

2.1 LATEX AND NATURAL RUBBER: PROCESSING TECHNIQUES FOR BIOMEDICAL APPLICATIONS[1]

The design of polymeric biomaterials for biomedical and regenerative medicine applications has become crucial for scientists and engineers to develop devices that can recover, augment, or replace the natural function of a defective organ or tissue by interacting with the biological system. The main requirement for regenerative medicine and tissue engineering is the formation of healthful tissue *in vivo* conditions, which is fulfilled by the biocompatibility, biodegradability, bioactivity, and superior mechanical properties of the natural or synthetic polymer (PARK; LAKES, 2007; WONG; BRONZINO; PETERSON, 2013). The association of synthetic polymers and natural polymers enables the improvement of the system functionalities, overcoming the individual limitations of each polymer (REDDY *et al.*, 2021). Some common synthetic polymers are polycaprolactone (RANJBAR MOHAMMADI *et al.*, 2020), poly(lactic acid) (DE LA MATA *et al.*, 2019), and poly(ethylene glycol) (SAVIN *et al.*, 2019). Natural polymers such as collagen (LI *et al.*, 2018), and alginate (TAEMEH *et al.*, 2020) have been extensively researched due to their natural abundance and low cost, however, the lack of necessary stretchability limits their application for soft tissue.

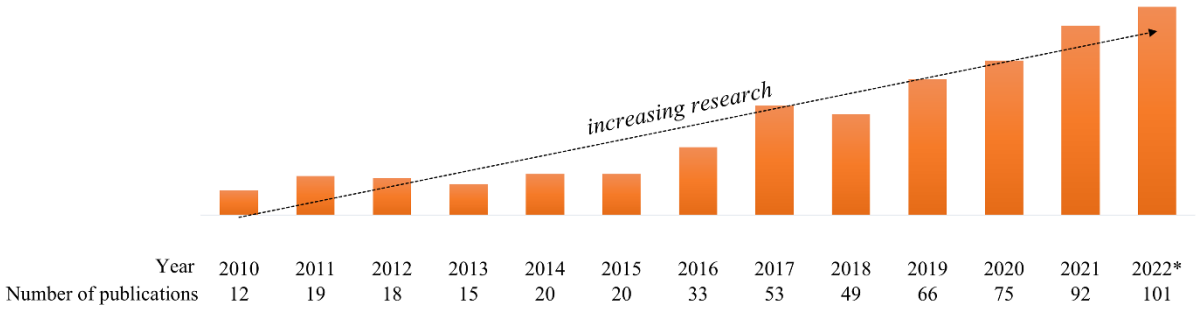
Among the polymers available in nature, natural rubber (NR) derived from natural rubber latex (NRL) extracted from *Hevea brasiliensis* stands out due to its elasticity under mechanical tensile (BHADRA *et al.*, 2019). NR matches important requirements of regenerative medicine like elastic extensibility of organic tissue by mimicking the extracellular matrix and offering suitable mechanical properties (AZARIAN;

[1] Based on the submitted article in Brazilian Journal of Chemical Engineering.

BOOCHATHUM, 2018; CHEN; LIANG; THOUAS, 2013). Compared to other biopolymers, NR provides a stretchable, flexible, and soft tissue, which could find high applicability to dressings and scaffolds requiring large transmission of forces and deformations. Also, NR becomes an alternative due to its high resilience, elasticity, abrasion resistance, impact resistance, and malleability in cold temperatures, also due to its availability and low cost (ABRAHAM *et al.*, 2012; MRUÉ *et al.*, 2004; RIPPEL; GALEMBECK, 2009; TSUCHII, 1995). The NR has mostly been applied externality to the human body for short-time implants or as a delivery matrix because of the lack of studies exploring the potentiality of this biopolymer in biomedical science. NR is capable of producing materials with greater biocompatibility as long as it is not heat-treated and chemical substances such as carbamates and sulfur are not added (HERCULANO *et al.*, 2009). Another essential property of biomaterials' production is biodegradability (ABRAHAM *et al.*, 2012; AZARIAN; BOOCHATHUM; KONGSEMA, 2019), but there is still a need for further studies when it comes to the use of NRL and NR.

With the great potential of NRL and NR devices for biomedical applications, many studies have been developed in the last decade (Figure 2). The number of studies published until July 2022 already shows a significant research interest in NRL and NR biomedical devices, promising further growth in the number of publications in this field.

Figure 2 - Evolution of the number of publications per year about NRL or NR applied to biomedicine. Queries correspond to ("natural rubber" or "*Hevea brasiliensis*" or "polyisoprene") and ("medicine" or "biomedical" or "tissue engineering") and ("wound dressing" or "wound healing" or "skin tissue"); (*searched until July/2022, ScienceDirect database).



The biomaterials' design is an important step to obtain a device that fits the desired biomedical application. Some processing techniques have been developed to manufacture NRL and NR devices with high potential in biomedical science. This includes membranes by casting, films by spraying and dip coating, and electrospun mats by electrospinning. Other

material shapes are also here addressed, such as bulk materials by compression and extrusion; gels, solutions, and creams by extraction; and spun mats by blow spinning.

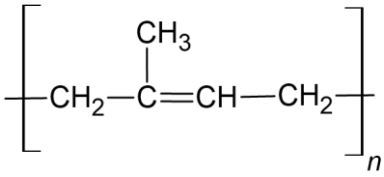
An overview of several important results that have been reported with NRL and NR devices can contribute to their improvement in biomedical applications. Thus, this work aims to review the state of the art regarding the processing techniques of NRL and NR in biomedical applications and regenerative medicine. First, a brief history of these materials, their chemical constitution, stabilization process, and potential biomedical are explained. Then, the main processing techniques are discussed. Finally, conclusions and remarks are pointed out to provide a basis for future research in the development of NRL and NR as biomaterials for biomedical applications and regenerative medicine. The number of works dealing with NRL and NR is scarce compared to other biomaterials, thus, this review sheds light on new developments in this field. The current search for more natural products (biodegradable and biocompatible) reinforces the need for further research.

2.1.1 Historical, Fundamental Aspects and Potential Biomedical Properties of NRL and NR from *Hevea brasiliensis*

The history of NR started in the late 14th century when Christopher Columbus brought it from America to Europe. With the discovery of the vulcanization technique in 1839 by Charles Goodyear, the automobile industry grew, along with the demand for rubber, and in 1890 Brazil became the world's largest producer and exporter of rubber. However, in 1877 rubber seeds were smuggled to England and later to Ceylon and Malaysia, leading to the end of Brazil's monopoly (D'AGOSTINI *et al.*, 2013). Currently, approximately 90% of NR production comes from Asian countries and the world's largest consumers are China, India, United States, and Japan (HO, 2013). *Hevea brasiliensis* has great genetic variability and its production comprises different clones (SILVA *et al.*, 2010), which allows for maximizing its productivity through the use of agronomic techniques for genetic improvement (PEREIRA *et al.*, 2020). In Brazil, the most used clone is the RRIM 600, due to its high yield in rubber (GONÇALVES *et al.*, 2000), with its production concentrated in the state of São Paulo (SILVA *et al.*, 2021b). Although NRL is synthesized by numerous plant species, high-quality NRL is nowadays produced only by the *Hevea brasiliensis* tree, which is the only economically and commercially viable source of NR (AGOSTINI; CONSTANTINO; JOB, 2008; SANSATSADEEKUL; SAKDAPIPANICH; ROJRUTHAI, 2011).

NRL is defined as a colloidal dispersion of NR in an aqueous medium, a turbid white liquid, similar in appearance to milk, containing rubber particles surrounded by a phospholipoprotein membrane which, due to its negative charge, provides the colloidal stability of the particles (HO, 2013; SANSATSADEEKUL; SAKDAPIPANICH; ROJRUTHAI, 2011). The density of NRL is 0.98 g/cm^3, its pH is in the range 6.5-7.0, and its average molecular weight ranges from 50,000 to 3,000,000 g/mol (KROSCHWITZ, 1990; ROBERTS, 1988). Approximately 50-60% of NRL is composed of water and the remainder is composed of various other substances (approximately 96% is poly(cis-1,4-isoprene), 1-2% protein, 0.4-1% neutral lipids, 0.5-0.6% polar lipids, and 0.4-0.6% inorganic components including traces of metals such as magnesium, iron, potassium, zinc, copper, among others) (AGOSTINI; CONSTANTINO; JOB, 2008; CABRERA *et al.*, 2013b). The diameter of the rubber particles contained in latex ranges between 5 and 3000 nm, which are surrounded by a mixture of highly complex proteins, lipids, and long-chain fatty acids. About 75% of these proteins are freely dissolved in the serum fraction, while the rest is bound to the surface of the rubber particles (RIPPEL; GALEMBECK, 2009). NR is a solid polymer derived from NRL coagulation and clot drying (BHADRA *et al.*, 2019; MORAIS; GUEDES; LOPES, 2016). This elastomer represents an elastic hydrocarbon polymer, poly(cis-1,4-isoprene) (Figure 3), which presents a high molecular weight, viscoelastic properties, and insulating, waterproofing, and plastic characteristics, not found in other biomaterials, making NRL and NR ideal for various biomedical applications (TAO *et al.*, 2015; UTHUP *et al.*, 2019).

Figure 3 - Chemical structure of poly(cis-1,4-isoprene).



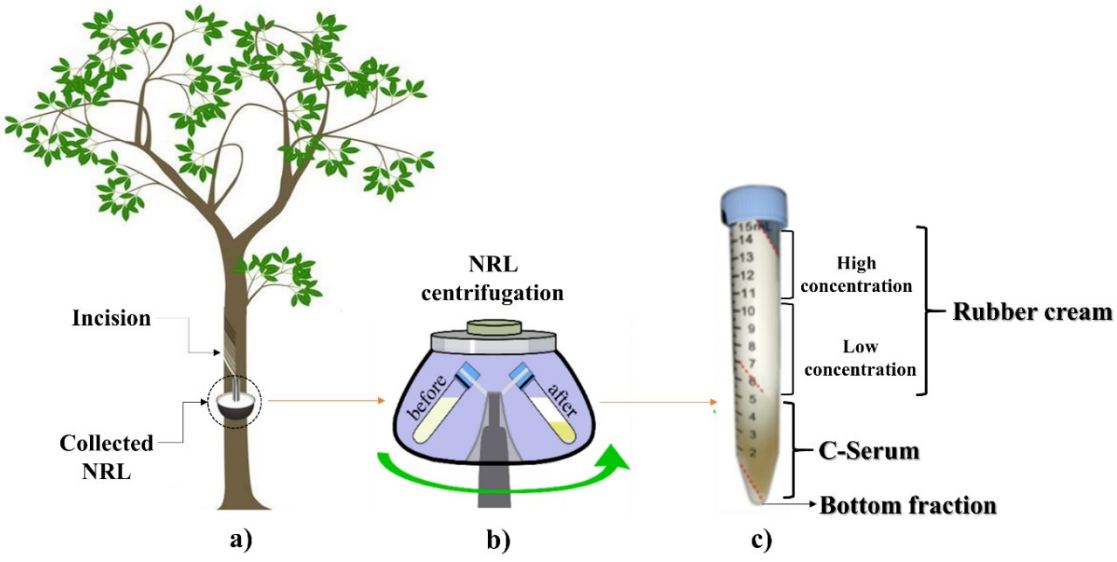
Recently, several studies have been conducted using NRL and NR for the most varied biomedical applications, proving that this bioactive material promotes cell adhesion, formation of extracellular matrix, and accelerating tissue repair with the increase of angiogenesis at the treatment site (RAHIMI; MASHAK, 2013; SANTOS KOTAKE *et al.*, 2018). Such results indicate the potentiality of these biomaterials in several applications in the biomedical area, being an alternative capable of binding biocompatibility and low cost, as well as providing

characteristics such as high elasticity, flexibility, and strength (MARCELINO *et al.*, 2018; MRUÉ *et al.*, 2004; ZIMMERMANN *et al.*, 2007).

2.1.1.1 Usual Collection, Stabilization, and Processing Methods

Latex extraction is done through the tapping process, by the removal of slices of bark from the surface of the tree, until reaching the disruption of the laticiferous vessels (Figure 4a) (HENG; JOO, 2017; HO, 2013). After the bleeding, the latex coagulates spontaneously or with the aid of coagulants (RIPPEL; BRAGANÇA, 2009). Spontaneous coagulation is due to the susceptibility of NRL to microbial and enzymatic attacks after collection (HO, 2013). Centrifugation is a method capable of separating material into distinct phases according to its densities (Figure 4b). Regarding NRL processing, after centrifugation, 3 phases are found (Figure 4c): rubber cream (upper fraction), C serum (intermediate fraction), and lutoids (bottom fraction) (ROLLAND; O'HEHIR, 2008). The centrifugation process requires some attention since most of the NRL proteins are present including those proteins that promote neovascularization and tissue repair (ZIMMERMANN *et al.*, 2007). In the rubber cream, poly(1,4-cis-isoprene) corresponds to approximately 40% of its dry volume, in which the low allergenicity protein fractions Hevein b1 and b3 are found (ROLLAND; O'HEHIR, 2008).

Figure 4 - Natural rubber tapping for collection of latex, b) centrifugation process and c) separation of latex into different phases after centrifugation.



The protein composition of NRL varies according to tree clone, ambient conditions, rain, soil, solar irradiations, and fertilizers, such as Ethephon, used for rubber cultivation. Besides, latex-producing rubber trees are susceptible to the invasion of microorganisms, especially fungi and insects that can damage or even kill the tree (KELLY; KELLY, 1987). As a defense, NRL presents several proteins and enzymes primordial for self-protection, but these can cause sensibility, clinical and allergenic reactions (YEANG *et al.*, 2002a, 2002b). Latex reactions have varied clinical presentations depending on the route, frequency, intensity, and time of exposure. Generally, cutaneous manifestations are frequent, and might be non-immunological (irritative contact dermatitis) or allergic (allergic contact dermatitis, contact urticaria, systemic urticaria, and angioedema) reactions. They can be manifested as respiratory complaints (rhinitis and asthma), ocular (conjunctivitis), or as severe, life-threatening allergic reactions (anaphylaxis) (GASPAR; FARIA, 2012)

The proteins found in the recently collected latex are identified in the final products, both in their natural and in a modified configuration, and may trigger the formation of neoantigens (KELLY; KELLY, 1987). The NRL processing represents a stage of great importance since for biomedicine, NRL must be free of allergenic proteins. In the case of non-immediate processing of the NRL, a small amount of a preservative compound is added to avoid its spontaneous coagulation (RIPPEL; BRAGANÇA, 2009), avoiding the proliferation of microorganisms that can degrade the NRL. Currently, the most used preservative for this purpose is ammonia hydroxide (JAWJIT; PAVASANT; KROEZE, 2015), which decomposes fatty acid esters and eliminates bacteria, stabilizing the system. The NRL can be designated according to the ammonia content present in its composition: low ammonia content NRL ($\leq$ 0.29 wt%), medium ammonia content (0.30 a 0.59 wt%), and high ammonia content ($\geq$ 0,60 wt%) (INTERNATIONAL STANDARD ORGANIZATION (ISO), 2012).

However, ammonia presents high toxicity (MURTHY *et al.*, 2001) and its use for biomedical applications requires great attention, as it may cause possible harmful effects on human health depending on its dosage (ARAUJO *et al.*, 2019). In the ammonium hydroxide stabilized composition of NRL, 16 different types of proteins can be found, each one presenting a specific activity. These proteins are known as Hevein (Hev), receiving the identification of Hev bX. For humans, some of these proteins have a high degree of allergenicity, as is the case of Hev b5, b6.01, and b6.02 (FAITA, 2014; ROLLAND; O'HEHIR, 2008). Araújo et al. evaluated the *in vitro* cytotoxicity and oxidative stress of NR biomembranes using different concentrations of ammonia. As of 2.0 v/v% of ammonia, exhaustion of cellular viability was observed with no adaptation, demonstrating the

cytotoxicity of this concentration for the lineage of study (ARAUJO *et al.*, 2019). Floriano et al. conducted a study with different collection methods and the biocompatibility of NRL from different clones. The study demonstrated that the biomembranes developed with all the clones were biocompatible, but the presence of ammonia caused cytotoxic and genotoxic effects in cell cultures and also caused necrosis and increased cell inflammation in the tissues of the rabbit near the implant realized. Furthermore, the research the possibility of using low temperatures for the preservation of NRL, thus being free of the ammonia additive (FLORIANO *et al.*, 2014).

It is worth noting that the contamination of NRL occurs during collection, in which the material is exposed to the environment and the most diverse forms of contamination (SALOMEZ *et al.*, 2014). Therefore, the collection must be performed cleanly to be free of contamination and the addition of ammonium hydroxide must be done sensibly so that its biomedical application does not lose effect or cause cellular cytotoxicity events (ARAUJO *et al.*, 2019; FLORIANO *et al.*, 2014). Thus, the immediate use of the material would be the most recommended, avoiding the addition of other substances. In some processing methods of this material, organic solvents are added to solubilize NR, which may generate residues in the biomedical device, causing some cytotoxicity. In addition, the efficient separation of angiogenic and bactericidal proteins from latex will enable the development of highly bioactive and non-toxic biomaterials. Therefore, further studies on the collection, its influence, and the use of NRL and NR solubilized in low or non-toxic solvents are needed for the development of safer materials.

2.1.2 Current Processing Techniques

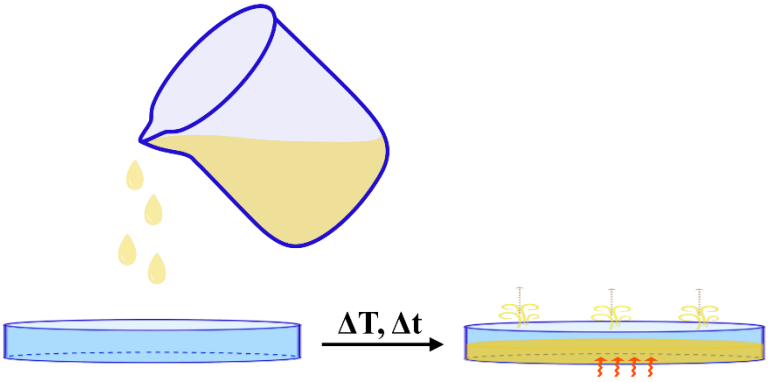
In the following section, the main techniques to process NRL and NR for biomedical applications are described, including casting, spraying, dipping, and electrospinning. The techniques of compression, extrusion, extraction, and blow spinning are also briefly discussed.

2.1.2.1 Casting

This technique is used to produce biomembranes from NRL or NR dissolved in some solvent (Figure 5). The process consists of the dissolved NRL or NR in a mold followed by solidification of the material with the application of high temperatures, freeze-drying or even

natural drying, and subsequent removal of the mold. Most biomembranes are processed with NRL, but for production from NR, solvents such as chloroform, toluene, formic acid, tetrahydrofuran, and dichloromethane are mentioned (ANDRADE *et al.*, 2022b).

Figure 5 - Casting technique.



NRL or NR biomembranes stand out as an important type of dressing in the treatment of skin lesions, including pain relief (FRADE *et al.*, 2012), promotion of neovascularization, healing, and tissue repair (ZIMMERMANN *et al.*, 2018). This type of biomembrane was first developed in 1994 at the University of São Paulo (Brazil), revealing success in the reconstruction of a dog's esophagus wall (MRUÉ *et al.*, 2004). The results showed that the membrane had biochemical properties capable of interfering in the process of tissue repair, favoring the rapid and regular formation of new tissue, besides being simple to handle, and dispensing complex techniques for its processing and use. Subsequently, several experiments with the application of this biomembrane began to be developed for a possible replacement of vessels, pericardium, and abdominal wall of animals, among other applications (CARLOS *et al.*, 2019; ERENO *et al.*, 2010; MOURA *et al.*, 2014; MRUÉ *et al.*, 2004).

The production of biomembranes using the casting technique enables their application as matrixes for drug administration (ANDRADE *et al.*, 2022b). Several studies have demonstrated the tissues' development with metronidazole, *Stryphnodendron sp.* (*S. barbatiman* in particular), *Casearia sylvestris* extracts, nanoparticles, diclofenac, bovine serum albumin, propolis, among others. The porosity control is widely desired for drug delivery and/or cell anchoring. Miranda et al. studied the effects of NRL biomembrane porosity on the release of compounds for biomedical applications. The membranes were prepared by diluting NRL in different concentrations in deionized water, followed by

lyophilization, and a conventional polymerized membrane dried at 37 °C for 48 h was also produced for comparison (not lyophilized). Bovine serum albumin was incorporated into the membranes for release evaluation. The conventional membrane showed no porosity, while the water-free lyophilized membrane showed few pores. As expected, the highest release of bovine serum albumin (88%) was found in the most porous membrane (lyophilized 5:1 water:latex v/v%). Lyophilized membranes showed less cytotoxicity and hemolytic activity than the conventional membrane, indicating that such porous membranes may be used as wound dressings and drug delivery systems (MIRANDA *et al.*, 2017). A similar result was observed with NR membranes prepared with different solvents (water, toluene, and chloroform) where pores were observed due to solvent evaporation in the drying process of the membranes (CESAR *et al.*, 2019; FAITA *et al.*, 2014).

Recently, Zancanella et al. evaluated the incorporation of three different types of propolis (green, red, and poplar) into biomembranes obtained from NRL. The mechanical properties of the NR membranes were verified after the incorporation of the three types of propolis, allowing the release of active compounds against *Candida albicans* (the main fungus responsible for burn injuries). Red propolis was the most active against the fungus, followed by poplar and green. New chemical bonds were not detected in the Fourie transform infrared spectra, i.e., the NR/propolis interactions were only physical, which is desirable, since this allows the release of propolis compounds from the membrane to the lesion. Regarding cell viability, red propolis presented the best values in eluate concentrations, followed by green propolis. The authors mentioned that propolis would be suitable for incorporation in NR membranes to develop a dressing (ZANCANELA *et al.*, 2019).

Important conditions of the casting technique include drying temperature and time. The preferred temperature is between 1 and 25 °C (BARROS *et al.*, 2018; BOLOGNESI *et al.*, 2015; PHAECHAMUD; ISSARAYUNGYUEN; PICHAYAKORN, 2016; ZANCANELA *et al.*, 2017), highlighting the use of room temperature between 23 and 25 °C. The preferred drying time is up to 25 h (ARAUJO *et al.*, 2019; MIRANDA *et al.*, 2017; PHAECHAMUD; ISSARAYUNGYUEN; PICHAYAKORN, 2016; ZANCANELA *et al.*, 2017) which ensures the drying of the biomembrane. The NRL is preferentially used when additives are introduced in the biomembrane since it already contains water for good dispersion of the additive. However, control of the additive concentration is limited and thus the use of NR and solvent has been further researched in the casting process.

The improvement of the membrane characteristics for biomedical purposes is conducted with the blending of NRL with other polymers (Table 1).

Table 1 - Overview of NRL membranes tuned with additives applied to biomedical science according to drying temperature and time (RT stands for room temperature).

Material / Concentration	**Drying temperature (°C)**	**Drying time (h)**	**Reference**
NRL:chitin nanofibers / 1:0.3 wt%	30	24	(DING *et al.*, 2019)
NRL: Polylactic Acid/ 3:1 wt%	RT	N/A	(CESAR *et al.*, 2019)
NRL:BSA / 5:1 wt%	-18	50	(WATTANAKAROON *et al.*, 2017)
NRL: poly(vinyl alcohol)-graft-isopropylacrylamide/ 3:7 wt%	RT	168	(SUKHLAAIED; RIYAJAN, 2017)
NRL:silk sericin:chitin whiskers / 1:0.2:0.02 wt%	60	24	(WATTHANAPHANIT; RUJIRAVANIT, 2017)

For example, nanocomposites formed by NR and chitin nanofibers showed improved strength and tenacity by adding a small amount of chitin (DING *et al.*, 2019). The blending of smart polymer poly(vinyl alcohol)-isopropylacrylamide with deproteinized natural rubber in the production of hydrogel enabled the improvement of traction resistance and rupture elongation. Moreover, the smart hydrogel was endowed with good sensitivity to pH-temperature (SUKHLAAIED; RIYAJAN, 2017). Even though the studies reported positive results regarding the use of biomembranes, more research should be carried out aiming at better use of their biocompatible, adaptable, elastic, impermeable, and non-toxic features that facilitate the interaction between tissues (ROSA *et al.*, 2019).

Copolymerization and polymer blending are excellent strategies to get synergistic and additive effects achieved from natural and synthetic polymers. Even though most of the research has been conducted on this issue, there is much more to explore, for example, the introduction of bioactive compounds and blending with other biopolymers to increase biomedical properties. Future advancements in blending with carrier polymers and/or additives may be the suitable hope for producing NRL and NR materials with the requirements to be applied to biomedicine.

2.1.2.2 Spraying and Dipping

NRL and NR films have been processed using spraying (Figure 6a) and dipping (Figure 6b) techniques (ANDRADE *et al.*, 2022b) (Table 2). These techniques were recently compared (DAVI; LOMBELLO; FERREIRA, 2019). Spraying was 10 times faster but required almost 12 times more solution (including for rinsing) than dipping. Moreover, spraying produced thinner films and better cell adhesion than dipping films. The authors explained that this improvement was due to a spontaneous selection of smaller NR particles on the surface induced by the spraying conditions.

Figure 6 – (a) Spraying and (b) dipping techniques.

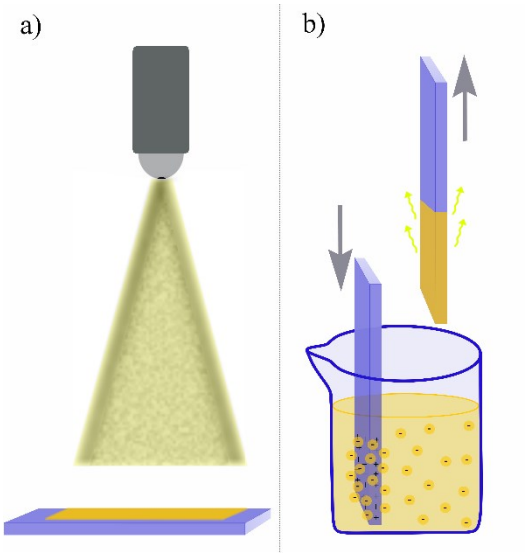


Table 2 - Overview of NRL and NR films applied to biomedical science.

Material	Solvent	Dipping time (min)	Reference
NRL	Deionized water	5	(FLORIANO *et al.*, 2014)
Sulphur prevulcanized NR	Deionized water	60	(SUTEEWONG *et al.*, 2019)
NR	N/A	N/A	(TRAN *et al.*, 2019)
NR	Ammonia	180	(KAWANO; YAMAMOTO; KADOKAWA, 2017)
NRL	Ultrapure water	N/A	(MIYAZAKI *et al.*, 2013)

Medical gloves were prepared by mixing mangosteen peel powder in NRL and then dipping a porcelain hand mold into the mixture (MOOPAYAK; TANGBORIBOON, 2020). The authors highlighted the anti-inflammatory, anti-allergy, antibacterial, antifungal, and

antiviral properties provided by mangosteen peel, which could be applied as NR film to wound dressing.

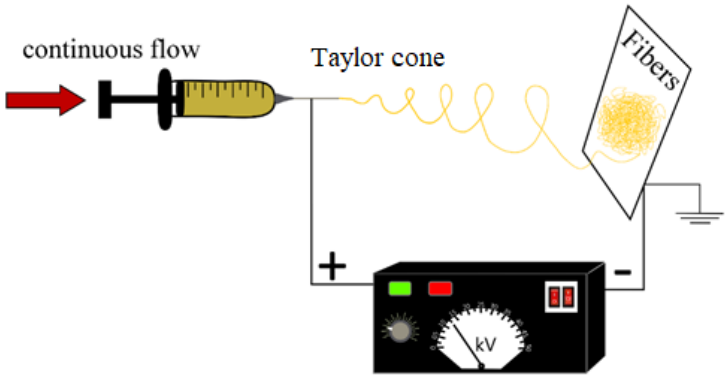
Surface modification of NR is effective in producing materials with antibacterial activity. Antibacterial sulphur prevulcanized NR film with high surface roughness and low cytotoxicity was prepared by dipping poly(methyl methacrylate) particles encircled with chitosan-coated silver nanoparticles (SUTEEWONG *et al.*, 2019).

The adsorption of silver nanoparticles in a poly(methyl methacrylate) core using a heterocoagulation technique promoted the surface roughness and was decisive for antibacterial activity against Staphylococcus *aureus* and *Escherichia coli.* Likewise, antibacterial coatings were prepared using di-functionalized oligoisoprenes from NR and acrylate monomer containing a guanidinium group as the active agent (TRAN *et al.*, 2019). NRL/magnetite nanoparticles-carboxymethyl-chitosan film was deposited onto NR membranes under bending of layer-by-layer driven by an external magnetic field (MIYAZAKI *et al.*, 2013). The authors highlighted that this method is advantageous for biomedicine, as there is no need for metallic electrodes, ionic transport, materials' swelling, and electrical currents.

2.1.2.3 Electrospinning

The electrospinning technique has attracted great interest in the field of biomedical science due to the possibility of manufacturing nanoscale structures with outstanding properties, such as high porosity and high surface area (REHMAN; HOUSHYAR; WANG, 2021). The polymer solution is extruded through the electrically charged metal needle (Figure *7*). Due to the presence of an electric field, a spherical drop is formed at the tip of the needle when this field reaches its limit. From this point on, the droplet deforms and assumes a conical shape known as a Taylor cone, resulting in the emergence of fibers that are collected in a metal collector (LEIDY; XIMENA, 2019). The whipping motion during electrospinning allows the polymer chains within the solution to stretch to form fiber with dimensions ranging from 3 nm to more than 5 μm (VALIZADEH; FARKHANI, 2014).

Figure 7 - Electrospinning process.



The electrospinning involves different operating parameters (e.g. voltage, tip-to-collector distance, flow rate, etc.), solution parameters (e.g. polymer concentration, solution viscosity, solvent, solution conductivity, etc.), and environmental parameters (e.g. humidity, temperature, etc.). The surface area, interconnectivity structure, and porosity can be fine-tuned by controlling the operating parameters. These features make electrospinning an important technique in the biomaterials field since the electrospun mats can enhance and improve their efficiency in mimicking biological signs. This technique excels in processing wound dressing mats that facilitate cell adhesion, proliferation, and differentiation, and act as a device for the delivery of drugs, growth factors, and other biomolecules (SOARES *et al.*, 2018). The electrospun scaffolds can be tailored according to their purpose to get a better attachment, proliferation, and differentiation (HAIDER; HAIDER; KANG, 2018). The porous electrospun mats provide scaffolds for oxygen and nutrient transfer for tissue engineering applications (COSME *et al.*, 2016). Moreover, the scale-up of electrospinning is possible by increasing the fiber jet through multiple needles and industrial-scale equipment is already available in the market to fulfill industry production requirements. Various studies have reported the development of electrospun mats of NR and epoxidized NR as shown in Table 3. However, these materials are difficult to electrospun and the carrier polymer is often the material in higher concentration, which may mask the effect of the rubber on the biomedical application. Thus, further studies are needed to enable the processing of NR via electrospinning by either using a higher concentration of the natural polymer with/without modification or adding compounds that increase the electrospinnability.

Table 3 - Overview of electrospun mats applied to biomedical science.

Material (carrier polymer:natural rubber wt%) (additive)	**Solvent (polymer concentration in solvent wt%)**	**Tip-to-collector distance (cm); flow rate ($ml \cdot h^{-1}$); voltage (kV)**	**Fiber diameter (nm)**	**Reference**
NR and Polyvinylpyrrolidone (50:50) (N/A)	Chloroform (1)	14; 0.40; 9	2400[1]	(ANDRADE *et al.*, 2022a)
NR (N/A) (N/A)	Tetrahydrofuran (3)	8; 2; 25	5300	(LI *et al.*, 2019)
Poly(vinyl alcohol) and NR (57.4:42.6) (Triton X-100 1wt%)	Distilled water (16.5)	25; 0.8; 20	1990	(PANICHPAKDEE *et al.*, 2019)
Poly(vinyl alcohol) and NR (61.5:38.5) (N/A)	Deionized water (13)	18; 0.6; 15	200[1]	(ZHOU *et al.*, 2019)
Poly(vinyl alcohol) and chloroacetated NR (91.7:8.3) (Fumed silica 2.5 wt%)	Distilled water, hydrogen peroxide, formic acid and chloroacetic acid (41)	20; 0.5; 10	41	(AZARIAN; BOOCHATHUM, 2018)
Poly(lactic acid) and Epoxided NR (75:25) (N/A)	Chloroform (N/A)	17.5; 0.5; 12	858	(COSME *et al.*, 2016)
Poly(caprolactone) and NR (85:15) (N/A)	Chloroform and toluene (8)	20; N/A; 12	312	(COSTA; MATTOSO; FERREIRA, 2013)

([1]Measured with ImageJ Software).

In this technique, an important aspect is the selection of a solvent to dissolve the polymer to afford sufficient solution viscosity and to avoid jet breakup toward the collector (MOKHENA *et al.*, 2020). Recently, Li et al. selected tetrahydrofuran, chloroform, dichloromethane, and toluene as solvents for NR electrospinning (LI *et al.*, 2019). Electrospun fibers with a diameter ranging from 2 to 7 μm were produced with no obvious influence of solvent. Tetrahydrofuran was further studied due to its relatively low toxicity and better solubility. The electrospun mats of pure NR showed high tensile strength with an elongation of 505% proving the elastic ability of NR. The increase in NR concentration resulted in larger fibers. In contrast, Costa et al. observed a decrease of about 454% in fiber diameter when increasing the NR concentration (COSTA; MATTOSO; FERREIRA, 2013).

The high molecular weight of NR increases the solution viscosity of the solutions which results in larger fibers when used alone, however, when used in a blend until a limited concentration of NR, the carrier polymer provides other features to the solution, such as viscoelastic behavior, packaging effect of NR molecules, and higher orientation of the polymeric chains. Nevertheless, the rheology of NR solutions is still not investigated for electrospinning of biomedical mats, despite being a main controlling parameter (CACCIOTTI *et al.*, 2015).

To be applied to biomedical engineering, the mats must be uniform and reproducible. The electrospinning of pure NR shows that a small amount of polymer already provides the necessary rheological properties, however, microfibers are obtained. Pore interconnectivity, high porosity, and surface area of electrospun tissues improve cellular adhesion and growth. Therefore, several works performed the electrospinning of NR together with a synthetic polymer that provides the necessary properties to produce nanofibers. Nevertheless, the immiscibility of the blends was also observed due to the incompatibility between the components with very weak interactions between the polymers (COSTA; MATTOSO; FERREIRA, 2013).

Panichpakdee et al. reported that the addition of surfactant helped in fiber morphology, but rough fibers were still produced (PANICHPAKDEE *et al.*, 2019). The authors mentioned that increasing the NR concentration from 10 wt% to 70 wt% related to poly(vinyl alcohol) concentration resulted in an increase of almost 86% in fiber size. Improvement in the mechanical properties of the electrospun mat was observed only with the 10 wt% NR concentration, which was attributed to the tighter packaging. The addition of NR to the blend with polycaprolactone also increased the tensile modulus, the ultimate elasticity, and the strain of electrospun mats (COSTA; MATTOSO; FERREIRA, 2013). High

elongation (238%) and swelling property (202%) were also obtained with the sample with 10 wt% NR (PANICHPAKDEE *et al.*, 2019). Nevertheless, the sample with a higher concentration of NR (90 wt%) resulted in higher elongation (687%) and maintenance of structural integrity in water after 24 h. These results show that the appropriate concentration of NR should be chosen based on the requirements of the biomedical device.

Recently Zhou et al. reported the processing of smooth hydrophilic electrospun ultrathin fibers with a blend of poly(vinyl alcohol):NR 8:5 wt% in water with remarkable flexibility (ZHOU *et al.*, 2019). The different morphologies reported in the literature are due to a difference in electrical polarity between NR and the carrier polymer, which hampered the compatibility between both compounds. Therefore, Cosme et al. employed epoxidized NR to improve the polarity of rubber and promote compatibility with poly(lactic acid) (COSME *et al.*, 2016). The researchers observed that epoxidized NR increased the crystallinity fraction of the blend with poly(lactic acid) by promoting extra mobility of the chains, which was also observed by Costa et al. when blending NR with polycaprolactone (COSTA; MATTOSO; FERREIRA, 2013).

Azarian and Boochathum investigated the silica effects on the biodegradation of nontoxic nanofibrous electrospun tissue of chloroacetated NR/poly(vinyl alcohol) (AZARIAN; BOOCHATHUM, 2018). The authors observed the compatibility of these compounds through thermogravimetric analysis. With fumed silica encapsulation, the mean diameter of nanofibers decreased by about 36% due to the increase in surface tension. Fumed silica also served as a thickening agent in electrospinning. The hydrophobic nature and low water absorption of chloroacetated NR were decreased after blending with poly(vinyl alcohol). Moreover, the encapsulation of fumed silica increased the biodegradability rate of chloroacetated NR/poly(vinyl alcohol) electrospun tissues by facilitating their chemical interaction. The mechanical properties were also improved after loading poly(vinyl alcohol) and fumed silica. Erosion properties were evaluated through enzymatic degradation, which showed a higher initial degradation rate of the electrospun tissues on the 7^{th} and 14^{th} days. This study corroborated the tailored biodegradability of NR by using inexpensive additives.

Andrade et al (2022b) reported the development of non-woven electro-woven fiber mats containing blends of NR and polyvinylpyrrolidone in different concentrations. The study demonstrated the possibility of adjusting wettability by changing the proportion of polymers in the blends, as attested by experimental measurements and theoretical modeling. The researchers state that the association of NR:PVP presents interesting characteristics for biomedical applications when there is a need to control the wettability of the system.

The electrospinning technique enables the development of highly porous dressings and scaffolds that resemble the native extracellular matrix, thus favoring the skin healing process and cell growth. It is worth mentioning the need to optimize the process parameters so that it is possible to produce fibers with smaller diameters and also, besides the rheological tests of the NRL and NR (ANDRADE *et al.*, 2022b).

2.1.2.4 Other Techniques

Blends of NR and polycaprolactone diluted in dichloropropane (60:40 and 40:60 NR: polycaprolactone wt%) were prepared by heating at 70 °C for 10 min followed by compression (150 °C/20 min) (LAI; LIU; HUANG, 2020). To increase the injury healing, blends were developed with polycaprolactone grafted with acrylic acid (polycaprolactone-g-2AA and polycaprolactone-g-4AA). A self-healing test was performed and the authors observed an increase in healing (63%) with the grafted blends (40:60 NR: polycaprolactone-g-4AA wt%). Moreover, the shape of memory-assisted self-healing increased to approximately 80% of the healing efficiency. It is important to mention that the use of grafted polymer with NR results in a semi-natural biomedical device.

Research involving the extraction of other constituents of NRL, such as proteins with biological properties, is explored by scholars (Table 4). The use of the NRL protein fraction currently stands out for presenting promising results regarding angiogenesis, tissue repair, and vascular neoformation (BALABANIAN *et al.*, 2006; DIAS *et al.*, 2019; FERREIRA *et al.*, 2009). After collecting and stabilization, NRL is coagulated with the addition of acetic acid (pH 5.0), and the serum fraction is obtained. Subsequently, the pH is increased to 9.0 with the addition of sodium hydroxide, and the material is filtered and chromatographically separated, where three sub-fractions are obtained (P-1, P-2, and P-3) (FERREIRA *et al.*, 2009; PAINI *et al.*, 2020). The extraction of P-1 (or F-1) has been explored in the biomedical area through the production of gels, solutions, and creams that are often incorporated into carrier agents (ANDRADE *et al.*, 2022b). For example, the anterior tibial muscle of rats after sciatic nerve crushing was evaluated through low-level laser therapy, use of P-1, or both in a combination. After 8 weeks, the treatment containing only P-1 proved to be the most efficient (MUNIZ *et al.*, 2015). In another work, the morphological and morphometric analysis showed that the association of P-1 with hyaluronic acid was the treatment that provided the most significant improvement in sciatic nerve recovery after 8 weeks of injury (BARREIROS *et al.*, 2014).

Table 4 - Overview of the extraction technique of NRL constituents applied to biomedical science.

Material	Carrier agent	Concentration of carrier agent (wt%)	Reference
NRL serum	N/A; Carboximetilcelulose	N/A; 99.5	(LEITE *et al.*, 2020; MENDONÇA *et al.*, 2010)
NRL	N/A	N/A	(FURUYA *et al.*, 2017; FURUYA; SHIMONO; OKAMOTO, 2017; KINOSHITA *et al.*, 2019; TINU *et al.*, 2012)
P-1	Hyaluronic acid	91	(BARREIROS *et al.*, 2014; CURY *et al.*, 2019; DIAS *et al.*, 2013, 2015, 2019; MUNIZ *et al.*, 2015)
P-1	N/A; Monoolein gel	N/A; 50	(IYOMASA *et al.*, 2012; MACHADO *et al.*, 2015)
NRL	N/A	N/A	(TINU *et al.*, 2012)
NRL cream-gel Regederm®	N/A	N/A	(BRANDÃO *et al.*, 2016)

Screw-assisted extrusion was used to develop 3D scaffolds coated with NRL P1 protein and graphene nanoparticles, with potential application in bone regeneration (CAETANO *et al.*, 2018). The authors observed the cultivation of the scaffolding of stem cells derived from human adipose in the absence of cytotoxicity. Scaffolding coated with graphene nanoparticles and P1 protein from NRL provided increased cell proliferation when compared to pure PCL scaffolding, in addition to promoting osteogenic differentiation due to the presence of the NRL protein.

Similar to electrospinning, porous mats can also be obtained by the blow spinning technique. In this process, pressurized gas flows around a polymer solution, creating fibers that are deposited in the direction of gas flow (DARISTOTLE *et al.*, 2016). Blow spinning was applied to processing a fibrous mat composed of NR and 45S5 Bioglass® (SOUSA *et al.*, 2019). First, the NR membrane was developed by the casting method, then NR solution (4 w/v%) was prepared by dissolving part of this membrane in chloroform, followed by the addition of Bioglass® particles. The mat was produced by coupling a syringe containing the solution to an injection system under favorable conditions. A good distribution of the Bioglass® particles was observed on the surface and inside the NR microfibers. The authors stated that blow spinning and the solution preparation method significantly influenced the mechanical and thermal properties of the biocomposite.

2.1.3 Conclusions and Final Remarks

The demand for biomaterials applied to biomedical science has grown continuously during the last decade. While the progress of natural polymers has increased lately, synthetic polymers still represent the majority of materials in biomedical applications. Thus, NRL and NR are promising materials to fill this gap due to their low cost, good mechanical properties, biodegradability, biocompatibility, bioactivity, and angiogenic properties, among others described in this review. These products fulfill the three pillars of sustainability: environmental by being bioavailable from a natural and renewable source, social by supporting rural communities, and economic by increasing the income of regions dependent on bioproducts.

In this review, the state-of-the-art developed in the last decade on processing techniques of NRL and NR biomedical devices were covered. Several studies have already proven the potential of products developed from NRL and NR in inducing angiogenesis and tissue repair. Despite the significant development faced in recent years, the design of more efficient NRL- and NR-based biomaterials for biomedical applications and your commercialization is still needed.

The commercialization of NR and NRL biomaterials is limited because the number of studies is still low. Even though the first study was published in 1994, some obstacles include 1) acceptance, based on previous allergy-related issues, which could be resolved with the advancement of processing technology; 2) material availability on a global scale, many medical and biomaterials research centers choose other polymers with greater availability and accessibility because the majority production of NRL takes place in Asia, and 3) complete understanding of NRL components. The lack of pattern in the composition can be an obstacle because it is a plant-based product, whose composition is prone to many variations depending on the time of year, soils, chemical or physical stimulation of the tree, clone, and other factors. However, with the quest for sustainability and the development of biomaterials and green products increasing lately, the authors believe that the number of NR and NRL studies will face growth in the coming years.

This review predicts the high potential of NRL and NR as polymeric biomaterials for biomedical science and the importance of knowledge about processing techniques. Among the various techniques used to produce biomedical materials from NRL and NR, the casting technique stands out for its simplicity of handling. Another technique that deserves to be highlighted, but has been little explored, is electrospinning, which can produce fibers with

diameters ranging from micro- to nanoscale by controlling the process parameters. Other techniques show potential for processing NRL and NR, such as NRL protein extraction and blow spinning.

Numerical and analytical modeling is beneficial for understanding structure-property relationships, however, no research has been reported in the literature. Improved models would help to better understand the hierarchical synergies and design parameters in NRL and NR. Finally, future approaches for NRL and NR in biomedicine include tighter regulation of drug delivery and dose rate because they demonstrate burst release in the initial hours. The utilization of nanoencapsulation and conductive elements in the NR and NRL matrix also suggests the possibility of drug delivery controlled by external stimuli. The usage of 3D printed NR and NRL devices also show significant promise for improving the effectiveness and safety of scaffolding and delivery systems.

2.1.4 Acknowledgments

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2.1.5 Authors' Contributions

Table 5 - Authors' contributions.

Author	Contributions
Andrade, K. L.	Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing
Ramlow, H.	Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing
Floriano, J. F	Formal analysis, Investigation
Acosta, E. D.	Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing

Table 5 - Authors' contributions (continuation).

Author	Contributions
Faita, F. L.	Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Visualization, Writing – review & editing
Machado, R. A. F.	Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Visualization, Writing – review & editing

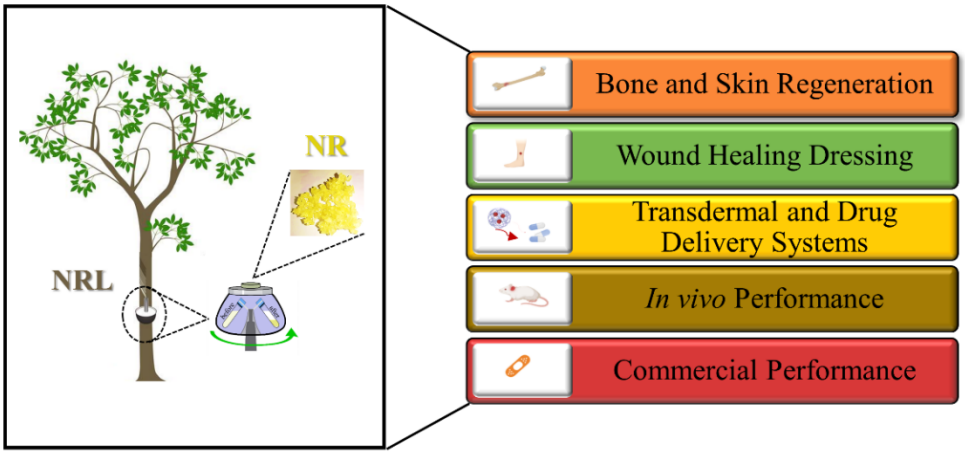
2.2 LATEX AND NATURAL RUBBER: RECENT ADVANCES FOR BIOMEDICAL APPLICATIONS[2]

Recent work has shown that NRL and NR are bioactive materials that promote cell adhesion, extracellular matrix formation, and accelerating tissue repair due to increased angiogenesis at the site of injury (RAHIMI; MASHAK, 2013; SANTOS KOTAKE *et al.*, 2018). NRL and NR polymers present biocompatibility and angiogenic properties that induce tissue healing, high elasticity, flexibility, and mechanical strength (BARROS *et al.*, 2015; CARVALHO *et al.*, 2018; FLORIANO *et al.*, 2016; MRUÉ *et al.*, 2004; RIBEIRO *et al.*, 2017; ZIMMERMANN *et al.*, 2007). A range of biomedical devices based on NRL and NR have been recently developed to accelerate tissue repair, including wound dressings, cellular scaffolds, as well as components of sustained drug delivery systems and transdermal drug delivery patches (BARROS *et al.*, 2015; CARVALHO *et al.*, 2018; GUERRA *et al.*, 2021) (Figure 8).

Although significant progress has been made in utilizing NRL and NR as functional biomaterials, there is a need to comprehensively document these developments for biomedical applications and regenerative medicine. This review aims to study and discuss the advances in the field of NR and NRL biopolymers and to foster a better conception of how these polymers have evolved as a field of significance in biomedicine. A summary of the biodegradability and biocompatibility of NRL and NR is first presented. Next, the application as a biomedical device and the incorporation of additives are discussed. Finally, the review presents the conclusions and remarks for the future growth of NRL and NR biomaterials for biomedical applications and regenerative medicine.

[2] Based on the published article: Andrade, K. L., Ramlow, H., Floriano, J. F., Acosta, E. D., Faita, F. L., & Machado, R. A. F. (2022). Latex and natural rubber: recent advances for biomedical applications. *Polímeros: Ciência e Tecnologia*, *32*(2), e2022015. https://doi.org/10.1590/0104-1428.20210114

Figure 8 - Recent advances for biomedical applications of NRL and NR.



2.2.1 Biocompatibility and Biodegradability

The most important characteristics of biopolymers with potential application in the biomedical field refer to their biocompatibility and biodegradability, making them promising alternative eco-friendly resources to non-degradable synthetic polymers, which are common in short-term applications in biomedicine (ABRAHAM *et al.*, 2012; SOARES *et al.*, 2018).

Biocompatibility describes the ability of a biomaterial to perform its intended purpose in medical therapy without causing harmful effects on the body (GEORGE *et al.*, 2020). The material is usually analyzed by *in vitro* cell culture studies, including cytotoxicity tests, biochemical measurements of cell activity, and evaluation of cell proliferation, growth, and morphology (SCHMALZ; GALLER, 2017). *In vitro* cytotoxicity analysis is standardized and regulated by a series of standards e.g. 'ISO 10993: Biological Evaluation of Medical Devices' that evaluate the materials intended for the manufacture of devices for biomedical applications. The *in vitro* evaluation has the advantage of limiting the experimental variables, and it is easy and fast to obtain meaningful data. When the non-toxicity of the material is proven, animal studies must be performed (INTERNATIONAL STANDARD ORGANIZATION (ISO), 2003, 2009; ROGERO *et al.*, 2003).

Several studies have already been performed regarding the biocompatibility of NRL and NR. According to the literature, the biocompatibility of NRL is well established (BORGES *et al.*, 2017; FLORIANO *et al.*, 2014; FURUYA; SHIMONO; OKAMOTO, 2017; MRUÉ *et al.*, 2004; ZIMMERMANN *et al.*, 2007). However, there are still some aspects to be considered for this property to become even more satisfactory, such as a safer collection method and adequate processing (GUERRA *et al.*, 2021). Both factors can directly influence

the biocompatibility of NRL and NR, interfering in their application. Floriano et al. observed that latex membranes in contact with ammonia during collection showed cytotoxic and genotoxic effects on cultures of NIH3T3 fibroblasts. All clones showed increased cell viability compared to the sample without ammonia (FLORIANO *et al.*, 2014). Twelve types of commercial NRL gloves were analyzed and showed that residual chemicals are the main cause of poor biocompatibility. Experiments indicated that solvent washing can effectively remove residues from medical devices (QAMARINA *et al.*, 2010). In return, NRL membranes showed no cytotoxicity and allowed adhesion, proliferation, and extracellular matrix deposition for MC3T3-E1 osteoblasts (BORGES *et al.*, 2017; FURUYA; SHIMONO; OKAMOTO, 2017).

Besides biocompatibility, biodegradability is another fundamental material property for biomedical materials. Biodegradable polymers are characterized by being broken down into biologically acceptable molecules through enzyme catalysis, involving hydrolysis or oxidation (BALAJI *et al.*, 2017). The biodegradability of NR has been widely studied due to the growing indiscriminate use of its by-products e.g. thousands of units of disposable gloves and NRL condoms that are discarded in nature, as well as the difficulties encountered in the reuse of these materials. For instance, the demand for personal protective equipment related to the circulation of the SARS-CoV-2 virus has increased since 2020. Given the limited space in landfills, the high cost of incineration, and the high potential risk to health and the environment, the studies on the biodegradability of NR become fundamental (ANDLER, 2020; NANTHINI; SUDESH, 2017; NOWAKOWSKI *et al.*, 2020).

The first studies developed on the degradation of NR by microorganisms started more than 100 years ago, but currently, there is still a shortage of biotechnological applications (ANDLER, 2020). Some studies reporting the use of microorganisms, enzymes, and composting in the biodegradation of NR are reported in the supporting material (Table 6).

When evaluating the degradation of NR in the presence of *Penicillium* and *Aspergillus*, Tsuchii et al. verified a 32% weight loss in 30 days (TSUCHII, 1995). Most NRL and NR biomedical materials are still not degradable or do not present absorption by the body due to slow microbiological biodegradation, making it necessary to remove the material after implantation (GUERRA *et al.*, 2021). The blending with other compounds provides higher levels of degradation of NR, for instance, NR blended with cellulose and sodium alginate showed a mass loss of 50% after 56 days (SUPANAKORN *et al.*, 2021).

Table 6 - Biodegradability of NR.

Material	Microorganism/ Enzyme/ Composting	Time (days) / Weight loss (%)	Application	Reference
NR	*Penicillium* and *Aspergillus*	30 / 32.0	General	(TSUCHII, 1995)
NR + nanocelullose; NR + crosslinked nanocellulose	*Eudrilus eugeniae*	60 / ~15.0; 120 / ~60.0	General	(ABRAHAM *et al.*, 2012)
Chloroacetated NR; Chloroacetated NR + polyvinyl alcohol; Chloroacetated NR + polyvinyl alcohol + kaolin; Chloroacetated NR + polyvinyl alcohol + starch	Amylase	35 / ~10.0; 35 / ~20.0; 35 / ~10.0; 35 / ~55.0	Tissue engineering	(AZARIAN; BOOCHATHUM; KONGSEMA, 2019)
NR + celullose; NR + celullose + fertilizer	Soil microorganisms	35 / ~12.2; 35 / ~16.0	General	(HARAHAP *et al.*, 2020)
NR + poly (3-hydroxybutyrate-co-3-hydroxyvalerate)	Aerobic composting	53 / 15.0	General	(ZHAO *et al.*, 2019)
Rubber gloves + fertilizer	Soil microorganisms	28 / N/A	Personal protection equipment	(MISMAN; AZURA, 2014)

Even when NRL and NR are combined with other biodegradable compounds, the problem remains. A possible solution to this fact would be deproteinization of the NRL which makes the material safe to remain inside the body for long periods without the need for removal (FLORIANO *et al.*, 2014). In addition, most of the studies concerning the biodegradation of NR are conducted on a laboratory scale. Another fact that deserves to be highlighted is the scarcity of studies involving the biodegradation of NR in biomedicine. There is still a need for the development of materials based on NRL and NR with a higher level of biodegradation with biomimetic characteristics, thus maintaining their structure and function for a longer time.

2.2.2 Application as a Biomedical Device

Among the various techniques used to produce biomedical materials from NRL and NR, the casting technique stands out for its simplicity of handling. Another technique that deserves to be highlighted, but has been little explored, is electrospinning, which can produce fibers with diameters ranging from micro- to nanoscale by controlling the process parameters. Other techniques show potential for processing NRL and NR, such as NRL protein extraction and blow spinning. Processing techniques including casting, spraying, dipping, and electrospinning, among others (more information is found in the Supporting Material), result in different NRL and NR biomedical devices, which have been applied mostly as drug delivery systems and scaffolds for skin and bone regeneration, while the application for wound healing dressing and transdermal drug delivery system has been less investigated. Some *in vivo* tests were conducted, however, commercial application of NRL and NR as biomedical devices is very limited. The biomedical applications of NRL and NR are described below.

2.2.2.1 Drug Delivery Systems

Drug delivery systems are responsible for the body internally delivering a drug or active compound in the desired dose to a particular region of the human body, which can improve efficacy and safety by controlling release rate, time, and location (ALMEIDA *et al.*, 2020; BRUSCHI, 2015). This system development allows a more selective and precise release to a specific site and requires a lower dosage because the delivery is *in situ*, with more consistent absorption and a decrease in toxic metabolites (ROBINSON; MAUGER, 1991).

Networks' formation by the isoprene chains works as a reservoir that allows the gradual release of compounds, highlighting its potential for drug delivery (BARROS *et al.*, 2015; FLORIANO *et al.*, 2018; ZANCANELA *et al.*, 2019). Using NR as a solid matrix for drug delivery systems is reported in several studies involving wound dressings (AZEVEDO *et al.*, 2014; CARVALHO *et al.*, 2018; MIRANDA *et al.*, 2018). Some studies have reported sustained release provided by NRL and NR occurring through diffusion, which can be facilitated through fractures and pores on their surface with the 'burst release' (AIELO *et al.*, 2014; BARROS *et al.*, 2018; FLORIANO *et al.*, 2018). Drug release kinetics can be altered by structure modifications of NRL and NR devices, such as porosity increase/decrease, increased drug incorporation into the bulk material or its surface, or into the shell (MIRANDA *et al.*, 2017). Combining NRL or NR with drugs or bioactive compounds promotes the incorporation of new properties to the material, which can provide even more satisfactory results in biomedical applications 'optimization'. This incorporation is preferably done with NRL because it is a liquid suspension and provides greater miscibility of the compound when compared to incorporation in NR, which is a solid material.

Table 7 mentions some drugs and bioactive compounds that have been used in formulations with NRL and NR, including ciprofloxacin, propolis, and *Casearia sylvestris Swartz.* Ciprofloxacin is an antimicrobial agent that has antioxidant potential when incorporated into any dressing, promoting the acceleration of the healing process (WATTANAKAROON *et al.*, 2017). It has long been known that silver is highly toxic to microorganisms, showing strong biocidal effects on bacteria and fungi (LIAU *et al.*, 1997). Propolis is also an antibacterial with relevant pro-activating characteristics (ROY *et al.*, 2010), which presents great advantages over the most common antibacterial agents, standing out due to its high biocompatibility, antimicrobial power, and natural source origin (MARTINOTTI; RANZATO, 2015; TORLAK; SERT, 2013). Propolis is widely used in biomedical dressings, representing a strategy that goes beyond the prevention of injury infections, because it still has pro-healing characteristics, triggering the acceleration of the injury healing process. *Casearia sylvestris Swartz* is a Central and South American tree from which its leaves are used in the treatment of gastric diseases and also for antiophidic, anti-inflammatory, anti thermal, and wound healing purposes (FERREIRA *et al.*, 2011).

Table 7 - Overview of drugs and active compounds added to NRL and NR applied to biomedicine, with respective concentrations and solvents.

Drug/active compound; concentration ($mg \cdot mL^{-1}$)	**Solvent for drug; active compound impregnation**	**Reference**
Bovine serum albumin; 2; 10	N/A; Deionized water	(MIRANDA *et al.*, 2017, 2018)
Casearia sylvestris; 0.25; 0.1; 1; N/A; 0.25	Ethanol; Ethanol; Ethanol; Ethanol and water; Ethanol	(AZEVEDO *et al.*, 2014; BOLOGNESI *et al.*, 2015; BORGES *et al.*, 2014; CARVALHO *et al.*, 2018; TRECCO *et al.*, 2014)
Ciprofloxacin; 3; 0.1; 10; 5; 0.01	N/A; Water; Water; Water; N/A	(ALMEIDA *et al.*, 2020; BOLOGNESI *et al.*, 2015; GARMS *et al.*, 2017; MURBACH *et al.*, 2014; WATTANAKAROON *et al.*, 2017)
Diclofenac; 3	N/A	(AIELO *et al.*, 2014; BARROS *et al.*, 2015)
Fluconazole; 10	N/A	(MARCELINO *et al.*, 2018)
Hydroxyapatite; 1, 2 and 3	Tetrahydrofuran	(DICK; SANTOS, 2017)
Ketoprofen; 10	Ethanol and water	(FLORIANO *et al.*, 2018)
Metronidazole; 10	N/A	(HERCULANO *et al.*, 2010, 2011a)
Propolis; 0.05; N/A; 0.05; 1, 2 and 3	Ethanol and water; Ethanol and water; Absolute ethyl alcohol and water; Absolute ethyl alcohol	(KRUPP *et al.*, 2019; SILVA *et al.*, 2014; ZANCANELA *et al.*, 2017, 2019)
Serjania marginata; 30	Ethanol and water	(BARROS *et al.*, 2018)
Silver; 0.1; 0.1; 679.5	Sodium borohydride; Deionized water; NRL diluted in water Mili Q	(GUIDELLI *et al.*, 2011, 2013; SUTEEWONG *et al.*, 2019)
Stryphnodendron obovatum; 0.1 and 5	Ethanol and water	(BORGES *et al.*, 2015)

Extract of *Casearia sylvestris Sw.* and ciprofloxacin was incorporated into NR films preserving the properties of the substances since no chemical interaction between materials was observed (BOLOGNESI *et al.*, 2015). The release rate of the extract was higher (~94%) than that of ciprofloxacin (~54%), both substances being adhered to the surface of porous NR films. With ciprofloxacin loading, the release of the drug was observed to be linearly proportional to the manufactured pore density (ALMEIDA *et al.*, 2020).

Serjania marginata extract was incorporated into the NR matrix, and 27% of the extract was released after 67 h preserving its antioxidant activity (BARROS *et al.*, 2018). A sustained delivery system for metronidazole was developed from NRL, with control of metronidazole according to the polymerization temperature of the NRL matrix. Polymerization at -100 °C showed the best potential for metronidazole release, with approximately 77% of metronidazole being released after 310 h, i.e., the release rate was slow (HERCULANO *et al.*, 2010).

These combinations provide the development of materials with antimicrobial, anti-fungal, and antioxidant activities, among other properties, that when associated with the biocompatibility of NRL and NR, demonstrate the great potential of these materials in biomedical applications. These materials reduce the cost of therapy, provide greater treatment efficacy, and improve the patient's quality of life. It is also worth highlighting the benefits of using NRL and NR in drug delivery systems due to their versatility and easy handling, being possible to modify their release kinetics according to the type of application.

2.2.2.2 Transdermal Drug Delivery Systems

Transdermal Drug Delivery System (TDDS) is a painless, non-invasive drug delivery technique, where the drug is simply made available from a skin patch or other transdermal method/device, running through the skin layers until it reaches the systemic circulation, reaching the specific organs for the treatment. Even with the advances in TDDS and the discovery of delivery devices for drugs of various origins (lipophilic, hydrophilic, and amphiphilic), dosage levels are still not competitive when compared to traditional delivery options (AKHTAR *et al.*, 2020; SUKSAEREE *et al.*, 2014). This type of system can be developed using both synthetic and natural polymers as matrices including NR.

To minimize common events triggered by this type of drug delivery, a TDDS of ketoprofen was developed by its incorporation in NR biomembranes. In this study, the chemical interaction of the drug with the membrane was not verified and a drug release of

60% was observed due to the portion of ketoprofen present on the membrane surface. The researchers concluded that this system is promising for drug administration, minimizing adverse effects caused by high dosages (FLORIANO *et al.*, 2018). TDDS composed of a deproteinized NR matrix, hydroxypropyl methylcellulose, and dibutyl phthalate, was developed aiming nicotine release. The experiments were conducted with and without the inclusion of a protective layer to prevent the volatilization of highly volatile nicotine (SUKSAEREE *et al.*, 2012). The authors identified a slower release and permeation of nicotine transdermal patches in the absence of support, while nicotine transdermal patches with a support layer were released and permeated more rapidly, indicating that the matrix is adequate as a TDDS system.

TDDS provides several advantages such as bioavailability and local drug concentration, which avoid difficulties caused by pH changes in the intestinal gastric tract and possible interactions with other drugs. TDDS can replace oral intake in cases of vomiting or diarrhea and, in cases of emergency (unconscious patient), a quick interruption can be done by removing the patch. Although some studies have already been carried out with NR involving this type of application, this subject is still not widespread and demands further investigation.

2.2.2.3 Regenerative Medicine and Tissue Engineering

Regeneration of skin, bone, cartilage, and organ tissues has been studied using patient cells cultivated on natural or synthetic substrates, followed by reinsertion, to regenerate damaged or lost body parts, restoring their function, the basis of regenerative medicine and tissue engineering (GUERRA *et al.*, 2018). Such substrates, known as scaffolding, are responsible for providing cellular fixation structure with cell proliferation/colonization, and a stable environment, helping tissue remodeling i.e. tissue regeneration. Scaffolding for regenerative medicine and tissue engineering should mimic the functions of the native extracellular matrix (CHAN; LEONG, 2008). Scaffolds can be produced by conventional molding methods such as casting, electrospinning, 3D printing, or by combining these techniques (ZHAO *et al.*, 2018).

Studies involving NRL or NR in scaffolds' processing have been developed to investigate potential applications in the regeneration of skin and bone tissue (BORGES *et al.*, 2017; GUERRA *et al.*, 2018; MACHADO *et al.*, 2015). An example of the application of

NRL and NR scaffolds with low cost is the treatment of thermal burns, a serious public health problem causing deaths and considerable psychological trauma.

Biomembranes developed from NRL for bone regeneration have shown promising results (ARAUJO; MASSUDA; HYPPOLITO, 2012; FLORIANO *et al.*, 2014, 2016). NRL biomembrane represents an alternative possibility of stimulation and potentiation of osteoconduction and guided bone regeneration, besides being biocompatible, potentially angiogenic, flexible, having mechanical properties, porosity, and permeability (BORGES *et al.*, 2017; CARLOS *et al.*, 2019; FLORIANO *et al.*, 2016). Additionally, Nascimento et al. showed that calcium/phosphorus compound is surrounded by NR particles due to electrostatic interactions, which can be easily changed in an ionic medium like body fluid, assisting in bone regeneration (NASCIMENTO *et al.*, 2014).

It is also worth mentioning the use of dressings commonly used in tissue engineering to improve natural skin healing. Dressings' composition should facilitate epidermal barrier restoration adhered to the lesion, absorbing exudates, preventing infection, dehydration, promoting tissue regeneration, and limiting the formation of granulation tissue (MAYET *et al.*, 2014; WATTANAKAROON *et al.*, 2017). Several investigations have been carried out regarding the use of NRL as a dressing for skin lesions (FRADE *et al.*, 2012; GARMS *et al.*, 2019; MIRANDA *et al.*, 2017; SILVA *et al.*, 2014). Moreover, NRL can be associated with other types of materials, improving their existing properties, or promoting new healing properties.

2.2.2.4 In vivo Performance

In vivo models aims to characterize the process and evolution of tissue response after implantation of a given biomaterial, that is, to evaluate the tissue-material interface (INTERNATIONAL STANDARD ORGANIZATION (ISO), 2007). Few works reported in the literature performed *in vivo* tests using NRL and NR, which include dogs (SOUSA *et al.*, 2011), rabbits (FLORIANO *et al.*, 2014, 2016; MENDONÇA *et al.*, 2010; MOURA *et al.*, 2014), rats (BRANDÃO *et al.*, 2016; CURY *et al.*, 2019; DIAS *et al.*, 2015, 2019; KRUPP *et al.*, 2019; LEITE *et al.*, 2020), and humans (FRADE *et al.*, 2012; NUNES *et al.*, 2015, 2016). Frade et al. applied an NR biomembrane on alternate days to treat chronic necrotic ulcers on the leg and foot of a 64-year-old patient (FRADE *et al.*, 2001). The authors observed the effects of granulation stimulation after 15 days of treatment, in addition to pain reduction. After 60 days, granulation tissue reached the edges of the ulcers, so the use of the

biomembrane was discontinued, followed by the use of chloramphenicol ointment. After 120 days of treatment, the ulcers were closed before clinical and histopathological reduction. The results were highly satisfactory, providing the patient with greater comfort at dressing changes. Similar data were found by Frade et al. when they evaluated this biomembrane in the treatment of skin ulcers and compared it with a treatment based on fibrinolysin and chloramphenicol. Lesions' healing was induced by intense vascular formation with subsequent re-epithelialization (FRADE *et al.*, 2012).

NR insole was prepared by using a negative alginate personalized mold, which was further applied to diabetic foot treatment to reduce the excessive pressure in the injured regions, significantly reducing the plantar pressures on the patient's feet by attenuating the total maximum force applied to them (NUNES *et al.*, 2015). The most significant decrease in plantar pressure occurred in the region of ante foot. In the middle region of the foot, the reduction of maximum force was observed. This customized insole was also used in association with a device having a red LED matrix to provide mechanical support and accelerate the healing of diabetic foot ulcers, providing comfort to patients. Patients were satisfied with the results, stating that the system was easy and simple to use contributing to the process of lesions' healing (NUNES *et al.*, 2016).

NRL serum was evaluated as a wound healer by *in vivo* tests in rats undergoing dermabrasion, treated with saline, antiseptic, or latex. The antiseptic solution was compared with a commercial saline solution *in vitro* tests and the effects of cell migration and proliferation were analyzed. The serum of NRL showed viability in concentrations of 1% and 0.1% and migration and proliferation activity with 0.01% of serum (LEITE *et al.*, 2020). Results showed that the serum did not present toxicity and, compared to other treatments, it was able to stimulate and accelerate the healing of lesions from abrasion.

The effects of applying P-1 (protein extracted from NRL) and Low-level Laser Therapy (LG) to the sciatic nerve of rats after crush injury were evaluated using hyaluronic acid as a carrier agent (1 wt%) with the incorporation of P-1 (0.1 wt%). The animals were anesthetized and the injury site was standardized: the upper and lower ventral spine. A ~2 cm skin incision was made perpendicularly and towards the middle region between the two mentioned points. After this, the muscle fascia was broken over the anterior femoral belly region of the biceps and gluteus maximus, and these muscles were divulsed, not requiring an incision. Finally, the nerve was exposed to the lesion by applying weight with a constant force of 15 kgf for 10 min, which caused the crushing of a circular area of approximately 0.6 cm in diameter. After finishing the lesion, the nerve was replaced and the skin was sutured,

followed by medication to prevent possible complications. After 4 weeks, improvements in lesion morphology and morphometry were observed in the LG, P-1 treated, and P-1 + LG groups (DIAS *et al.*, 2013). The researchers found that this improvement increased with treatment time.

2.2.2.5 Commercial Performance

Research on NRL began in 1994 in Brazil at the Department of Biochemistry of the University of São Paulo by Professors Dr. Joaquim Coutinho Netto and Dr. Fatima Mrue (MRUÉ *et al.*, 2004; ROSA, 2016). In 2002, a patent was filed by the University and the company PeleNova Biotecnologia S/A was created, which registered in 2004 the product Biocure®, a biomembrane derived from NRL responsible for inducing the formation of new blood vessels to induce angiogenesis. According to Rosa, its application was recommended for chronic diabetic, vascular, pressure ulcers, post-surgical or traumatic, being applied directly to the surface of the lesion. The first change was recommended 24 h after application (ROSA, 2016). The membrane was discontinued, due to the difficulty of application and maintenance of the product in the patient, and replaced by an ointment called Regederm®, a NR-derived compound in gel-cream form (isolated angiogenic fractions free of compounds that could cause allergy), being registered in Anvisa (Agência Nacional de Vigilância Sanitária) in 2012. During this same period, PeleNova partnered with a Canadian dermatological company, Valeant. In 2017, PeleNova was taken over by the former Brazilian administrators and two years later, the company returns with its market operations, providing bioactive products to licensed companies. The following year, it restructured its operations and became part of Biocure Pharma Biotechnology, a Brazilian group that projects strong development in the markets of therapeutics, cosmetics, and actives for various segments (BIOCURE PHARMA BIOTECHNOLOGY, 2021). Currently, Regederm® is not being marketed, possibly due to the company's product reformulation after its restructuring.

Another commercially available membrane is Cellprene®, composed of poly(lactic-co-glycolic acid) and polyisoprene, the main component of NR. Cellprene® was developed and patented by the Federal University of Rio Grande do Sul (Brazil) in 2013 for application in tissue engineering (GUERRA *et al.*, 2018; MARQUES *et al.*, 2011). According to the literature, Cellprene® has been used in recent studies demonstrating that this biomaterial can act in the maintenance of epithelial cells (GUERRA *et al.*, 2018; HENCKES *et al.*, 2019; SANTOS *et al.*, 2019).

2.2.3 Comparison with other Biopolymers

Recently, matrices obtained from electrospun fibers have gained much prominence and have been widely studied as wound dressing and scaffolds in biomedicine due to the ability to modulate cell behavior. Wound dressing and scaffolds are the main devices manufactured from NRL and NR for biomedical applications, thus, a brief discussion is made hereafter to compare the use of different biopolymers in the development of these devices. It is worth noting that, a direct comparison between the studies is difficult due to the different characteristics evaluated in each research.

A high degree of porosity and appropriate pore size are the main characteristics required for wound dressings and scaffolds to provide adequate space for cell propagation and migration, allowing for the proper exchange of nutrients and waste between the scaffold and the environment (SOLIMAN *et al.*, 2011). Pores smaller than bacteria help prevent infections through the sieve effect and therefore, these devices should have high porosity, preferably at the micro-and nanoscale (DWIVEDI *et al.*, 2017; MURUGAN; RAMAKRISHNA, 2006). The porosity and pore sizes of electrospun scaffolds depend mainly on the fiber diameter. Larger fiber diameters provide lower porosity and larger pore size (NELSON *et al.*, 2012; SOLIMAN *et al.*, 2011). Table 8 some data regarding the diameters of electrospun fibers from different biopolymers.

Table 8 - Comparison of electrospun fibers' diameter from different biopolymers.

Biopolymer	**Solvent**	**Fiber diameter (µm)**	**Suggested application**	**Reference**
NR	Tetrahydrofuran; Chloroform; Di-chloromethane; Toluene	~2.0-6.0; ~3.0-6.0; ~2.0-5.0; ~3.0-5.0	Soft tissue engineering	(LI *et al.*, 2019)
NRL NRL + Poly(vinyl alcohol)	Deionized water	N.A ~1.0-4.5	General	(PANICHPAKDEE *et al.*, 2019)
NR Polycaprolactone	Toluene Chloroform	N.A ~1.4	General	(COSTA; MATTOSO; FERREIRA, 2013)
Polycaprolactone	Di-chloromethane	~1.0	Scaffold	(WUTTICHAROENMONGKOL *et al.*, 2006)

The literature shows that poly(vinyl alcohol) and polycaprolactone electrospun fibers present diameters thinner than ~2 µm, while NR fibers have larger diameters, ranging from ~2 to 6 µm. This fact may hinder the production of NRL and NR devices suitable for biomedical

purposes since the polymer chains limit the manufacturing of high-porous biomaterials. Although NRL is inherently hydrophilic, after the drying process, it becomes predominantly hydrophobic (AMBEGODA *et al.*, 2021). For biomedical applications, a surface with hydrophilic properties is needed for adhesion, dissemination, and cell proliferation (LIU *et al.*, 2019).

NRL fibers can be manufactured by solubilizing in water, but this procedure is little reported in the literature. Most studies involve the production of fibers from NR, which is obtained after drying centrifuged NRL. Thus, another factor that deserves attention is the use of solvents during the production of NR fibers that can cause damage to the cells due to their toxicity. It is also worth mentioning that the studies involving the use of NR in the production of fibers for the development of scaffolds and wound dressing suggest certain applications, i.e., there is still a gap of scientific evidence proving satisfactory results of clinical applications of these devices.

2.2.4 Conclusions and Final Remarks

This review described and discussed the advances of NRL and NR biopolymers in biomedical applications and regenerative medicine, highlighting the development of drug delivery systems, scaffolds, wound dressing, and transdermal drug delivery systems. The research on these biomaterials is in full development, referring to applications in skin lesions in the form of dressings, cellular supports, bone regeneration, and release of bioactive molecules, among others. Studies show the high potential of NRL and NR due to the promotion of interesting biological properties and satisfactory biocompatible characteristics.

The recent advances in biomedical applications of NRL and NR have demonstrated the multidisciplinarity required for future research that includes the study of the biopolymer (engineering and chemistry), the manufacture of the biomaterial (engineering), and the final application (biology). Current results show that these materials can considerably contribute to medical advancement through the treatment of individuals that requires less time for the cure in an accessible way. The literature lists many suggestions for NRL and NR applications, but *in vivo* tests are still little mentioned, and therefore represent an important gap to be filled. It is necessary to show and prove the real potentiality of these materials, thus, more studies should be developed focusing on the application.

With the application of these materials proven through satisfactory results, the products derived from NRL and NR will present greater chances of being commercialized,

exempting the possibility of being discontinued. The simple addition of information on the packaging of the product and scientific communication is indispensable for the popular acceptance of NRL and NR biomedical devices, which present the high commercial potential for products focused on tissue engineering and regenerative medicine.

2.2.5 Acknowledgments

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2.2.6 Authors' Contributions

Table 9 - Authors' contributions.

Author	Contributions
Andrade, K. L.	Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing
Ramlow, H.	Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing
Floriano, J. F	Formal analysis, Investigation
Acosta, E. D.	Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing
Faita, F. L.	Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Visualization, Writing – review & editing
Machado, R. A. F.	Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Visualization, Writing – review & editing

3 ELECTROSPUN NONWOVEN MATS BASED ON NATURAL RUBBER: DETERMINATION OF THE BEST POLYMERIC ASSOCIATION FOR BIOMEDICAL APPLICATIONS

This chapter presents the materials, experimental procedures, and results obtained in tests using the association of Natural rubber:Polycaprolactone (NR:PCL), and Natural rubber:Polyvinylpyrrolidone (NR:PVP), which made it possible to designate the best conditions and parameters for the development of Chapters 4 and 5.

3.1 INTRODUCTION

The structure of the skin, as well as its functions, can be compromised by various types of injuries, such as surgical incisions, diseases, cuts, and burns (MÜHLSTÄDT; THOMÉ; KUNTE, 2012). After an injury, the skin structure and functions need to be restored as soon as possible. For this to happen, the healing process starts immediately after the incidence of a skin injury, avoiding the risk of bacterial contamination (MÜHLSTÄDT; THOMÉ; KUNTE, 2012; SIEDENBIEDEL; TILLER, 2012). With treatment, this healing can occur more quickly, providing better functional and aesthetic results to the victims, when compared to healing that occurs naturally or spontaneously (MÖRSCHBÄCHER *et al.*, 2011).

A method that has been disseminated in the biomedical area for the production of materials with potential use in wound healing is the use of electro-woven fibrous surfaces (BALAJI *et al.*, 2016; CUI; ZHOU; CHANG, 2010; JAGANATHAN; MANI, 2019; LIU *et al.*, 2017). Electrospinning is a very efficient technique for obtaining continuous, uniform fibers with diameters ranging from micrometers to nanometers (BHATTARAI *et al*., 2018). Polymeric electrospun nonwoven mats attract broad interest as functional materials (RODRÍGUEZ-TOBÍAS; MORALES; GRANDE, 2019), acting in the delivery of DNA, RNA, proteins, and cell growth factors and, due to the high surface-to-volume ratio of these fibers, assisting in the enhancement of mass transfer and cell attachment and proliferation processes (BHATTARAI *et al.*, 2018; TORRES-MARTINEZ *et al.*, 2018).

The electrospinning technique is interesting because it can result in the production of porous structures that aid in cell attachment, spreading, proliferation and differentiation. In addition, it results in significant time and cost savings for the biomedical industry by allowing the use of various classes of polymers. In this context, the choice for the electrospinning

technique has shown to be promising, given the feasibility of reproducing the morphology of a native extracellular matrix with a biofunctional and biocompatible material, using the mixture of natural rubber (NR) and synthetic polymers, such as PCL and PVP

PCL is a polymer with biodegradable and biocompatible characteristics, but some researchers report its limitation in biomedical applications due to the presence of hydrophobic properties (WANG; WINDBERGS, 2017). The high surface porosity of PCL fibers and the weak interfacial interaction of the material with other compounds may be an obstacle, but its association with other polymers may represent a good alternative (BUI *et al.*, 2014; ZHOU *et al.*, 2019). Unlike PCL, PVP is a hydrophilic polymer, but also has biodegradable and biocompatible characteristics, in addition to being bioactive, non-toxic, temperature resistant, and pH stable. Because it has versatile properties, PVP has been widely used in the development of materials for biomedical purposes, from various processing technologies, such as electrowinning (KURAKULA; KOTESWARA, 2020).

The fibrous morphology obtained in the electrospinning is favorable not only to the growth and repair of tissue cells, but also to pathogenic microorganisms, therefore, the development of polymeric electrospun nonwoven mats with biocidal properties, but the absence of cytotoxicity is fundamental (RODRÍGUEZ-TOBÍAS; MORALES; GRANDE, 2019). Dressings containing antibacterial and healing-accelerating properties are emerging as valuable options for the wound-healing process (KHODABAKHSHI *et al.*, 2019). Thus, the objective of this chapter was to establish the best experimental conditions for the production of biocompatible fibers from the blends of NR:PCL and NR:PVP by the electrospinning technique, with potential use in biomedical applications.

3.2 ELECTROSPUN NONWOVEN MATS FROM NR:PCL FOR BIOMEDICAL APPLICATIONS

3.2.1 Materials and methods

PCL (molecular weight of 80,000 $g.mol^{-1}$, Sigma Aldrich) and, chloroform (as a solvent, purity degree ≥ 99.8% - Dinâmica Química Contemporânea LTDA) were used. Natural rubber latex (NRL) was collected from RRIM 600 clones of *Hevea brasiliensis* trees, in the city of Bauru - SP, which was made available due to collaboration between research groups of the Polymerization Process Control Laboratory (LCP) from Federal University of Santa Catarina (UFSC) and São Paulo State University (UNESP). For the collection of NRL,

the conventional method was used, through a spiral cut in the trees, followed by stabilization of the material with 5 w/v% ammonium hydroxide. The collected material was stored in a glass container and kept under refrigeration (5 °C) until its use.

The Dry Rubber Content (DRC) present in the NRL was performed in triplicate following the method described by Tillekeratne *et al.* (1988) with adaptations. Petri dishes previously cleaned and dried were used followed by the addition of 5 mL of the NRL. Subsequently, the plates were taken to the oven at 55 °C to allow for evaporation of the liquid content. New measurements were performed daily until the constant weight of the plates was obtained. The DRC was determined by Equation (1), according Tillekeratne *et al.* (1988), considering the density of NR, W_2 being the weight of the dry rubber or the total solid weight remaining and W_1 being the weight of the initial NRL.

$$DRC = 100\ x\ \frac{W_2}{W_1} \quad (1)$$

The NRL was subjected to refrigerated centrifugation (Eppendorf Centrifuge 5804R) at 5 °C and 11000 RPM for 60 minutes. After centrifugation, the phase separation of the NRL was observed and then the upper fraction of the material was removed, the rubber cream, which was packed in a Petri dish and subjected to drying in an oven at 55 °C for 48 hours, obtaining at the end the dry NR.

The dried NR was solubilized in chloroform on a stir plate for about 60 h at room temperature at the concentration of 50 $mg.mL^{-1}$ (NR-50). The solubilization of PCL in chloroform occurred on a stir plate for 2 h at room temperature at the concentrations of 100 and 120 $mg.mL^{-1}$. From the pure solutions of NR and PCL, the blends NR:PCL-100 and NR:PCL-120 were produced in the ratio of 30:70. Homogenization of the solutions was carried out on a stir plate for 2 hours at room temperature. The fibers were produced from the pure solutions and blends, in the proportion of 30:70, using the following electrospinning parameters: voltage of 16 kV, distance between the receiver and the needle of 9 cm and flow rate of 0.83 $mL.h^{-1}$, with a static collector.

Succeeding the production of the fibers, characterization of the chemical bonds present in the samples was evaluated by Fourier transform infrared (FTIR) spectroscopy with attenuated total reflectance accessory (ATR-FTIR, Cary 660, Agilent Technologies). Thirty-two scans were acquired in the range 4000-650 cm^{-1} at a resolution of 4 cm^{-1}.

The samples evaluated were PCL-100, NR:PCL-100 and the *in natura* latex membrane (NRL membrane), developed by casting method and submitted to oven drying at 55 °C for 48 h, for comparison.

The morphology of the blends (NR:PCL-100 and NR:PCL-120) was verified by scanning electron microscopy (SEM) analysis, with the equipment model TM3030, Hitachi. The samples were coated with a gold layer to avoid electrostatic charging. The average fiber diameter was measured using ImageJ software (version 1.51j8, developed by Wayne Rasband),

Wettability of the surfaces from electro-wet blends (NR:PCL-100 and NR:PCL-120), electro-woven PCL-12 pure solution, and the NRL membrane was determined by measuring the contact angle with a Ramé-Hart goniometer (model 250-F1, Mountain Lakes, NJ). Consistent volumes (1 µl) of deionized water were used as a droplet. Dropped liquid images were recorded and analyzed with the DROP-image CA software package (Ramé-Hart Instrument Co.).

The nomenclature of the samples is listed in the Table 10.

Table 10 - List of samples.

Name	Sample characteristics
NR-50	Electrospun fiber mats from NR solution with 50 $mg.mL^{-1}$ concentration
NRL membrane	Cast membrane from NRL *in natura*
PCL-100	Electrospun fiber mats from PCL solution with 100 $mg.mL^{-1}$ concentration
PCL-120	Electrospun fiber mats from PCL solution with 120 $mg.mL^{-1}$ concentration
NR:PCL-100	Electrospun fiber mats from NR:PCL-100 blend solution: 30:70 wt% of ratio
NR:PCL-120	Electrospun fiber mats from NR:PCL-120 blend solution: 30:70 wt% of ratio

3.2.2 Results and discussion

The NRL used showed a DRC of 43 wt% agreeing with the value reported in the literature, which is 30-50 wt% (RIPPEL; GALEMBECK, 2009).

The NR-50 solution did not show feasibility for fiber production. The solutions of PCL-100, NR:PCL-100 (Figure 9), and NR:PCL-120 showed similar characteristics that allowed the formation of a thin, flexible, whitish fibrous membrane.

Figure 9 - Fibers obtained from NR:PCL-100.

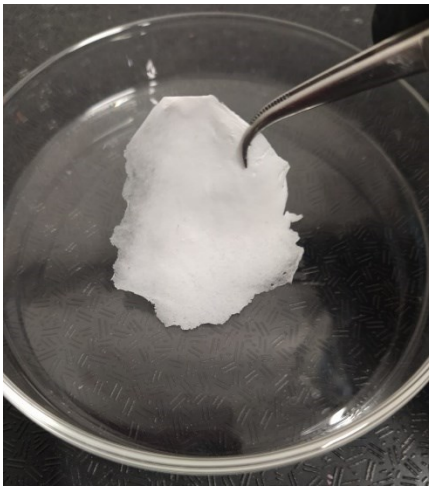


Figure 10 shows the FTIR characterization of the NRL membrane, PCL-100, and NR:PCL-100. The main bands and the functional groups assigned to these groups are listed in Table 11.

Figure 10 - FTIR spectra and main bands of the analyzed samples.

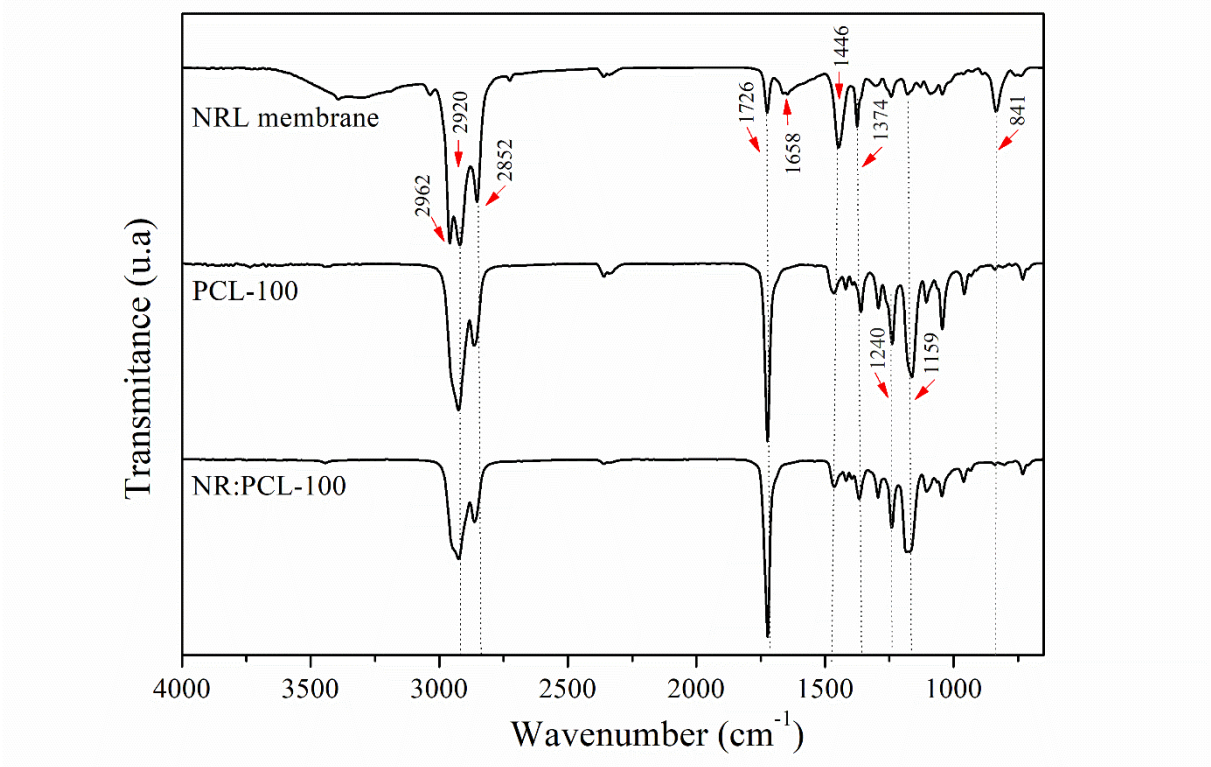


Table 11 - Frequency and assignments of functional groups.

Wavenumber (cm^{-1})	**Assignment***
2962	Asymmetric $\nu(CH_2)$ of pyrrole rings
2920	Symmetric $\nu(CH_2)$ of chains
2852	Aliphatic C–H
1726	C=O stretching
1658	C=C stretching
1446	C-H deformation of CH_2
1374	δ(C-H)
1240	asymmetric C–O–C stretching
1159	symmetric C–O–C stretching
841	-CH=CH of plane (cis 1,4 unit.) bending

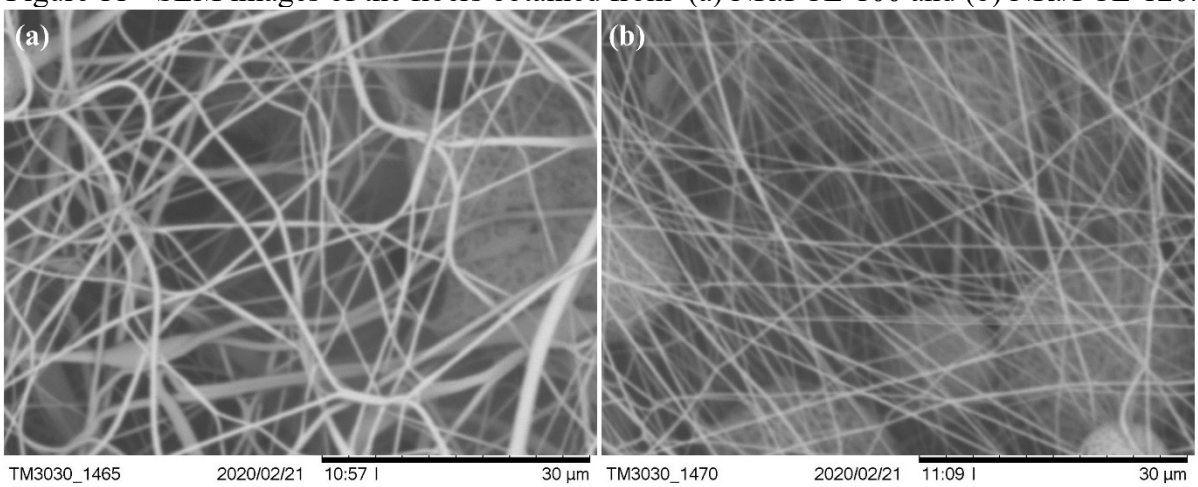
*(AZIZI et al., 2018; MANOHAR et al., 2017; SAFAEIJAVAN et al., 2014)

The characteristic IR modes of pure NR latex were observed at 2962 and 1658 cm^{-1}. These bands were not identified in the blend, which may be due to its low concentration in the final material. The 1240, 1159 and 954 cm^{-1} bands are associated with PCL and were identified in the fibers from the NR:PCL. Additionally, infrared results indicate the bands at 2920, 2852, 1726, 1446, 1374, 1159, 1048, and 841 cm^{-1} from both polymers, also found in the fibers. Therefore, the obtainment of a physical mixture of NR and PCL in the formation of NR/PCL-100 was confirmed.

Figure 11 shows the images from SEM analysis of the morphological structure of the fibers obtained from the blends. The diameters of the electrospun membrane fibers from the NR:PCL-100 solution ranged from 0.440 to 1 μm, while the NR:PCL-120 fibers these values were from 0.344 to 0.925 μm. This result allows to verify the fibers of different diameters, denoting the heterogeneity of the surfaces. Figure 11(a) presents fibers with few defects but with inhomogeneous diameters. Figure 11(b) shows the formation of fibers with more homogeneous diameters, but with the occurrence of "droplet" defects (beaded fibers).

Defects such as bead formation, presence of interconnected fibers and inhomogeneity of fiber diameters may be related to solution concentration and high solvent evaporation rate. Also, increasing the applied voltage, exceeding a critical value, can lead to the formation of fibers with beads or crimped fibers (COSTA; MATTOSO; FERREIRA, 2013; SYED BAKAR *et al.*, 2019). This can be explained by decreasing the size of the Taylor cone and maximizing the jet speed and flow rate (HAIDER; HAIDER; KANG, 2018). Another relevant factor is the distance between the capillary and the collector, in which the formation of defective fibers with large diameters are formed in front of a small distance (MATABOLA; MOUTLOALI, 2013).

Figure 11 - SEM images of the fibers obtained from (a) NR:PCL-100 and (b) NR:/PCL-120.



The contact angle of the NRL membrane, used as a reference, was 72.2° ± 1.1 (Table 12), which indicates that the surface shows a wetting tendency (Θ < 90°), while the PCL-120 fibers are denoted as surfaces with a non-wetting tendency (Θ > 90°). The results from NR:PCL-100 and NR:PCL-120 fibers were 118.9° ± 2.3 and 134.8° ± 1.7, respectively.

When considering the NRL membrane as a reference, it can be stated that the addition of PCL to NR caused the increase of the non-wetting tendency according to the increase of PCL concentration, since both materials present hydrophobic characteristics. Regarding the contact angle value of PCL-120 fibers (136.7 ± 0.9), a slight decrease was observed when incorporating NR (134.8 ± 1.7).

Table 12 - Contact angle values of the samples.

Samples	**Contact angle ($\theta \pm \sigma$)**
NRL membrane	72.2 ± 1.1
NR:PCL-100	118.9 ± 2.3
NR:PCL-120	134.8 ± 1.7
PCL-120	136.7 ± 0.9

According Costa (2014), it is possible to increase the wetting tendency of NR:PCL fibers with increasing NR concentration. In general, the obtained fibrous surfaces showed hydrophobicity and this characteristic may be undesirable for certain biomedical applications, such as dressing for skin lesion. For this application, a moisturizing material that prevents the formation of crusts is desirable, because it maintains the water content of the lesion and helps its healing, besides avoiding its adhesion to the lesion surface, a fact that facilitates its removal (PARK *et al.*, 2017; THAKUR; THAKUR, 2015). Therefore, it is necessary to improve the developed material to achieve its desirable characteristics.

3.2.3 **Conclusions**

The electrospinning from the NR:PCL blend was possible and allowed the production of fibers ranging from 0.344 to 1 μm. Small defects were observed in the fibers of the NR:PCL-100 blend, while in the NR:PCL-120 blend a greater presence of "droplet" type defects was evidenced, possibly from the electrospinning process. The developed fibers presented the surface with a non-wetting tendency, which is evidenced in the presence of the highest concentration of PCL, which is not desirable for application in skin lesions. Based on these results, the parameters used to obtain homogeneous fibers from NR:PCL without defects can be improved resulting in a compatible material for application in skin lesions.

3.3 ELECTROSPUN NONWOVEN MATS FROM NR:PVP FOR BIOMEDICAL APPLICATIONS

3.3.1 Materials and methods

Polyvinylpyrrolidone (PVP K120; M_W=1300 kDa) was purchased from Sigma Aldrich and chloroform, used as a solvent (≥ 99.8% of purity) from Dinâmica Química Contemporânea LTDA. NRL was collected from *Hevea brasiliensis* RRIM 600 clones, in the city of Colina, SP (from Colitex Indústria e Comércio de Látex LTDA). The NRL collectionwas performed by conventional procedure, followed by stabilization in 1.5 w/v% ammonium hydroxide. After the stabilization, the natural latex was centrifuged for concentration of its DRC in ± 60 wt%, this process was performed by the company that supplied the material. To obtain NR, the process was carried out according to item 3.2.1.

NR was solubilized in chloroform at room temperature under continuous magnetic stirring for approximately 60 h. Then, preliminary electrospinning tests were performed with the NR solutions (30, 20, and 15 $mg.mL^{-1}$) using the following parameters: 0.40 $mL.h^{-1}$ flow rate, the voltage of 9 kV, the distance between collector and needle of 14 cm. Static and rotating collecting were tested to verify which technique was more suitable to obtain fibers for further association to PVP.

After determining the ideal concentration of NR solution for fiber production, PVP was solubilized in chloroform at a concentration of 100 $mg.mL^{-1}$ (PVP-100) during 2 hours under magnetic stirring. The PVP-100 solution and the NR:PVP mixtures, (ratios 10:90, 25:75, 40:60, 50:50, and 75:25) were used in the electrospinning process with the same

parameters used for the NR tests, but using a rotating collector. The samples were evaluated by SEM (item 3.2.1) and also the contact angles were measured. Finally, PVP solutions at concentrations of 150 and 200 $mg.mL^{-1}$ were used for fiber production using the same parameters as described and analyzed by SEM (according to item 3.2.1). The nomenclature of the samples is listed in the Table 13.

Table 13 - List of samples.

Name	Sample characteristics
NR-30	Electrospun fiber mats from NR solution with 30 $mg.mL^{-1}$ concentration
NR-20	Electrospun fiber mats from NR solution with 20 $mg.mL^{-1}$ concentration
NR-15	Electrospun fiber mats from NR solution with 15 $mg.mL^{-1}$ concentration
PVP-100	Electrospun fiber mats from PVP solution with 100 $mg.mL^{-1}$ concentration
NR:PVP 10:90	Electrospun fiber mats from NR-15:PVP-100 blend solution: 10:90 wt% of ratio
NR:PVP 25:75	Electrospun fiber mats from NR-15:PVP-100 blend solution: 25:75 wt% of ratio
NR:PVP 40:60	Electrospun fiber mats from NR-15:PVP-100 blend solution: 40:60 wt% of ratio
NR:PVP 50:50	Electrospun fiber mats from NR-15:PVP-100 blend solution: 50:50 wt% of ratio
NR:PVP 75:25	Electrospun fiber mats from NR-15:PVP-100 blend solution: 75:25 wt% of ratio
PVP-150	Electrospun fiber mats from PVP solution with 150 $mg.mL^{-1}$ concentration
PVP-200	Electrospun fiber mats from PVP solution with 200 $mg.mL^{-1}$ concentration

3.3.2 Results and discussion

From the preliminary tests, it was possible to verify that NR-30 and NR-20 solutions were not suitable to obtain homogeneous fibrous surfaces (Figure 12(a) e Figure 12(b), respectively). The formed fibers had large diameters, which could be visually identified; The NR-15 solution proved to be more effective, allowing the formation of a more homogeneous fibrous structures (Figure 12(c)). Thus, the NR-15 solution and the rotating collector were identified as the best conditions for further fiber development with PVP association.

SEM images of the electrospun samples of NR-15, PVP-100 and the mixture of these polymers are seen in Figure 13. The electrospun samples of PVP, NR:PVP 10:90, 25:75,

40:60 and 50:50 showed low fiber production, defects and presence of solvent. Samples NR:PCL 75:25 provided higher fiber yield and better alignment, with no defects and some crossing points.

Figure 12 – NR electrospinning tests.

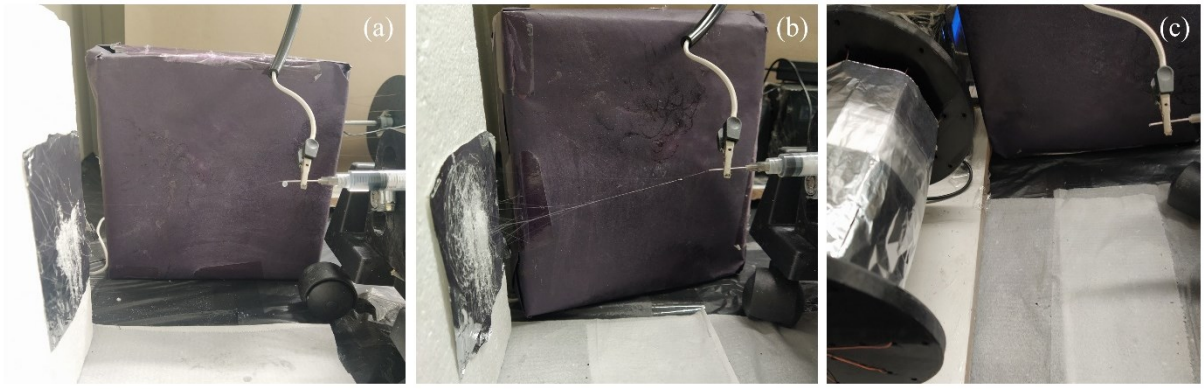
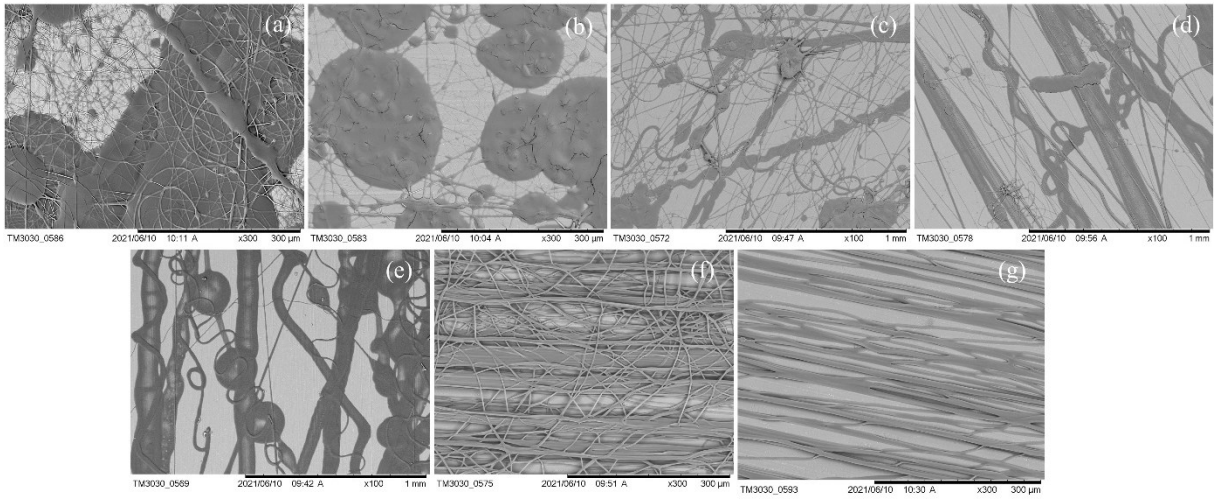


Figure 13 - SEM images of the electrospun nonwoven mats from (a) PVP, NR:PVP (b) 10:90, (c) 25:75, (d) 40:60, (e) 50:50, (f) 75:25, and (g) NR.



Regarding the electrospinning of PVP-150 and PVP-200 solutions, the formation of defects was observed although in smaller proportion, being more evident in the PVP-150 fibers, as well as the crossing points (Figure 14). Thus, the PVP-200 solution demonstrated to be the most suitable for producing fibers in NR association.

By analyzing the wettability characteristics of the developed fibers, it was possible to identify that NR is responsible for making the surface properties more prone to hydrophobicity (Table 14). The incorporation of PVP provided a decrease in the contact angle values, showing a linear relationship with the decrease in the proportion of NR added to the

mixture. This fact disagrees with the data found in the study of Zhou *et al.* (2019), where the incorporation of NR into polyvinyl alcohol (PVA - a hydrophilic polymer) caused the contact angle values to decrease according to the increase of NR in the solution (68.2; 59.3 and 42.8° for the association of 1, 3 and 5 wt% of NR to PVA, respectively).

Figure 14 – (a) PVP-150 and (b) PVP-200 electrospinning tests.

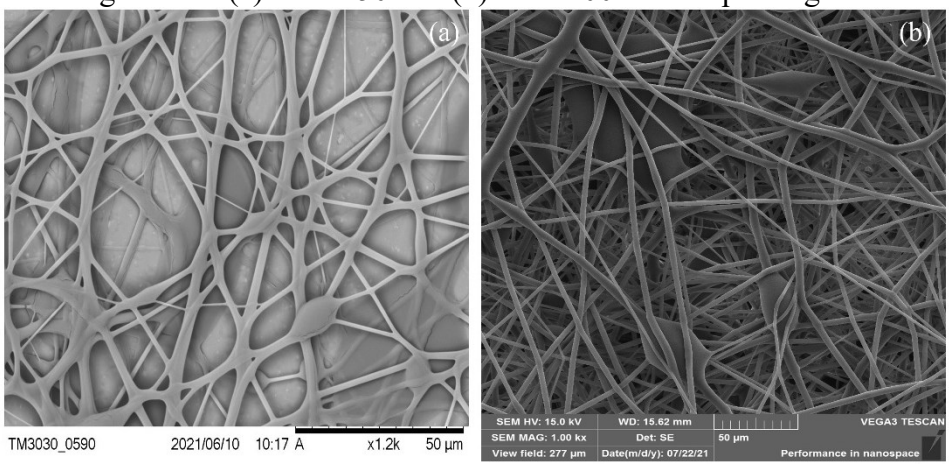


Table 14 - Contact angle values of the samples.

Samples	Contact angle (Θ ± σ)
NR-15	127.5° ± 2.8
NR:PVP 75:25	126.9° ± 2.5
NR:PVP 50:50	87.5° ± 4.3
NR:PVP 40:60	-
NR:PVP 25:75	57.2° ± 16.4
NR:PVP 10:90	-
PVP-100	33.6° ± 1.1
PVP-150	30.1° ± 2.0
PVP-200	24.2° ± 3.8

- Reading was not possible.

3.3.3 Conclusions

The NR-15 solution was the most suitable composition for fiber production using the spinning collector as the ideal technique. The fibers obtained with this solution in association with PVP-100 exhibited defects, presence of solvent and low yield, requiring process improvements. In addition, it was verified that the incorporation of PVP enabled the modification of the surface characteristics of the samples, allowing the obtainment of hydrophilic surfaces, where the wetting tendency was evidenced according to the increase of the proportion of this polymer in the material. The use of the PVP solution with the highest

concentration tested (PVP-200) provided the formation of fibers with fewer defects and a surface with a higher wetting tendency. Thus, it is possible to state that the association between NR-15 and PVP-200 presents great potential and compatibility for biomedical applications in the regenerative capacity of skin lesions.

4 WETTABILITY TUNING OF NATURAL RUBBER AND POLYVINYLPYRROLIDONE ELECTROSPUN NONWOVEN MATS[3]

This chapter presents the study of the development of nonwoven fiber mats from natural rubber and polyvinylpyrrolidone, as well as the wettability adjustment of these mats, corresponding to a published experimental paper.

4.1 INTRODUCTION

In recent years, numerous research studies on biomaterials have emerged to articulate and connect their physical and biological properties of greater complexity, allowing considerable advances in the development of new materials. These scientific advances have demonstrated, especially, investigations directed to the biomaterial surface, enabling the development of intelligent materials that connect themselves to their environment (TIBBITT *et al.*, 2015; TODROS; TODESCO; BAGNO, 2021). Biomaterials are considered those that interact with biological systems, where the classes of synthetic and natural polymers stand out (NASSER *et al.*, 2011; PARK; LAKES, 2007; WILLIAMS; DAVID, 1986; WONG; BRONZINO; PETERSON, 2013).

Among natural polymers, natural rubber (NR), from latex *Hevea brasiliensis* trees, is highlighted in many studies, with various applications of strategic importance, including biomedical purposes. *Hevea brasiliensis* latex is defined as a colloidal dispersion of NR in an aqueous medium, where approximately 40% of its constitution is given by the hydrocarbon poly(cis-1,4-isoprene), with the chemical formula $(C_5H_8)n$ and high molecular weight (HO, 2013; ROBERTS, 1988; ROLLAND; O'HEHIR, 2008). It is worth mentioning that several hevein proteins are found in this latex that can cause allergenicity in humans (YEANG *et al.*, 2002a, 2002b). Thus, its processing by centrifugation, where it is separated into 3 phases (rubber cream, C-serum, and bottom fraction), becomes necessary to produce a safer final product when its use in biomedical applications is aimed. The rubber cream is the portion with a high poly(cis-1,4-isoprene) polymer ratio. In addition, it contains a small portion of hevein proteins (Hev b1 and Hev b3) with low allergenicity (ROLLAND; O'HEHIR, 2008).

[3] Based on the published article: ANDRADE, KARINA LUZIA; FAITA, FABRÍCIO LUIZ ; DO NASCIMENTO, RODNEY MARCELO; CUNHA, RICARDO SOUSA; BRESOLIN, DANIELA; DIZ ACOSTA, EMANOELLE; MACHADO, RICARDO ANTONIO FRANCISCO . Wettability tuning of natural rubber/polyvinylpyrrolidone electrospun nonwoven mats. SURFACES AND INTERFACES, v. 32, p. 102129, 2022. https://doi.org/10.1016/j.surfin.2022.102129

Thus, the rubber cream is the source of purified NR with low allergenicity. NR favors the promotion of cell adhesion, formation of extracellular matrix, and acceleration of tissue repair via angiogenesis (FAITA *et al.*, 2014; RAHIMI; MASHAK, 2013; SANTOS KOTAKE *et al.*, 2018). Furthermore, it has high elasticity, providing adequate mechanical properties (AZARIAN; BOOCHATHUM, 2018; BHADRA *et al.*, 2019; CHEN; LIANG; THOUAS, 2013), biocompatibility, biodegradability, environmental friendliness (ABRAHAM *et al.*, 2012; AZARIAN; BOOCHATHUM; KONGSEMA, 2019; BORGES *et al.*, 2017; FLORIANO *et al.*, 2014; FURUYA; SHIMONO; OKAMOTO, 2017; TERTYSHNAYA *et al.*, 2021; TSUCHII, 1995; ZIMMERMANN *et al.*, 2007), and hydrophobic characteristics (VUDJUNG *et al.*, 2014). Regarding synthetic polymers, polyvinylpyrrolidone (PVP), a highly hydrophilic polymer with chemical formula $(C_6H_9NO)_n$, is widely explored for biomedical purposes due to its characteristics of bioactivity, non-toxicity, biodegradability, and biocompatibility (KURAKULA; KOTESWARA, 2020; LIU *et al.*, 2013; SARODE; KUMBHARKHANE; MEHROTRA, 2018; TIRON; VLAD; BALTĂ, 2018).

The development of blends from synthetic and natural polymers has been extensively studied to obtain optimal characteristics for each application, e.g. for biomedical applications (AZARIAN; BOOCHATHUM, 2018; AZARIAN; BOOCHATHUM; KONGSEMA, 2019; COSME *et al.*, 2016; COSTA; MATTOSO; FERREIRA, 2013; HUSAIN *et al.*, 2018; SOARES *et al.*, 2020). We hypothesized that the physical (in terms of modifying the surface topology) and chemical (in terms of the phases' mixing) combinations of natural rubber could control surface interactions with the liquid medium, where cells are embedded. Modulation of the surface physicochemical properties entails wide possibilities for the rational design of biomaterials. One successful physiochemical tunable parameter is in the surface wettability, measurable by the contact angle between liquid droplets and surfaces, which translates to affect the biological response, such as blooding interface and cell viability (GITTENS *et al.*, 2014; NASCIMENTO *et al.*, 2019c; SHABALOVSKAYA *et al.*, 2013). In addition, surface wettability is of paramount importance since it is a critical characteristic in determining cell behavior (LOURENÇO *et al.*, 2012). Thus, the hydrophobicity of some biomaterials is a problem for biomedical purposes where the interaction is predominantly with an aqueous medium. The cell membrane and water surface tensions exhibit similar behaviors during the first interactions with the substrate surface with low optimized angle values, generally below 60°, therefore, requiring hydrophilic character. On the other hand, the increase in hydrophobicity may useful for implants (or coatings to implant) that require hydrophobic

properties to decrease protein adhesion, avoid blood clots and reduce overall thrombotic responses (FEDOROV *et al.*, 2014; NASCIMENTO *et al.*, 2019b, 2019c).

It is worth mentioning that certain characteristics of the materials may be undesirable for biomedical applications, but these can be overcome by combining them with other materials, such as mixing hydrophobic polymers with hydrophilic ones (LIU *et al.*, 2013). Also, surface modification of these mixtures is a known method to reach better performances of such materials (GAUTAM *et al.*, 2014; HOSSEINI; EMADI; KHARAZIHA, 2017; LIU *et al.*, 2013). An example of this is the electrospinning technique, which has attracted significant interest for providing the production of fibrous materials on a micro-scale from biodegradable and biocompatible polymers. As an advantage, these materials present high surface area, easy surface modification, ―functionalization potential, excellent thermal and mechanical properties, and also, a process that allows adjustment of variables with low production cost (MISHRA *et al.*, 2019; SÁNCHEZ *et al.*, 2016; SILVA *et al.*, 2021a; YADAV; AMINI; EHRMANN, 2020). The morphology of the electrospun fiber mats is reported to be of great importance for biomedical applications due to the morphological similarity with natural biological tissues, favoring a better interaction between the material and the target cellular medium (BALAKRISHNAN; THAMBUSAMY, 2020; JUN *et al.*, 2018; TAN *et al.*, 2020). Moreover, welding in the fiber's cross points is important to obtain the hierarchical scaffolds and control the porosity (MISHRA *et al.*, 2019).

This study reports the development of micro-structured surfaces with tunable wettability. Films and nonwoven electrospun mats blends comprising NR and PVP polymers were produced at different ratios. The samples were analyzed by rheology and characterized by scanning electron microscopy (SEM), Fourier transformed infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), atomic force microscopy (AFM), and contact angle measurements. We address the nonwoven electrospun effects in modulating the surface properties by monitoring wettability. The tunable surface wettability of NR is discussed using appropriate chemical phases and theoretical modeling for relevant possible biomedical applications. Finally, dissolution tests of the fibers under distilled water were performed.

4.2 MATERIALS AND METHODS

The natural rubber latex (Dry Rubber Content - DRC = 66% stabilized with ammonium hydroxide at 1.5% of volume) was provided by Colitex Indústria e Comércio de Látex LTDA, Brazil. This latex was collected from RRIM 600 *Hevea brasiliensis* clones

(Colina city, São Paulo state, Brazil). The polyvinylpyrrolidone (PVP K120; M_W=1300 kDa) was purchased from Sigma Aldrich and chloroform (≥ 99.8% of purity) from Dinâmica Química Contemporânea LTDA. Except for the latex that was submitted to the purification process by centrifugation, all the reagents were used as received.

The natural rubber latex was centrifuged under 11000 RPM for 1 h in a refrigerated centrifuge at 5 °C (Eppendorf Centrifuge 5804R). After centrifugation, the upper fraction of the material (rubber cream) was removed and dried at 55 °C for 48 h, obtaining the dry NR. NR was cut into small pieces and solubilized with chloroform at room temperature under continuous magnetic stirring for approximately 60 h. Thus, NR solution with 15 $mg.mL^{-1}$ of concentration was obtained. The PVP solution was prepared by dissolving the polymer in chloroform with 200 $mg.mL^{-1}$ of concentration. The mixture was kept to constant magnetic stirring at room temperature for 2 hours until a viscous and homogeneous solution was obtained. Three NR:PVP (75:25, 50:50, and 25:75 wt%) solutions from mixing the previously described NR with PVP solution were performed considering the ratio between the dry mass of polymers (Table 15). The NR:PVP blended solutions were magnetic stirred at room temperature for 2 h.

Table 15 - List of samples.

Name	**Sample characteristics**
$NR^{e\text{-}spun}$	Electrospun fiber mats from NR solution
$75NR^{e\text{-}spun}$	Electrospun fiber mats from NR:PVP blend solution: 75:25 wt% of ratio
$50NR^{e\text{-}spun}$	Electrospun fiber mats from NR:PVP blend solution: 50:50 wt% of ratio
$25NR^{e\text{-}spun}$	Electrospun fiber mats from NR:PVP blend solution: 25:75 wt% of ratio
$PVP^{e\text{-}spun}$	Electrospun fiber mats from PVP solution
NR^{Cast}	Cast membrane from NR solution
$75NR^{Cast}$	Cast membrane from NR:PVP blend solution: 75:25 wt% of ratio
$50NR^{Cast}$	Cast membrane from NR:PVP blend solution: 50:50 wt% of ratio
$25NR^{Cast}$	Cast membrane from NR:PVP blend solution: 25:75 wt% of ratio
PVP^{Cast}	Cast membrane from PVP solution

The electrospun nonwoven mats were produced by using a homebuilt electrospinning apparatus. The NR, PVP, and NR:PVP solutions were poured into a 5 mL syringe fitted with a 22-gauge metallic needle, which was placed on an infusion syringe pump to ensure a constant feed rate of 0.40 mL/h. Several conditions of the rate flow, applied voltage, distance needle-collector, and speed rotation of collector, among other variables, were tested to obtain homogeneous micron fibers without beads. Thus, the best electrospun nonwoven fiber mats were obtained using an applied voltage of 9 kV to generate the electric field and accelerate the

polymeric solutions towards the collector placed at 14.0 cm from the needle. The collector was kept under constant rotation at 65 RPM. The environmental conditions of relative humidity (RH) ranged from 35 to 50% and temperature from 20 ± 3 °C. In addition, 1 mL of each solution was used to produce continuous membranes: NR^{Cast}, $75NR^{Cast}$, $50NR^{Cast}$ $25NR^{Cast}$, and PVP^{Cast} (Table 15) from casting, to evaluate the wettability properties.

The morphologies of the fibers and cast membranes were analyzed by SEM at 15 kV and 10 mA using Tescan Vega 3 (model 51-ADD0007). The samples were covered with a thin layer of gold using a Sputter Coater SCD 005, BAL-TEC, Liechtenstein. The micrographs were analyzed with ImageJ® software (National Institutes of Health, USA), and 200 random measurements for each sample were conducted to estimate the mean fiber diameter. AFM measurements were performed using a Nanosurf FlexAFM microscope, operating in tapping mode with a TAP150Al tip under ambient conditions on a scanning rate of 1.0 Hz and 512 x 512 pixels. The AFM data were analyzed with the WSxM 5.0 software, and the mean surface roughness (RMS) was obtained.

Parallel plate rotational rheology of the polymer solutions was carried out in a Thermo Scientific Haake Mars II rheometer (Thermo Fisher Scientific, USA) using a PP60 measuring geometry (60 mm diameter). The shear rate varied from 0.1-250 s^{-1} in 60 s, and a 0.30 gap was used in the tests. All measurements were performed at a constant temperature of 25 ºC.

The chemical bonds of the nonwoven electrospun samples were evaluated by Fourier transform infrared spectroscopy (FTIR) with attenuated total reflectance accessory (ATR-FTIR, IR Prestige-21, Shimadzu, Japan). For each sample, 28 scans were acquired in the range 4000–700 cm^{-1} with a resolution of 4 cm^{-1}. DSC analysis was employed to investigate the thermal transitions like transition glass and/or melting point of the pure and blended samples. The DSC curves were recorded using a Perkin Elmer calorimeter (Jade-DSC equipment model) from -70 ºC to 250 ºC and a heating rate of 10 ºC/min under flowing nitrogen. All enthalpies change values were given in Joule per gram of total sample weight ($J.g^{-1}$). The glass transition temperature (Tg) and melting temperature (°C) values were calculated using the manufacturer's software and Origin 8.5 Data Analysis and Graphing Software.

The wettability was evaluated experimental and theoretical the surface characteristics in the form of films and fibers, as well as the surface modifications upon different conformations. From the experimental point of view, we investigated the liquid-solid interface by contact angle measurements, through the sessile drop method, using a Ramé-hart® goniometer, model 250. The measurements were carried out from cast membranes and

nonwoven electrospun samples. From the theoretical point of view, values of *cos* θ^* shown in Figure 21 were estimated based on the spherical cap, polymer phase ratios, interfacial energies, boundary conditions, and thermodynamic rules.

In summary, the description of the system free energy (*F*) of droplets deposed on the polymeric surfaces can be given by:

$$F = VE_i + S_w\gamma_w + S_i(\gamma_i - \gamma_s) + S_s\gamma_s \quad (1)$$

where V, S_w, S_s, and S_i are the volume of the water droplet, water surface area, solid surface area, and water-solid interfacial area, respectively, while E_i, γ_s, γ_w and γ_i are the internal energy of the water droplet, solid surface energy, water surface energy, and interfacial energy, respectively. Based on the geometry of the water droplet (spherical cap), a circular contact line associated with an ideal surface, which is smooth, homogeneous, isotropic, and non-deformable, can be written as:

$$S_i\gamma_i = 2\pi R^2 \sin^2\theta\gamma_i \quad (2)$$

However, in our study system, the surface is not homogeneous, since the surfaces are composed of two different solids (NR:PVP), resulting in a water-Natural Rubber contact ratio f_{W-NR} (NR ratio) and a water-PVP contact ratio f_{W-PVP} (PVP ratio) due to the nominal fraction of the polymers. Therefore, we can express Equation (2) by:

$$S_i\gamma_i = S_i(\gamma_i f_{W-NR} + \gamma_i f_{W-PVP}) \quad (3)$$

Writing expression (1) as a function of θ and *R*, as described by a spherical cap, i.e., $F = F(\theta, R)$ which holds the necessary condition for the minimization of the energy ($\delta F/\delta\theta = 0$ and $\delta F/\delta R = 0$) at the optimal contact angle θ^* (steady-state). Then, the minimization of energy results can be expressed by:

$$\gamma_i = \gamma_s - \gamma_s \cos\theta^* \quad (4)$$

Where:

$$\cos\theta^* = f_{W-NR}\cos\theta_{NR} + f_{W-PVP}\cos\theta_{PVP} \quad (5)$$

Of note is that equation (5) is like the equation obtained by Cassie (CASSIE, 1948). Finally, from the linearization of equation (5) to obtain a data set that correlates the phase fractions and wettability regimes.

The dissolution process was investigated to $50NR^{e\text{-}spun}$ sample by a modified wetting time procedure from the literature (LI *et al.*, 2013; TORRES-MARTÍNEZ *et al.*, 2020). The experiment was performed in duplicate at room conditions (23 ºC ± 1 °C and 1 atm). Two

pieces with 3 cm^2 from $50NR^{e\text{-}spun}$ sample were cut and individually fixed in 9 cm diameter Petry dishes which were immersed in 50 ml of distilled water. Different wetting times were applied to each pair of the samples and the wetting process was stopped after 1 h, 3 h, 6 h, and 24 h. SEM images in secondary electron mode were performed from the dried and thin layer gold-covered samples using the JEOL JSM-6390LV microscope at 15 kV.

4.3 RESULTS AND DISCUSSION

Figure 15 shows the SEM images from the nonwoven electrospun fiber mat at different magnification levels. The $NR^{e\text{-}spun}$ and $75NR^{e\text{-}spun}$ fiber mat samples show very prominent welding at their cross points, and the structures and porosity of the fiber were retained (Figure 15(c), Figure 15(d), Figure 15(g), and Figure 15(h)).

The welding in the fiber's cross points also was observed in the $50NR^{e\text{-}spun}$ sample. Thus, the welding is more restricted to the touchpoint at the fiber crossings for the 50:50 wt% polymers blend (Figure 15(l)). For the $25NR^{e\text{-}spun}$ sample, the welding is absent (Figure 15(p)) due to the high magnification of the SEM image, and the observed region is not representative of the whole. Thus, the welding can be observed in Figure 15(m), Figure 15(n), and Figure 15(o) where the magnification is lower, and a larger region of the sample is seen. Finally, the $PVP^{e\text{-}spun}$ sample showed considerable welding with the emergence of beads along some fibers (Figure 15(r), Figure 15(s), and Figure 15(t)). Increasing the PVP ratio in the blends reduced the welding close to zero as observed for the blended sample with 75 wt% of PVP. In this way, this polymeric blend system allows obtaining different levels of welds, maintaining the structure of the fibers and mat porosity. This is important to obtain the hierarchical scaffolds whit high porosity that is desired for biological applications (MISHRA *et al.*, 2019). Besides the high porosity obtained, another important point to note is the orientation of the fibers. A random orientation benefits the repair of tissues that are arranged in a disorganized manner (LEVENGOOD *et al.*, 2017; LI *et al.*, 2020; YOSHIMOTO *et al.*, 2003). Therefore, one of the potential biomedical applications of the fibers obtained in the present study would be bone, skin, and cartilage repair.

Figure 15 - SEM images of (a)-(d) $NR^{e\text{-}spun}$, (e)-(h) $75NR^{e\text{-}spun}$, (i)-(l) $50NR^{e\text{-}spun}$, (m)-(p) $25NRe^{\text{-}spun}$ and (q)-(t) $PVPe^{\text{-}spun}$ samples. The images were recorded at a magnification of 500×; 1,000×; 5,000×; and 10,000× respectively.

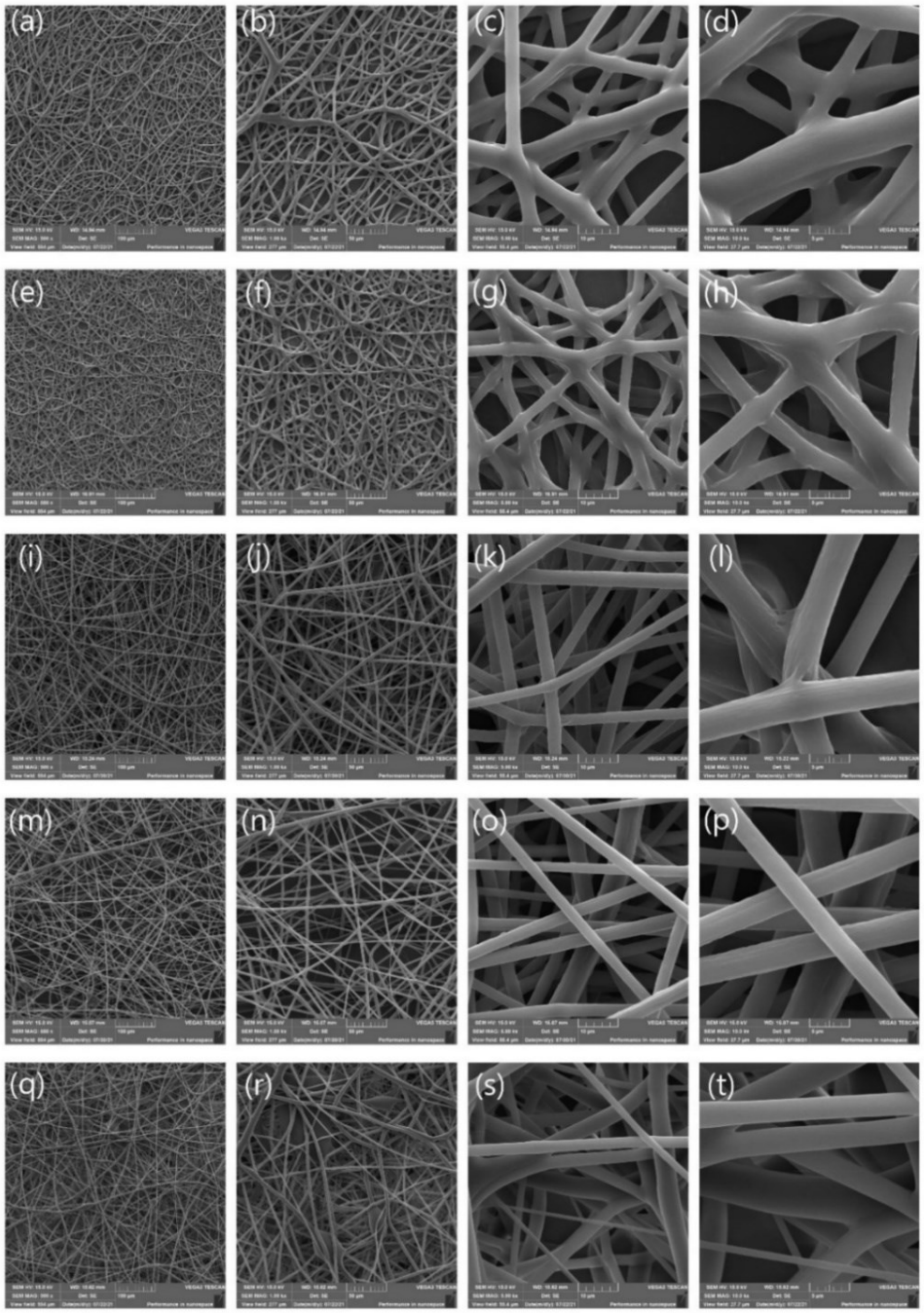
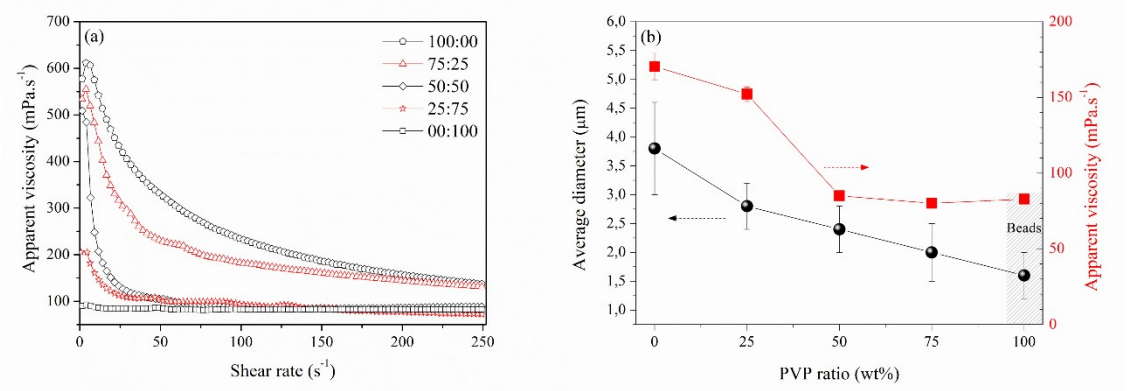


Figure 16(a) presents the typical apparent viscosity curves as a shear rate function of the samples. Regarding rheological behavior, the analysis of the curves shown plainly distinguishes two groups. The behavior of samples having a percentual of less than or equal to 50 wt%. of NR has a strong Newtonian behavior to their regime. As a result, the increase in shear rate has no remarkable influence on viscosity. Shear-thinning behavior is more prominent for samples with greater NR concentration (>50 wt%). This characteristic

viscoelastic behavior can be ascribed to polymer chain alignment in the direction of applied shear stress, which reduces the viscosity of the corresponding solutions with higher shear rates through disentanglement (SHENOY *et al.*, 2005).

When correlating the viscosity of the solutions with the produced fiber diameters, a trend of decreasing fiber diameter with decreasing solution viscosity is observed. The same trend is found for the relationship between mean fiber diameter and solution concentration, where it was observed that the decrease in NR concentration provided thinner diameters (Figure 16(b)).

Figure 16 - (a) Dependency of the viscosity according to shear rate for solutions with different compositions (NR:PVP ratio), and (b) dependence of average fiber diameter on the apparent viscosity and the relationship between fiber diameter and polymer solution with different compositions.



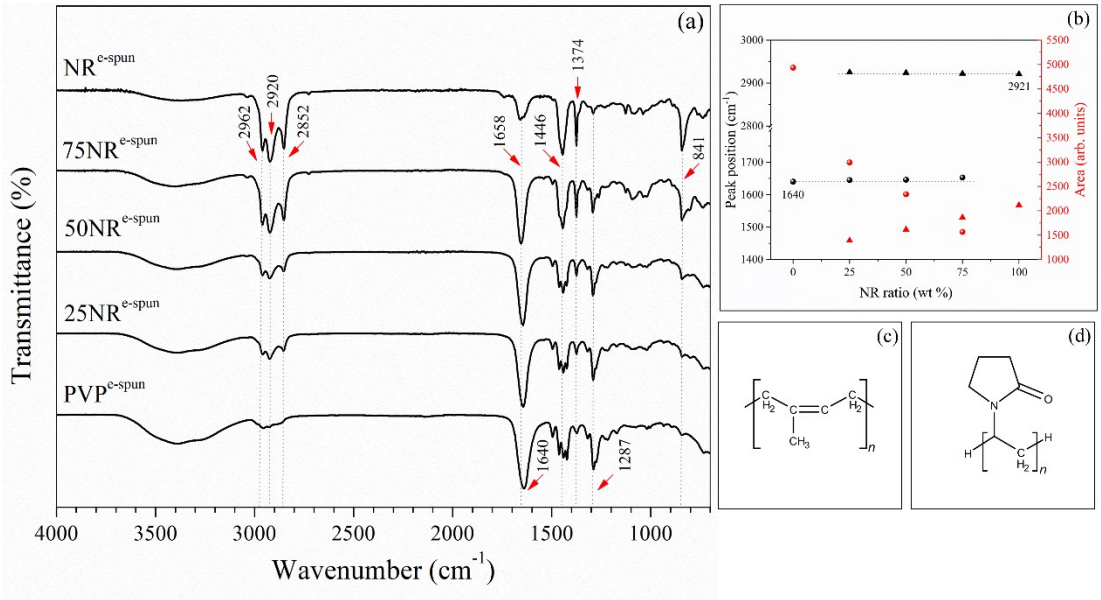
The solution composed of only NR showed the largest average diameters (3.8 ± 0.8 µm) and fiber interlacing, being observed in the formation of smooth and uniform microfibers, without the formation of beads. By blending NR and PVP, the formation of smooth fibers was observed with a proportional decrease in mean diameter size according to the increase of the PVP proportion in the solution. For the $75NR^{e\text{-}spun}$, the mean diameter size was 2.8 ± 0.4 µm and interlacing of the fibers was also observed. Moreover, the sizes of the mean diameters obtained from the $50NR^{e\text{-}spun}$ and $25NR^{e\text{-}spun}$ were 2.4 ± 0.4 µm and 2.0 ± 0.5 µm respectively. The PVP solution allowed the formation of fibers with the smallest diameters (1.6 ± 0.4 µm), nevertheless, small granule-like defects were observed. The degree of morphological homogeneity of the fibers was also evaluated, which is given by calculating the coefficient of variance (CV) (ratio of standard deviation to average diameter). Fibers with a CV of 0.21, 0.14, 0.17, 0.25, and 0.25 were observed for $NR^{e\text{-}spun}$, $75NR^{e\text{-}spun}$, $50NR^{e\text{-}spun}$, $25NR^{e\text{-}spun}$, and $PVP^{e\text{-}spun}$, respectively, which indicates that all of them are considered

homogeneous because they present CV smaller than 0.3 (EDIKRESNHA *et al.*, 2019; MATULEVICIUS *et al.*, 2016). The highest degree of morphological homogeneity was found in the 75NR$^{e\text{-}spun}$ sample.

Similar trend behavior of the changes in the mean diameter size fibers from electrospun PVP and PVP-blends was observed by Rahmani et al. The authors observed the mean fiber diameters of 49 nm and 104 nm respectively for PVP and PVP:PVA (50:50) electrospun mats. These results corroborate our observations since the association of PVP with another polymer results in an increase in the mean diameter size of the fibers. The difference in the mean diameter sizes between the obtained by Rahmani et al. and this work can be attributed to the different materials (PVP K90 - 360,000 g.mol^{-1}), solvents (deionized water), and electrospinning conditions (20 kV voltage, 0.5 mL.h^{-1} flow rate, and 15 cm) (RAHMANI *et al.*, 2021).

The FTIR spectra of PVP$^{e\text{-}spun}$, NR$^{e\text{-}spun}$, and NR:PVP blend samples are shown in Figure 17(a). Because NR and PVP have a certain similarity in their chemical structures (Figure 17(c) and Figure 17(d)) similarity in the spectra of the individual solutions and the mixtures is observed.

Figure 17 - (a) FTIR spectra and main bands of the analyzed samples, (b) peak position and area on the function of NR ratio. Chemical structures of (c) poly(cis-1,4-isoprene) and (d) polyvinylpyrrolidone.



In the analysis was possible to observe characteristic IR modes from PVP at 1640, 1461, 1422, and 1287 cm^{-1}. Additionally, the characteristic IR modes of pure NR latex were observed at 2962, 2920, 2852, 1658, 1446, 1374, and 841 cm$^{-1,}$ and the assignment attributed

to each identified IR mode peak is shown in Table 16. Moreover, a broad and intense peak was observed in the $PVP^{e\text{-}spun}$ sample in the region of 3690-3020 cm^{-1} (centered at 3390 cm^{-1}) and at 1640 cm^{-1}. These bands are attributed to the O-H stretching and bending/scissors, respectively, due to bonded-water presence and the hydrophilic character of the polymer (SRIYANTI *et al.*, 2017). For the NR:PVP blend samples, the coexistence of all IR modes from $PVP^{e\text{-}spun}$ and $NR^{e\text{-}spun}$ was observed. The peak intensity is related to the higher concentrations of the polymer in the mixture. A similar phenomenon has already been observed by Sriyanti and coauthors (SRIYANTI *et al.*, 2018). For the authors, the effect is due to a large amount of hydroxyl present in both compounds. In our case, the intensity of the bands around 2962 cm^{-1}, 2920 $cm^{-1,}$ and 2852 cm^{-1} increased, as a consequence of CH_2 and CH linkages presence. Lorentz fits were applied to investigate the peak position and area variation on the function of NR concentration. Figure 17(b) shows the results from the most intense bands, a very subtle variation in the peak position was comproved. On the other hand, the areas of the bands have been changing almost linearly with the NR ratio variation. Furthermore, it is possible to confirm that only a physical mixture of NR and PVP was obtained in the NR:PVP blend sample to all investigated concentrations.

Table 16 - Frequency and assignment of functional groups.

Sample	**Wavenumber (cm^{-1})**	**Assignment***
$PVP^{e\text{-}spun}$	3390	O-H stretch
	2962	Asymmetric $\nu(CH_2)$ of pyrrole rings
	2920	Symmetric $\nu(CH_2)$ of chains
	2852	Aliphatic C–H
	1640	ν(C=O)
	1461	-CH_2 wagging ν(C-N)
	1422	-CH_2 wagging ν(C-N)
	1374	δ(C-H)
	1287	-CH_2 wagging ν(C-N)
	1019	C-C, CH_2 rock
	934	C-C bond
	837	C=C
$NR^{e\text{-}spun}$	2962	Asymmetric CH_3 stretch
	2920	C-H stretch
	2852	Symmetric -CH_2 stretch
	1658	C=C stretching
	1446	C-H deformation of CH_2
	1374	Scissoring vibration of -CH_3
	1128	C-C stretching
	1037	C-C stretching
	841	-CH=CH of plane (cis 1,4 unit.) bending

*(BAGANIZI *et al.*, 2017; MALINA *et al.*, 2012; MANOHAR *et al.*, 2017; RAHMA *et al.*, 2016).

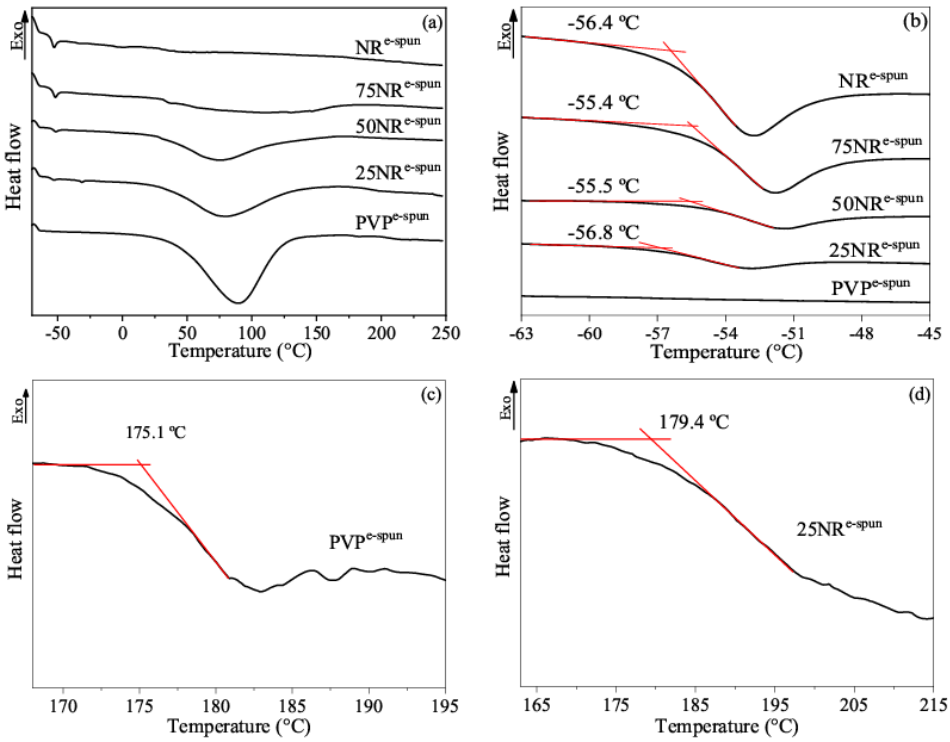
The thermal behavior of the electrospun samples was evaluated by DSC analyses and the results from the first cycle without annealing to stress releasing are shown in Figure 18(a). The DSC curve from $NR^{e\text{-}spun}$ shows an endothermic process at -52.6 ºC with $\Delta H = 3.4\ J.g^{-1}$ of energy involved attributed to the glass transition of the NR polymer (MAHMOUD; MAKLED, 2012). Moreover, the DSC curve of $PVP^{e\text{-}spun}$ shows a broad and intense endothermic peak between ~30 ºC to ~130 ºC with a center position at 89.4 ºC with enthalpy variation of $\Delta H = 433.3\ J.g^{-1}$ that can be associated with evaporation of absorbed water (ASAWAHAME *et al.*, 2015; SETHIA; SQUILLANTE, 2004). An important observation is the absence of the melting point of the water which indicates a non-freezing state (PING *et al.*, 2001). So, only two water molecules can be adsorbed in each C=O of the amide group via hydrogen bonds. Therefore, this interaction (C=O/water) ensures the formation of a secondary layer of water in the non-freezing state (PING *et al.*, 2001). These results are corroborated by the FTIR analyses that show significant O-H stretch mode (Table 16).

Through the glass transition region of PVP, it was possible to observe only $PVP^{e\text{-}spun}$ and $25NR^{e\text{-}spun}$ samples at 175.1° C and 179.4 ºC, respectively Figure 18(c)), and Figure 18(d)). The T_g region to PVP is reported in the literature as up to 180 ºC (TURNER; SCHWARTZ, 1985). Thus, the reduced values obtained can be due to the residual stress stored in the samples that were induced by the electrospinning process. For the $PVP^{e\text{-}spun}$ sample, the difference in the T_g is bigger than the $25NR^{e\text{-}spun}$ sample and we can attribute this to the residual stress reduction due to the elastic properties of the NR polymer. Complementary, it is possible to observe cracks in the surface of $25NR^{cast}$ samples (Figure 19 (h) and Figure 19(i)) that can be attributed to high NR deformation by the contraction of the PVP stretched in the drying process.

The glass transition region of the NR was observed close to -56 ºC (Table 17) for all electrospun blends (Figure 18(b)). Different values of the T_g region from NR are reported in the literature (-75 ºC (NASKAR; DE, 2010), -66 °C (CABRERA *et al.*, 2013a) for *in-natura* or low purified latex, and -53 ºC (HU *et al.*, 2021) from the centrifuged latex.

As it is known, T_g values can vary due to several reasons, such as different DSC scan rates, molecular weight composition, and/or residual stress. For this work, we have attributed the difference in T_g to the NRL purification process via cryo-centrifugation which results in a polymeric solution free of many NRL compounds and restricts the molecular weight range of the polyisoprene chains. Moreover, the enthalpy variation involved in this process decreased by decreasing the NR ratio in the blend, as was expected for the blended polymers.

Figure 18 - (a) DSC thermogram, (b) NR glass transition, (c) PVP and (d) 25NR$^{e\text{-}spun}$ glass transition for analyzed samples.



It is possible to identify from the DSC curves a broad peak for the 25NR$^{e\text{-}spun}$, 50NR$^{e\text{-}spun}$, and 75NR$^{e\text{-}spun}$ blends samples centered at 78.5, 74.2, and 70.6 ºC, respectively. These bands are attributed to water evaporation and the decrease in the T_{ev} can be due to the weakening of hydrogen bonds in the C=O groups. Moreover, the enthalpy variation involved the water loss process, which was gradually reduced by increasing the NR ratio, corroborating that this endothermic process is associated only with the adsorbed water in the PVP. Therefore, the DSC and FTIR analyses are in accordance and exhibit that the NR:PVP samples are constituted by only physically blended polymers.

Table 17 - Thermal transition temperatures and their respective enthalpy variations.

Sample	**NR glass transition**		**Water evaporation on PVP**		**PVP glass transition**
	T_g (°C)	**ΔH (J.g^{-1})***	**T_{ev} (°C)**	**ΔH (J.g^{-1})**	**T_g (°C)**
NR$^{e\text{-}spun}$	-56.4	1.6	-	-	-
75NR$^{e\text{-}spun}$	-55.4	1.2	70.6	86.0	undetected
50NR$^{e\text{-}spun}$	-55.5	0.6	74.2	179.0	undetected
25NR$^{e\text{-}spun}$	-56.8	0.3	78.5	229.0	179.4
PVP$^{e\text{-}spun}$	-	-	89.4	433.3	175.1

*ΔH values from the enthalpic recover peak close to the T_g region of NR.

As aforementioned, surface wettability is an important physicochemical parameter for biomedical applications. To assess the effects of the mixed NR:PVP, and electrospinning process on the wetting regimes, contact angle measurements were employed on the surfaces of cast membranes and electrospun fiber mats of NR, PVP, and their blended samples. The obtained contact angle values are listed in Table 18.

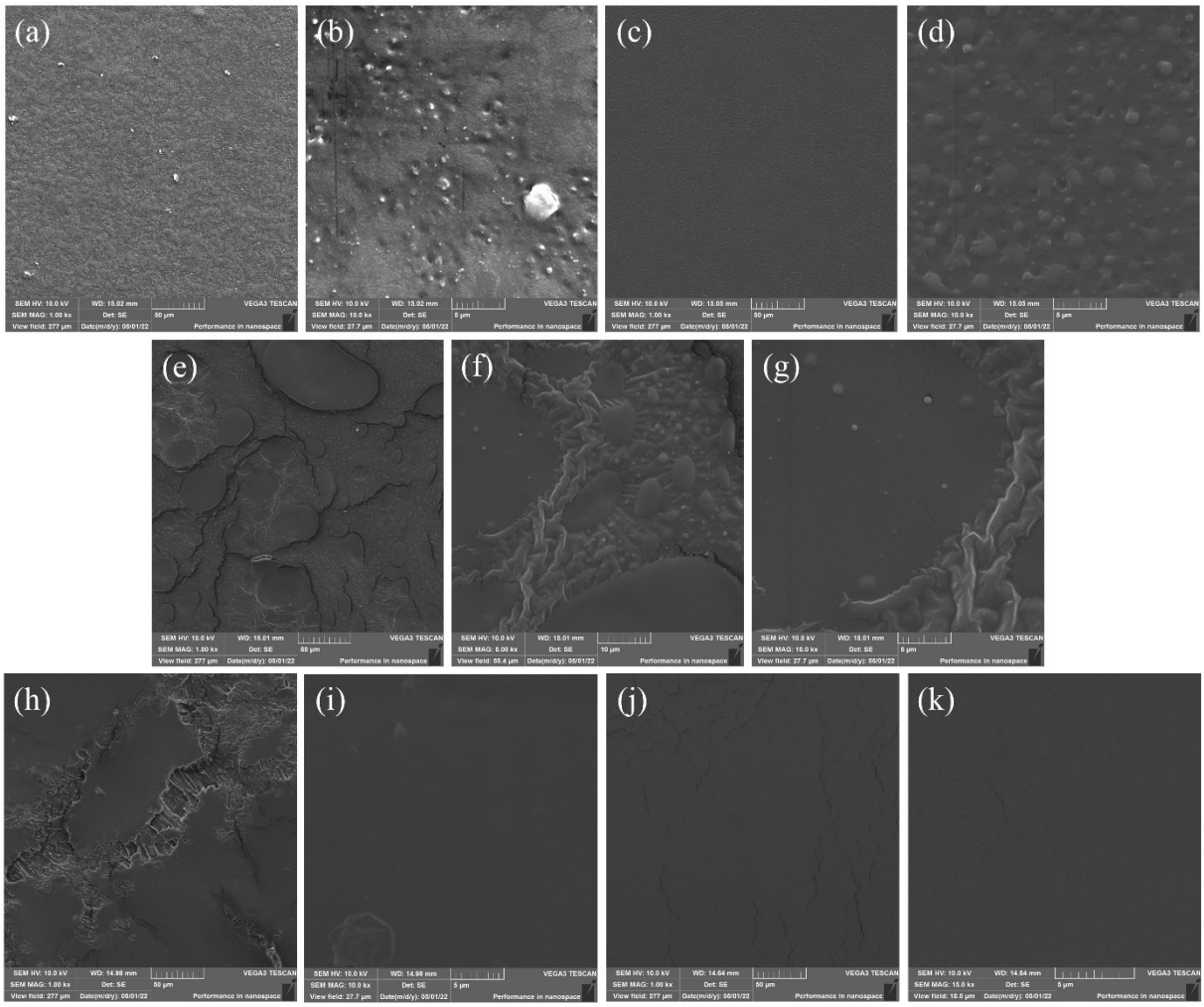
Table 18 - Contact angle values of the electrospun fiber mats and cast membranes samples and Roughness RMS values for cast membranes samples.

Sample	**Contact angle ($\theta \pm \sigma$)**	**Sample**	**Contact angle ($\theta \pm \sigma$)**	**Roughness RMS (nm)**
$NR^{e\text{-}spun}$	120.1° ± 6.4	NR^{Cast}	95.2° ± 1.8	38.53 ± 1.5
$75NR^{e\text{-}spun}$	116.1° ± 5.3	$75NR^{Cast}$	70.5° ± 1.8	49.51 ± 2.1
$50NR^{e\text{-}spun}$	52.0° ± 1.6	$50NR^{Cast}$	64.5° ± 3.6	59.51 ± 3.6
$25NR^{e\text{-}spun}$	38.1° ± 5.6	$25NR^{Cast}$	60.5° ± 1.3	33.13 ± 0.8
$PVP^{e\text{-}spun}$	23.8° ± 8.4	PVP^{Cast}	56.2° ± 5.3	0.33 ± 0.05

In this perspective, a significant change in wetting regimes was observed depending on sample morphology and phase concentration. For cast membranes, we observed phase separation on the surface (Figure 19). This effect was not observed in the electrospun membranes and may be justified due to the electrospinning process where the fibers dry stretched and/or the reduced surface area on each fiber. The maximum discrepancy in the morphologies was observed for $50NR^{cast}$ sample. This character is in accordance with RMS roughness obtained in the AFM measurements. The AFM images show a granular surface for the rich NR ratio that is typical of NR surfaces (Figure 20). Moreover, by increasing the PVP ratio was possible to see flat plates on the surfaces and a decrease in the RMS roughness. Well, looking at NR ratio, first the RMS roughness increase to the maximum value for $50NR^{cast}$ sample and only decrease after the PVP content is the majority on the sample due to the flat plate formations.

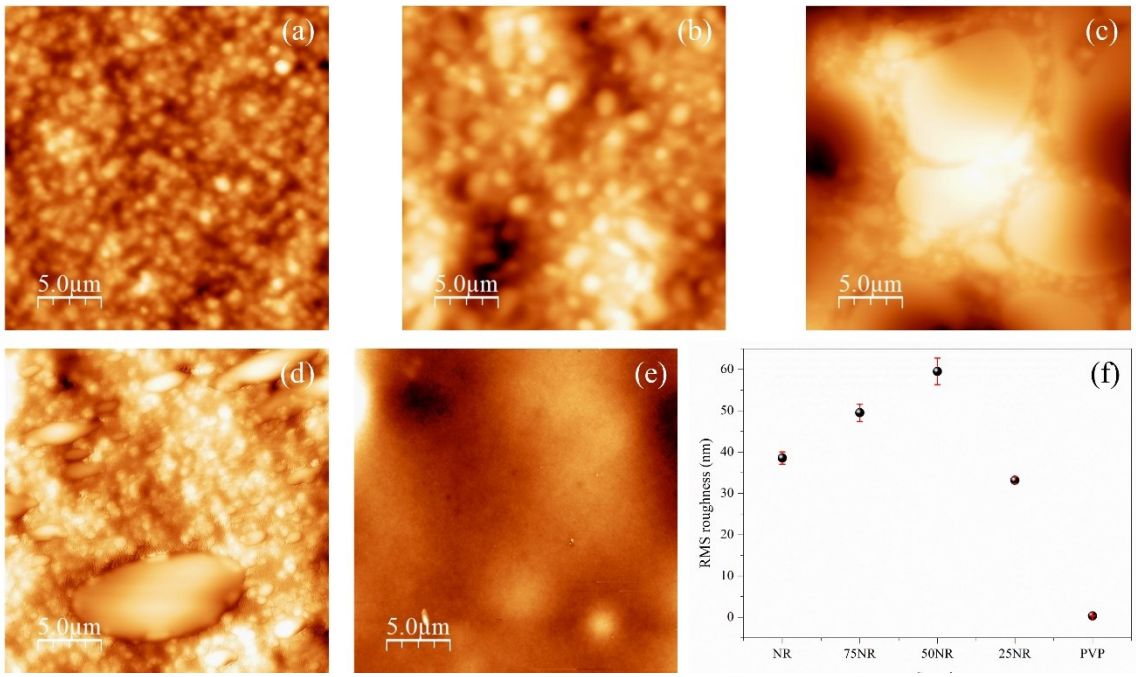
The SEM image Figure 19(f) was added between the Figure 19(e) and Figure 19(g) images because was recorded at an intermediate magnification and can help to show with details the wrinkles region. Moreover, these wrinkles can be attributed to the NR region under compressive tensile stresses that create wrinkles due to their elastomeric character. An opposite effect must be occurring in the $25NR^{cast}$ sample, the low NR ratio can generate regions with straining tensile stresses creating cracks in the surface. Small cracks can be observed also in PVP^{cast} sample but with a very flat surface. In accordance with these observations, the RMS roughness obtained for $25NR^{cast}$ and PVP^{cast} samples shows the lowest values among all studied samples.

Figure 19 - SEM images of (a)-(b) NR^{Cast}; (c)-(d) $75NR^{Cast}$; (e)-(g) $50NR^{Cast}$, (h)-(i) $25NR^{Cast}$, (j)-(k) PVP^{Cast} samples at different magnifications.



The RMS roughness to the NR^{cast} membrane is close to the previously observed (FAITA *et al.*, 2014; NASCIMENTO *et al.*, 2021) and changed non-linearly with the polymer ratio variation (Table 18). The maximum difference was at around 60 nm between PVP^{cast} and $50NR^{cast}$ membranes samples. The non-linearly on RMS roughness may be due to the height difference between ad two distinct polymeric regions. Additionally, wrinkles are observed in the SEM images, which must be from the natural rubber phase (Figure 19(f), and Figure 19(g)). This result suggests that the considerations about the surface energy as the main contribution in the theoretical model for the contact angle are correct.

Figure 20 - AFM measurements of (a) NR^{Cast}; (b) $75NR^{Cast}$; (c) $50NR^{Cast}$; (d) $25NR^{Cast}$; (e) PVP^{Cast} samples; (f) RMS roughness vs. polymer ratio.



For the electrospun membranes, the roughness is not possible to obtain by the AFM technique. In this case, the surface variation is in the same order of magnitude as the diameter of the fibers and changes linearly with NR:PVP ratio (Figure 16(b)) but with significant variation (~2.2 µm) between the extreme values observed from the unblended electrospun mats. Again, the morphology/topography variation does not seem to be governing the wettability variation in this system, but the surface energy variation as a function of the polymeric blend variation.

The results show a decrease of the hydrophobic characteristic with decreasing NR concentration in the blend samples for both cast membrane and electrospun fibers samples. However, when comparing the type of sample conformation, the data show that the NR^{Cast} sample presents a lower contact angle value (95.2° ± 1.8) than the $NR^{e\text{-}spun}$ sample (120.1° ± 6.4). An opposite configuration is observed for PVP^{Cast}, with higher contact angle (56.2° ± 5.3) in comparison with the $PVP^{e\text{-}spun}$ sample (23.8° ± 8.4).

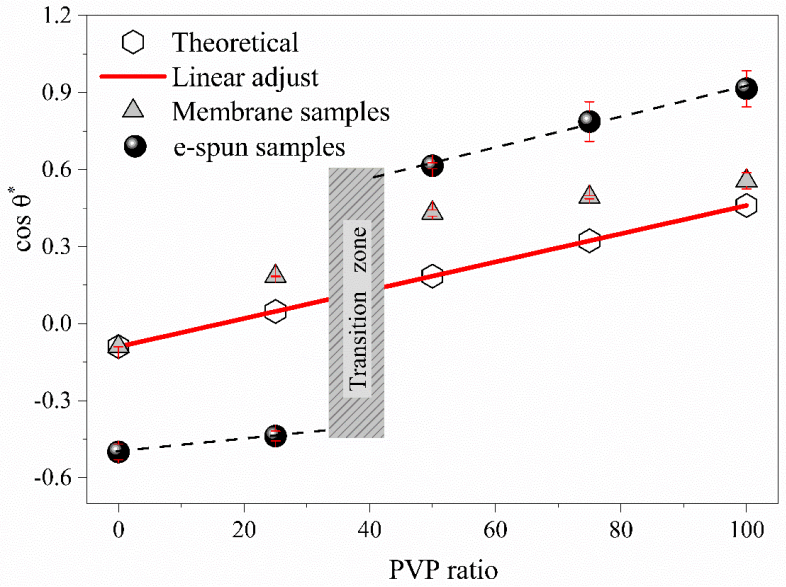
Additionally, beyond the $NR^{e\text{-}spun}$ sample, the $75NR^{e\text{-}spun}$ sample also has a hydrophobic character with contact angles of 116.1º ± 5.3, denoting them as predominantly non-wetting surfaces (Θ>90°) (GOMES; DE SOUZA; SILVA, 2013). According to Edikresnha et al., the wettability of fibrous surfaces can be related to the fiber diameter, since larger average diameters have larger contact angles (EDIKRESNHA *et al.*, 2019), which

corroborates with the data found in the present study (see Figure 16(b), and Table 18). It is worth noting that, in many cases of biomedical applications such as implants and/or coating to implants hydrophobicity is widely desired, as it avoids blood clots, decreases protein adhesion, and can reduce overall thrombotic responses (FEDOROV *et al.*, 2014). On the other hand, the $50NR^{e\text{-}spun}$ and $25NR^{e\text{-}spun}$ samples exhibited respectively values of 52.0º ± 1.6 and 38.1º ± 5.6, which denote surfaces with predominant wetting (Θ < 90°) and present potential for use in biomedical applications involving cell growth, since wettability is a desirable characteristic (LOURENÇO *et al.*, 2012).

From a technological point of view, the combination of incorporating PVP in NR in a physical blend using the electrospinning technique allows tuning the wettability to lower values. Conversely, the wettability of the PVP can be increased by blending with NR polymer, so, this system appears as a two-way path. Moreover, modifications in the wetting regime can be a result of several factors in materials physics, such as surface free energy, surface charge, or roughness integrating a major modulation due to the appearance of the contact angle measurements. In this work, the modulation of the surface wettability of the NR:PVP blend samples can be a clue to further address the surface heterogeneity on the effective contact angle measurements. To support this explanation, we refer to the chemically heterogeneous surface modeling given by Equação (5) using the values of $f_{W\text{-}NR}$ (NR ratio - from Table 15) and the values of θ_{NR} and θ_{PVP} (from Table 18), so it was possible to plot $\cos\theta^*$ *vs*. PVP ratio as displayed in Figure 21.

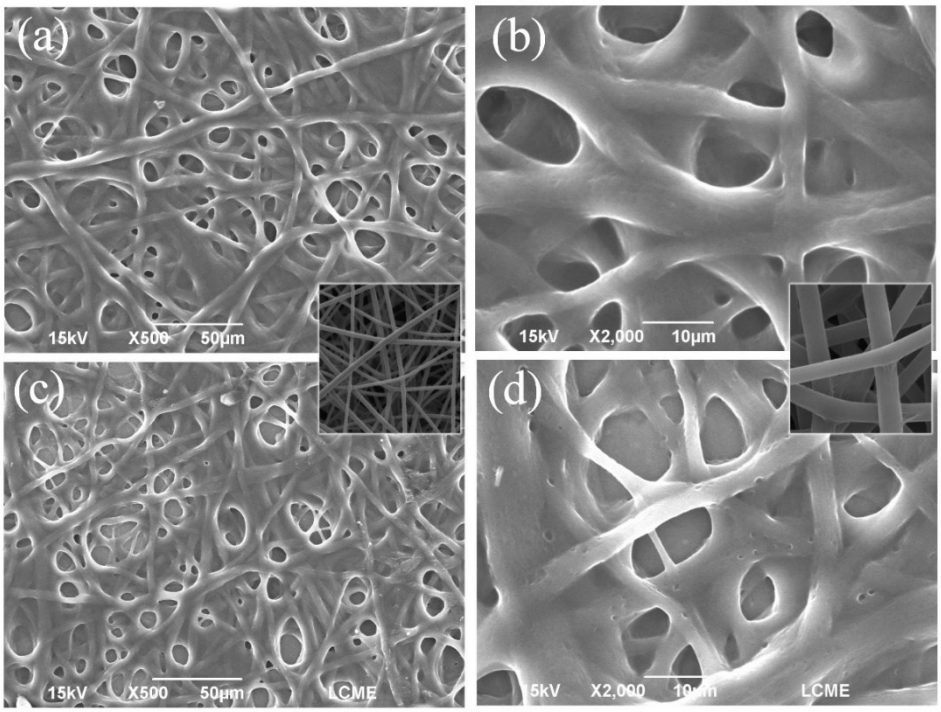
The progressive increase of $cos\,\theta^*$ means that the wettability is induced by PVP incorporation. However, an abrupt change in the wetting regime is observed by comparing the experimental values of the cos Θ of the cast membranes to the electrospun fibers mats, which is here called the transition zone. Thus, the type of transition is currently undefined, but due to the abrupt change, it suggests a first-order transition. It is important to emphasize that the wettability transitions occur exclusively in the electrospun fiber mat samples. Further studies on phase mixing effects probed by this modeling are imperative to help future studies addressing NR:PVP systems for wide applications in biomaterials.

Figure 21 - Concentration dependence of the contact-phase angle on the experimental cos θ* vs. polymer ratio.



Furthermore, beyond wettability, the polymeric dissolution in aqueous media is an important feature for biomedical applications. In this way, the dissolution process by wetting time was investigated and SEM images (a)-(b) for the shortest (1 h) and (c)-(d) for the longest (24 h) investigated time are shown in Figure 22.

Figure 22 - SEM images (a)-(b) after 1 h and (c)-(d) 24 h of wetting. The insets show the unwetted electrospun mats SEM images recorded at the same magnification.



It is possible to observe an extreme morphological modification already after 1 h of the wetting with a fused/weld membrane shape. This result suggests that significant changes for the $50NR^{e\text{-}spun}$ sample occur at short wetting times and must be related to the fraction of PVP present in the sample. On the other hand, a fibrous structure was retained, and this part should be due to the remaining fraction of NR. Additionally, by increasing the wetting time to 24 h no significant changes in the morphology can be observed when comparing SEM images (a) and (c). However, comparing the greatest magnifications of SEM images (b) and (d) several holes can be observed along the welded fibers.

Thus, this result suggests that the PVP dissolution was not complete until 1 h after wetting and the process proceeded for more time. As future research, the incorporation of bioactive agents into the NR:PVP mixture will be carried out, as well as their gradual release. Thus, this time the results presented in this work make the NR:PVP blend a promising candidate for in vitro and/or in vivo testing for the biomedical purpose.

4.4 CONCLUSIONS

We report in this work on the development of nonwoven electrospun fiber mats blends with natural rubber (NR) and polyvinylpyrrolidone (PVP) at different polymer ratios. The rheological results showed that higher NR concentration solutions have higher viscosity (170.4 ± 8.7 mPa.s^{-1}) leads to larger diameters sizes (3.8 ± 0.8 μm) of electrospun fibers and larger contact angles ($120.1° \pm 6.4$). In addition, solutions with mixtures below 50 wt% of the NR polymer exhibit Newtonian behavior while a shear behavior was more prominent for samples with higher NR concentrations. The mean diameter sizes of the fibers were obtained by SEM images and all samples show fibers of a few micrometers. Moreover, a decreasing sequential variation in fiber size was observed, going from the highest percentage to the lowest of NR polymer. The FTIR spectra and DSC curves show the physical blend of NR and PVP for all investigated polymer concentrations. The NR:PVP blend favored the formation of surfaces with tunable superficial wettability, confirmed by modeling the chemically heterogeneous surface given by the simplified Cassie model. The SEM and AFM analyses showed the cast membranes with a bi-phasic surface. On the other hand, this character is absent in all electrospun fibers mats blends. Additionally, the RMS roughness from the cast membranes changes nonlinearly with polymer ratio variation and the wettability is more dependent on surface energy than on roughness. The dissolution time test showed an extreme morphological modification already after 1 h of wetting with a fused/welded membrane

shape, increasing the wetting time to 24 h, no significant morphological changes were observed. Thus, this result suggests that the PVP dissolution was not complete until 1 h after wetting and the process proceeded for more time. The electrospinning process allowed obtaining samples with microstructured surfaces, which significantly altered wettability when compared to membrane samples. Tunable wettability allows for a wide range of applications in biomaterials, for instance, improving cell attachment to substrates in the presence of the hydrophilic character or avoiding blood coagulation. Therefore, using polymer mixtures associated with surface modifications by electrospinning is the first step to achieving different wetting regimes considering the characteristics of each material.

4.5 ACKNOWLEDGEMENTS

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4.6 AUTHORS' CONTRIBUTIONS

Table 19 - Authors' contributions.

Author	Contributions
Andrade, K. L.	Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Writing review & editing, Visualization
Faita, F. L.	Conceptualization, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing, Visualization, Supervision
Nascimento, R. M.	Formal analysis, Investigation, Data curation, Writing – review & editing, Visualization
Cunha, R. S.	Formal analysis, Visualization
Bresolin, D.	Formal analysis, Visualization
Acosta, E. D.	Writing – review & editing, Supervision
Machado, R. A. F.	Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Visualization, Writing – review & editing

5 NATURAL RUBBER/POLYVINYLPYRROLIDONE ELECTROSPUN NONWOVEN MATS FUNCTIONALIZED WITH PROPOLIS FOR BIOMEDICAL APPLICATIONS

This chapter presents the study of the development of NR:PVP electrospun nonwoven mats with propolis incorporation, corresponding to an experimental article to be published.

5.1 INTRODUCTION

The emerging clinical demands of the last decades have forced the progress and development of new biomaterials, with emphasis on their functionality, performance, and applications (GUERRA *et al.*, 2021; TODROS; TODESCO; BAGNO, 2021). Polymer-based biomaterials are among the most used in the biomedical area, presenting as advantages the ease of fabrication from various conformations, such as particles, films, wires, and fibers. Additionally, they have reasonable cost and availability of materials with mechanical and physical characteristics that are desirable for specific applications (ANDRADE *et al.*, 2022a, 2022b; KALIRAJAN *et al.*, 2021; NASCIMENTO *et al.*, 2019a; PIRES; BIERHALZ; MORAES, 2015). Amid these developed devices are biosensors, blood circulation tubes, hemodialysis systems, implantable materials such as sutures, plates, bone substitutes, tendons, heart valves, lenses, teeth, devices to release drugs in different conformations, artificial organs, and dressings, among others (FRADE *et al.*, 2012; KRUPP *et al.*, 2019; PIRES; BIERHALZ; MORAES, 2015).

To be used in these types of applications and to perform functions in tissue engineering, tissue repair, and controlled drug delivery, devices must be developed from biocompatible and bioactive materials (GUERRA *et al.*, 2021). Due to the biocompatibility, non-toxicity, ability to form polymer complexes, and high versatility of polyvinylpyrrolidone (PVP), this hydrophilic synthetic polymer is widely used to produce materials for different applications, including biomaterials for biomedical purposes (KURAKULA; KOTESWARA, 2020; TEODORESCU; BERCEA, 2015). It is worth mentioning that polymer blends from synthetic and natural polymers have been widely studied to obtain improved characteristics and suitable for specific biomedical applications (ANDRADE *et al.*, 2022a).

Natural rubber (NR), a polymer derived from natural rubber latex (NRL) obtained from the *Hevea brasiliensis* rubber tree, has emerged as a promising biomaterial from a

renewable source with biocompatible and biodegradable properties and has shown great potential as biomaterial in biomedical applications (ANDRADE *et al.*, 2022b; FLORIANO *et al.*, 2014; MIRANDA *et al.*, 2017; MRUÉ *et al.*, 2004). Several biomedical devices based on NRL and NR have already been developed aiming at improving tissue repair in chronic lesions and even bone defects, besides the projection of design of systems to deliver drugs and bioactive molecules in a controlled manner and a specific location (AZARIAN; BOOCHATHUM; KONGSEMA, 2019; BARROS *et al.*, 2015, 2019; FLORIANO *et al.*, 2016, 2018; GUERRA *et al.*, 2021; HERCULANO *et al.*, 2011b; MIRANDA *et al.*, 2018; ROMEIRA *et al.*, 2012; TRECCO *et al.*, 2014; ZANCANELA *et al.*, 2019).

Sources of bioactive molecules with potential application and relevance in the development of toxicity-free formulations for the treatment of injuries, they provide interesting and innovative therapies, considering their availability and low cost (MARTINOTTI; RANZATO, 2015; RYALL *et al.*, 2022; SEHN *et al.*, 2009). In this sense, propolis has been the focus of much research due to its interesting biological properties. Its constitution presents some complexity and can vary according to the plant flora, bee species, geographical area, collection period, and illumination. More than 300 chemical substances can be found, including organic and inorganic compounds (BANKOVA; CASTRO; MARCUCCI, 2000; CASTALDO; CAPASSO, 2002; HUANG *et al.*, 2014; ORYAN; ALEMZADEH; MOSHIRI, 2018). Propolis exhibits antimicrobial, antifungal, antiallergic, antitumor, anti-inflammatory, and regenerative activity. The molecules responsible for the biologically active and therapeutic properties of propolis are the phenolic compounds, such as flavonoids (CASTALDO; CAPASSO, 2002; CONTE *et al.*, 2022; DE OLIVEIRA CARDOSO *et al.*, 2022; ŠURAN *et al.*, 2021; VIUDA-MARTOS *et al.*, 2008). The presence of propolis flavonoids on the surface of electrospun matrices has already been studied and showed additional functionalities in matrices developed from electrospinning (KIM *et al.*, 2014).

The use of agents with antibacterial functions in dressings represents a strategy that goes beyond the prevention of infection of lesions, because these substances may also have pro-cicatrizing characteristics, triggering the acceleration of the healing process (HE *et al.*, 2015; MANNERUNG; TOKURA; RUJIRAVANIT, 2008; MUTHUKUMAR *et al.*, 2014). Thus, the objective of this study was to produce biocompatible fibers from NR:PVP, functionalized with propolis for potential biomedical application.

5.2 MATERIALS AND METHODS

Natural rubber latex from RRIM 600 *Hevea brasiliensis* clones was supplied by Colitex Indústria e Comércio de Látex LTDA. The material presented Dry Rubber Content - DRC = 66% and had been stabilized with ammonium hydroxide at 1.5 v/v%. The selected propolis is prevenient from the sting bee species *Apis melifera* and was collected at the Cidade das Abelhas, Universidade Federal de Santa Catarina - UFSC, (Florianópolis – Santa Catarina, Brazil). Chloroform solvent (≥ 99.8% purity) was obtained from Dinâmica Química Contemporânea LTDA.

The procedure to obtain the printing solution was performed according to Andrade *et al.* (2022). The natural rubber latex was centrifuged at 5 °C (Eppendorf Centrifuge 5804R), 11000 RPM during 60 min. After this step, the upper fraction of the material (rubber cream) was separated from the rest of the centrifuged material and dried at 55 °C for 48 h. Subsequently, the dried NR was cut into small pieces and solubilized in chloroform for about 60 hours under continuous magnetic stirring at room temperature. Finally, a NR solution with a concentration of 15 $mg.mL^{-1}$ ($NR^{e\text{-}spun}$) was obtained. The PVP solution was prepared by dissolving the polymer in chloroform with 200 $mg.mL^{-1}$ of concentration ($PVP^{e\text{-}spun}$).

Propolis (*Apis mellifera*) extracts were solubilized in different solvents: chloroform, toluene, tetrahydrofuran and ethanol, after magnetic stirring for 24 h, followed by determination of the flavonoid content of the extracts based on the methodology reported by Woisky and Salantino (1998), with adaptations. A 2 mg of the extract was added to 1 mL of ethanol and dispersed in an ultrasonic bath. An aliquot of 0.15 mL of the solution with the propolis extract, 0.15 mL of aluminum chloride solution ($AlCl_3$ 2%) and 0.7 mL of ethanol were mixed to develop the final solution. Another solution was prepared in the same way, but without the addition of the $AlCl_3$ solution (blank solution). Absorbance readings of the mixtures were taken in a UV-VIS spectrophotometer (FEMTO 800xi) at 415 nm after the solution had been kept at rest for 30 minutes. An analytical curve with quercetin solution at concentrations of 0.0039 to 0.125 $mg.mL^{-1}$ for comparison ($y = 10.57X - 2.29$; $R^2 = 0.999$) was constructed. The analysis was performed in triplicate and the flavonoid content was expressed as quercetin equivalents (mg $EQ.g^{-1}$ of plant sample). After curve construction, the extract with the highest presence of flavonoids was used for incorporation into NR:PVP. The extract was dried at room temperature and then 5 wt% of propolis (according to the weight of NR:PVP used) was added to the solution to be used for electrospinning ($50NR^{e\text{-}spun+prop}$). The sample used to perform the incorporation of propolis in this new study was the mat that

showed the greatest potential for biomedical application as a wound dressing in the previous study (ANDRADE *et al.*, 2022a), this being the $50NR^{e\text{-}spun}$. After functionalization with propolis, this sample was named as $50NR^{e\text{-}spun+prop}$.

The electrospun nonwoven mats were produced according to Andrade *et al.* (2022), with adaptation. The $50NR^{espun+prop}$ solution was packed into a syringe (5 mL) with a metal needle (22 gauge). The syringe was then placed in an infusion syringe pump to ensure a constant feed rate of 0.42 $mL.h^{-1}$, using an applied voltage of 9 kV, 14 cm distance between collector and needle. The collector was kept under constant rotation at 65 RPM. Conditions of relative humidity (RH) ranged from 35 to 50% and the temperature was kept at 20 ± 3 °C. In parallel, 1 mL of the solution was used to produce the $50NR^{Cast+prop}$ membrane from the casting to evaluate the wettability properties.

The morphological characteristics of propolis functionalized fibers were analyzed by SEM at 15 kV and 10 mA using Tescan Vega 3 (model 51-ADD0007). A thin gold layer using a Sputter Coater SCD 005, BAL-TEC, Liechtenstein covered the samples to be analyzed. For estimation of the mean fiber diameter, ImageJ® software (National Institutes of Health, USA) was used, totalizing 200 random measurements for each sample.

Characterization of the chemical bonds present in the nonwoven electrospun sample was evaluated by Fourier transform infrared (FTIR) spectroscopy with attenuated total reflectance accessory (ATR-FTIR, IR Prestige-21, Shimadzu, Japan). Twenty-eight scans were acquired in the range 4000-700 cm^{-1} at a resolution of 4 cm^{-1}.

The experimental wettability was evaluated to verify the surface characteristics in the form of films ($50NR^{Cast+prop}$), and fibers ($50NR^{e\text{-}spun+prop}$), as well as the surface modifications in different conformations. The investigation of the liquid-solid interface was done by contact angle measurements, through the sessile drop method, using a Ramé-hart® goniometer, model 250.

Cytotoxicity was assessed by the MTT assay, which is based on the ability of viable cells to metabolically reduce the yellow-colored MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) salt into formazan, which is a purple, water-insoluble product (MOSMANN, 2016). The MTT assay was performed according to the protocol described by Beltrame *et al.* (2021), with adaptations, in samples of fibers without polymer association ($NR^{e\text{-}spun}$ and $PVP^{e\text{-}spun}$) and from the polymer mixture ($50NR^{e\text{-}spun}$ and $50NR^{e\text{-}spun+prop}$), using McCoy cells (murine fibroblasts), acquired from the Instituto Adolfo Lutz (São Paulo). Cells were grown in RPMI 1640 medium supplemented (GIBCO, Baltimore, USA) with fetal bovine serum (10%), penicillin (100 $U.mL^{-1}$) (GIBCO, Baltimore, USA), and streptomycin

(100 μg.mL^{-1}) (GIBCO, Baltimore, USA) and maintained in an atmosphere containing 5% CO_2, 95% humidity at 37 °C. The samples were sterilized by immersion in alcohol 70º (10 min, performed three times) and subsequent exposure to UV light (365 nm, 20 min). Only samples of standard sizes (10 mm X 10 mm X 0.2 mm) were used to perform the assays. McCoy cells (11,700 cells per well) were seeded in 24-well plates containing the previously sterilized samples. Subsequently, the plates were incubated during 24 h for cell adhesion. The medium in the wells was replaced by fresh medium (750 μL), and the plates were incubated for 72 h. After this time interval, the culture medium was removed, the wells were washed three times with PBS, and 750 μL of an MTT solution (0.5 mg.mL^{-1}) diluted in culture medium. The plate was incubated for 2 h. The formazan crystals were solubilized by adding 750 μL of DMSO per well. Finally, 100 μL of the DMSO solution was transferred to wells of 96-well plates and the absorbance was measured at 570 nm (Multiskan FC, ThermoScientific, Massachusetts, USA). For the negative control, McCoy cells were seeded into wells without sample, following the procedure cited above. To determine the cytotoxicity induced by the samples, the absorbance of the control was considered as 100% cell viability. The level of significance was determined using oneway ANOVA (Analysis of Variance), followed by Bonferroni's test ($p < 0.05$, $n = 2$), using GraphPad Prism software (San Diego, USA).

The nomenclature of the samples used in the development of this study are listed in Table 20.

Table 20 - List of samples.

Name	**Sample characteristics**
$NR^{e\text{-}spun}$	Electrospun fiber mats from NR solution
$PVP^{e\text{-}spun}$	Electrospun fiber mats from PVP solution
$50NR^{e\text{-}spun}$	Electrospun fiber mats from NR:PVP blend solution: 50:50 wt% of ratio
$50NR^{e\text{-}spun+prop}$	Electrospun fiber mats from NR:PVP blend solution: 50:50 wt% of ratio, functionalized with propolis
$50NR^{Cast}$	Cast membrane from NR:PVP blend solution: 50:50 wt% of
$50NR^{Cast+prop}$	Cast membrane from NR:PVP blend solution: 50:50 wt% of ratio, functionalized with propolis

5.3 RESULTS AND DISCUSSION

From the extracts produced (Figure 23), the total flavonoid content was determined using the quercetin standard as a reference, which is one of the main natural flavonoids. Figure 24 shows the calibration curve of quercetin obtained from the ethanolic solutions. The absorbance readings and the mg Q.g^{-1} values are listed in Table 21, which shows that only the

mg $Q.g^{-1}$ values obtained in the readings of propolis extracts with chloroform and tetrahydrofuran showed significant data, which were within the values of the quercetin calibration curve (range of 0.5 to 0.0039 $mg.mL^{-1}$). The extraction in chloroform provided higher values of quercetin equivalents (0.020 mg $Q.g^{-1}$) and, therefore, this extraction was used for the next step of the research sequence that involved the incorporation of propolis in NR:PVP.

Figure 23 - Propolis extracts produced in different solvents: (a) ethanol, (b) tetrahydrofuran, (c) chloroform and (d) toluene.

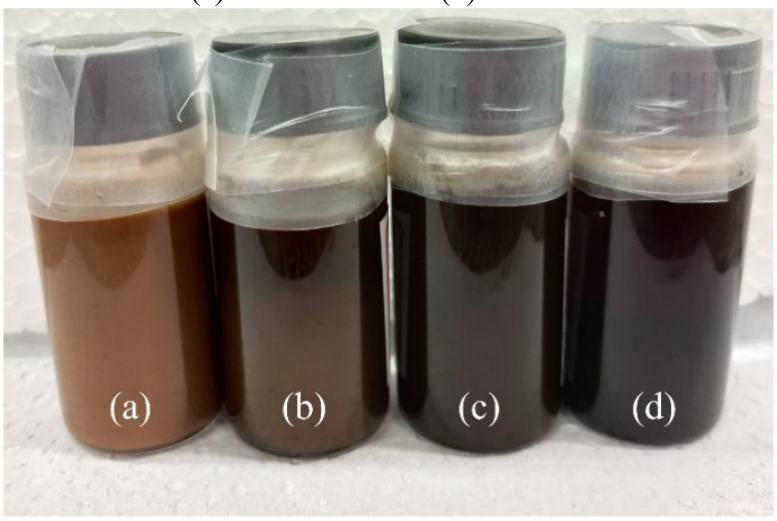


Figure 24 - Quercetin calibration curve.

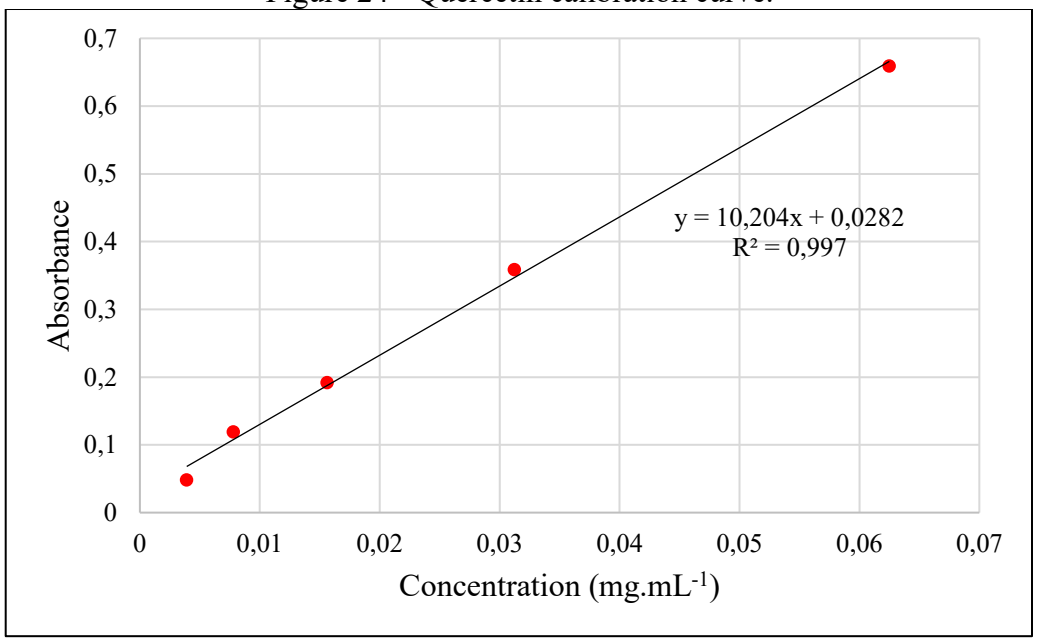


Table 21 – Average values of the absorbance readings and the mg $Q.g^{-1}$ values for the different types of extractions.

Solvents	Average absorbance	mg $Q.g^{-1}$
Chloroform	0.228	0.020
Toluene	0.035	0.001
Tetrahydrofuran	0.180	0.015
Ethanol	0.042	0.001

After verifying the best extraction method for propolis, a solution of NR:PVP with propolis incorporation ($50NR^{e\text{-}spun+prop}$) was obtained for the production of fibers. Figure 25 shows the electrospinnable yellowish solution (due to the presence of propolis).

Figure 25 - Solutions of (a) $50NR^{e\text{-}spun}$ and (b) $50NR^{e\text{-}spun+prop}$.

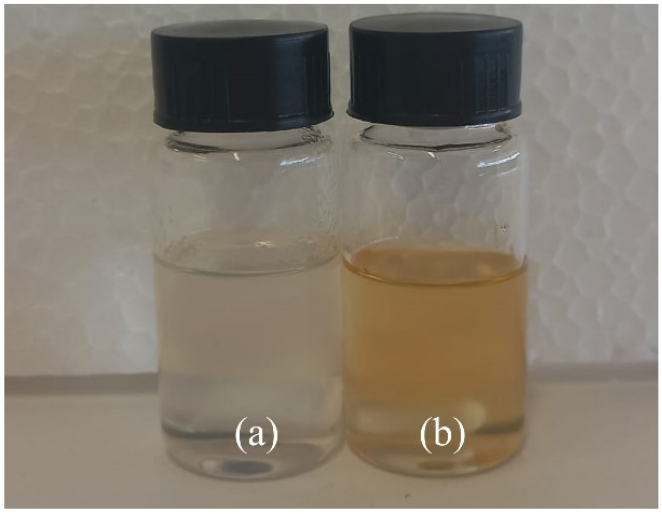
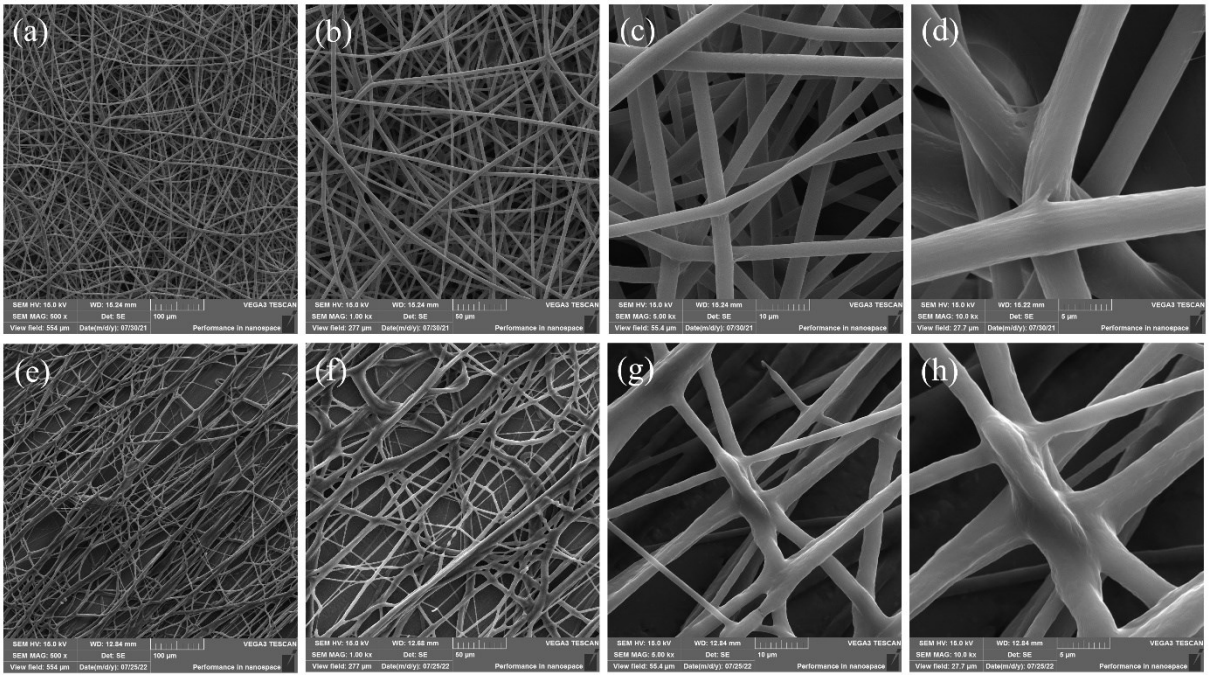


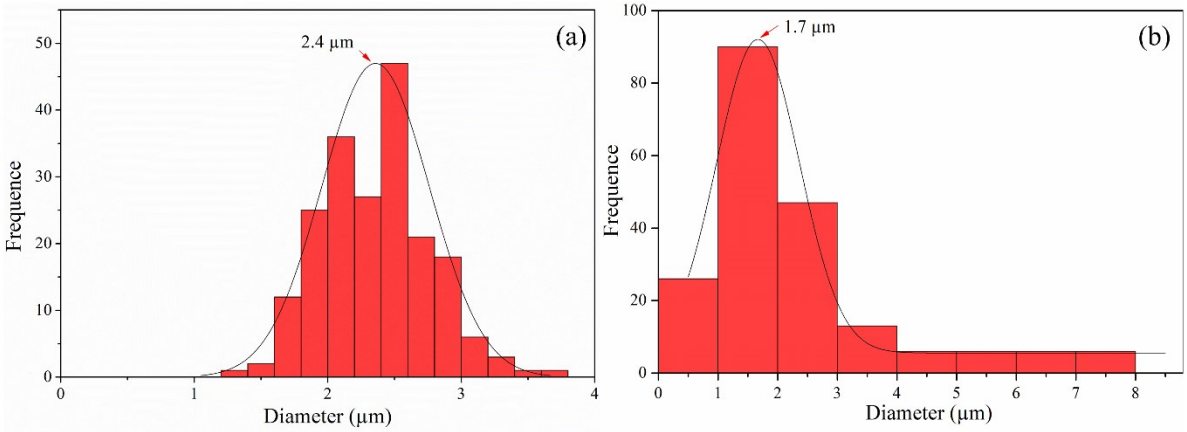
Figure 26 displays the SEM images of the electrospun nonwoven fiber mat of $50NR^{e\text{-}spun}$ (ANDRADE *et al.*, 2022a) and $50NR^{e\text{-}spun+prop}$, at different magnifications. The incorporation of propolis formed less fibers, the appearance of defects, and greater prominence of crossing points (Figure 26(e)-(h)). Figure 27 indicates the decrease in the average fiber diameter with the functionalization of propolis. Unlike Asawahame *et al.* (2014) verified an increase in the average diameter of PVP fibers incorporated with 5 wt% propolis, observing a value of 0.4 ± 0.1 μm for PVP fibers and 1.20 ± 0.3 μm for PVP fibers with propolis, these values being smaller than those found in the present research.

Figure 26 - SEM images of (a)-(d) 50NR$^{e\text{-}spun*}$ and (e)-(h) 50NR$^{e\text{-}spun+prop}$ samples. The images were recorded at a magnification of 500×; 1,000×; 5,000×; and 10,000× respectively.



*Data obtained in the previous study (ANDRADE *et al.*, 2022a).

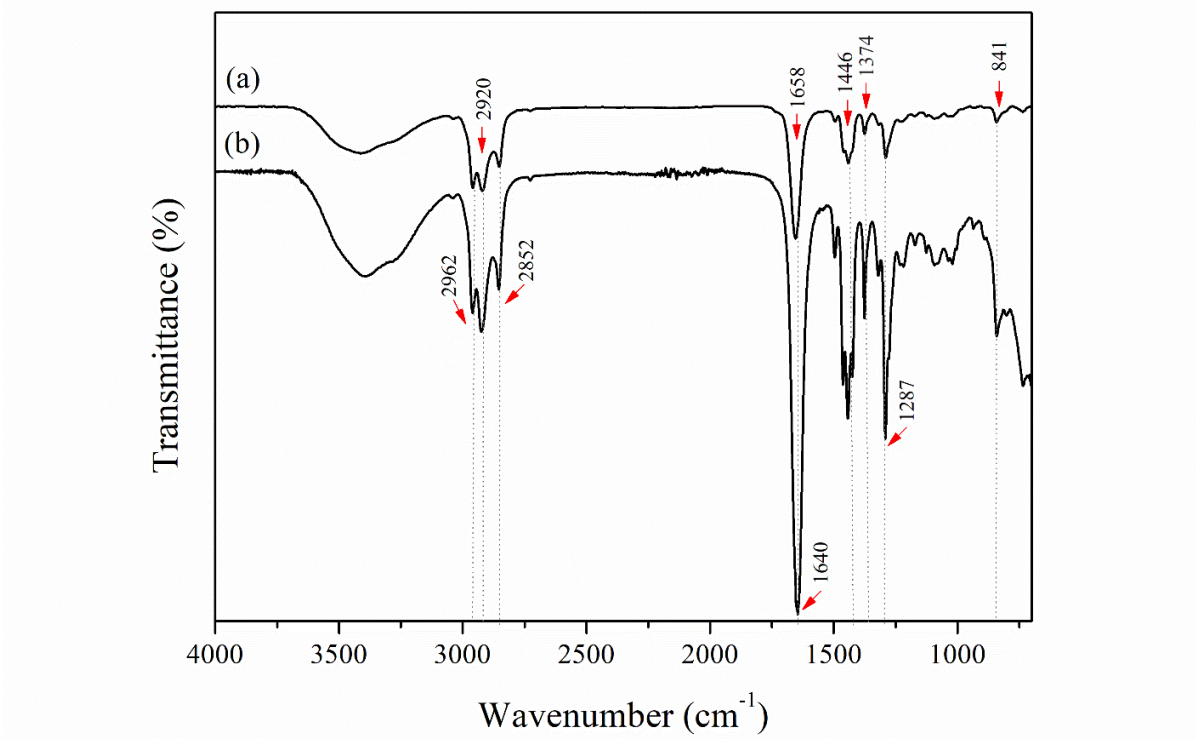
Figure 27 - Fiber diameter distribution and SEM image of (a) 50NR$^{e\text{-}spun*}$ and (b) 50NR$^{e\text{-}spun+prop}$.



*Data obtained in the previous study (ANDRADE *et al.*, 2022a).

The spectra of the 50NR$^{e\text{-}spun}$ and 50NR$^{e\text{-}spun+prop}$ fibers are shown in Figure 28. The typical characteristics of the NR and PVP bands were similar to those found in our previous report (ANDRADE *et al.*, 2022a). Sample 50NR$^{e\text{-}spun+prop}$ showed an increase in the intensity of the bands referring to NR and PVP, for example at 1287, 1446, and 2920 cm^{-1}. The peak at 1640 cm^{-1} (C=O stretching vibration), is typical of aromatic rings and polyols and flavonoids, characteristic of propolis (KIM *et al.*, 2014; OLIVEIRA *et al.*, 2016; SHARAF; HIGAZY; HEBEISH, 2013; ZANCANELA *et al.*, 2017), confirming a physical mixture between NR, PVP, and propolis.

Figure 28 - FTIR spectra and main bands of the analyzed samples (a) 50NR$^{e\text{-}spun*}$ and (b) 50NR$^{e\text{-}spun+prop}$.



* Data obtained in the previous study (ANDRADE *et al.*, 2022a).

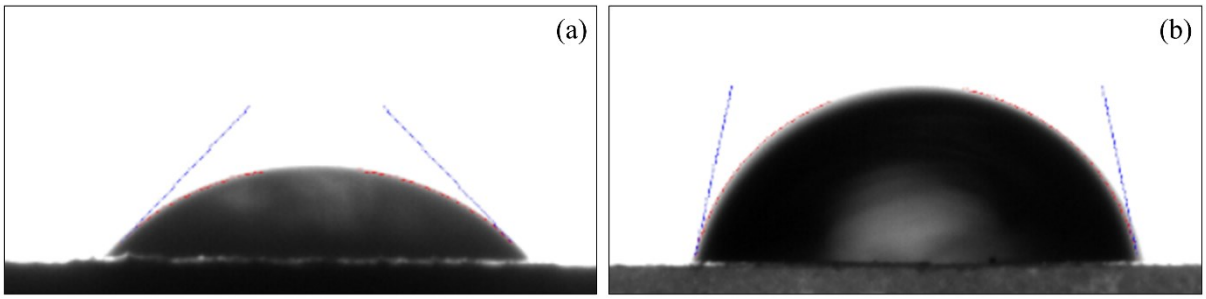
The contact angle values of the developed samples are listed in Table 22 and the images of the readings are found in Figure 29. The sample 50NRe-spun+prop showed a decrease in the contact angle value (46.0° ± 3.1) when compared to the sample without propolis (52.0° ± 1.6). About the samples obtained by casting, an increase in the contact angle value was observed for 50NR$^{e\text{-}spun+prop}$ (77.7° ± 1.8). Therefore, it can be said that the incorporation of propolis did not interfere with the wettability characteristics of the samples, both for the sample obtained by electrospinning and the one produced by casting, since the hydrophilic characteristic of the material (θ<90°) was the same. Also, it can be mentioned that the casting technique provides a surface with higher contact angle values when compared to the electrospinning technique.

Table 22 - Contact angle values of the electrospun fiber mats and cast membranes samples.

Sample	**Contact angle (θ ± σ)**	**Sample**	**Contact angle (θ ± σ)**
50NR$^{e\text{-}spun*}$	52.0° ± 1.6	50NR^{Cast*}	64.5° ± 3.6
50NR$^{e\text{-}spun+prop}$	46.0° ± 3.1	50NR$^{Cast+prop}$	77.7° ± 1.8

*Data obtained in the previous study (ANDRADE *et al.*, 2022a).

Figure 29 - Images of the contact angle reading of the samples 50NR$^{e\text{-}spun+prop*}$ and 50NR$^{Cast+prop.}$

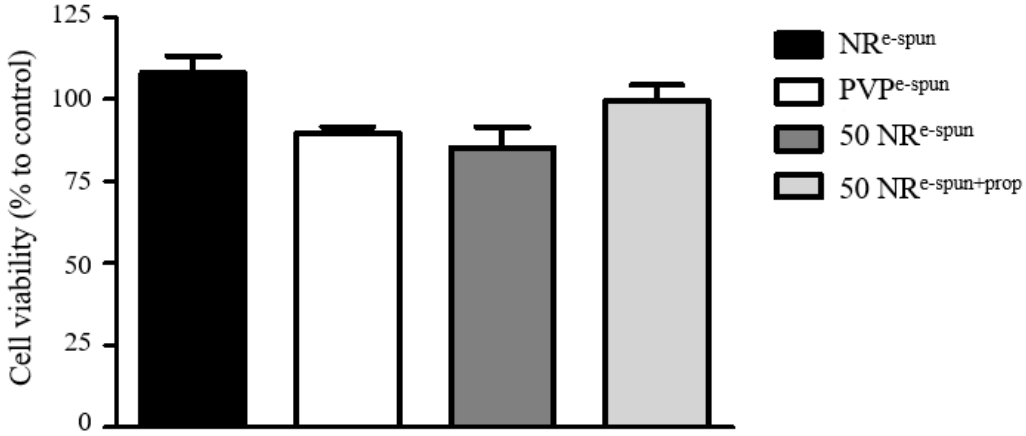


*Data obtained in the previous study (ANDRADE *et al.*, 2022a).

It is known that the surface characteristics are essential to determine the application of biomaterials, thus wettability is considered one of the most important properties of a solid surface, being able to interfere in several biological processes and biomolecular behaviors, such as adsorption, lubrication, wetting, adhesion, friction and resistance to microorganisms (CHENAB; SOHRABI; RAHMANZADEH, 2019; HOWELL *et al.*, 2016). The presence of hydrophilic properties directly affects the cytocompatibility of biomaterials. Events such as cell adhesion and growth are directly influenced by surface wettability since most cells prefer to anchor to surfaces with hydrophilic characteristics (ESPOSITO *et al.*, 2007; LIU *et al.*, 2019).

The viability of MCCoy fibroblasts in the samples was estimated by MTT assay after 72 h as described in section 5.2, Figure 30 shows the results.

Figure 30 - Cytotoxicity - MTT assay of the fibers.



The results obtained demonstrate that none of the samples evaluated induced significant cytotoxicity, since viability percentages above 80% were observed (INTERNATIONAL STANDARD ORGANIZATION (ISO), 2009). Furthermore, no

significant differences in cell viability were observed when comparing all tested samples. This fact highlights the potential of the materials obtained for use in biomedical applications, suggesting the development of a biomimetic environment that can facilitate cell adhesion and proliferation. The highlight is the $50NR^{e\text{-}spun+prop}$ sample, the focus of this investigation, which due to the biological characteristics provided by the presence of propolis, enhances the biomedical application of the NR:PVP system.

5.4 CONCLUSIONS

The chloroform proved to be the best solvent, among those studied, for extraction of propolis, because it ensured higher values of quercetin equivalents in the final extract. When compared to the propolis-free fibers, the incorporation of this substance caused a lower fiber production, besides causing the appearance of defects and greater prominence of the crossing points. The fibers presented greater heterogeneity of fiber diameters and also, a decrease in these values. In the same way, the functionalization with propolis interfered in the wettability of the samples, enhancing the hydrophilic properties of the material. Furthermore, no sample induced significant cytotoxicity, as viability percentages of more than 80% were observed.

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5.6 AUTHOR'S CONTRIBUTION

Table 23 - Authors' contributions.

Author	Contributions
Andrade, K. L.	Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing
Bettega, K. F.	Formal analysis, Methodology, Validation
Santos, P. H.	Formal analysis, Methodology, Validation
Acosta, E. D.	Supervision, Visualization, Formal analysis, Writing – review & editing
Faita, F. L.	Project administration, Supervision, Visualization, Writing – review & editing
Machado, R. A. F.	Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Visualization, Writing – review & editing

6 CONCLUSIONS

The results obtained showed that obtaining fibrous surfaces from the association of NR-50 and PCL (100 and 120 $mg.mL^{-1}$) was possible, but the data did not show suitability for the material to be used in skin lesions because they have hydrophobic characteristics.

The association of NR:PVP (NR-15 and PVP-200) provided the development of surfaces with adjustable properties according to the proportion of each polymer, , demonstrating to be suitable for fibers production aimed at the proposed application.

FTIR analysis showed the physical mixing of the polymers in the NR:PVP association. The morphological analysis demonstrated the formation of fibers on the micrometer scale, free of defects and with the presence of crossing points. The addition of PVP in NR caused a decrease in the average diameter of the fibers (concentrations ≥ 50%), allowing the obtainment of a hydrophilic material, compatible with applications in skin lesions.

The fibrous sample with the highest potential application in skin lesions was NR:PVP 50:50 ($50NR^{e\text{-}spun}$), which was used to incorporate propolis. Chloroform was the most efficient solvent for the extraction of this bioactive. The incorporation of propolis interfered in the average diameter of the fibers and in the wettability characteristics, enhancing the hydrophilicity of the material. Moreover, no significant cytotoxicity was observed in the samples evaluated, since viability percentages of more than 80% were observed.

It is concluded then that the incorporation of PVP in NR positively affected the surface properties of the biomaterial, allowing its use in applications such as skin lesions. Furthermore, the possibility of maintaining and improving the biological properties of the biomaterial by functionalization with propolis is highlighted.

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APPENDIX A – RELEVANT SCIENTIFIC PRODUCTIONS

Table 24 - Relevant scientific productions developed during the Ph.D. period – Book chapter.

Book/Publisher	Title	Authors
Chitosan-based Nanocomposite materials: Fabrication, Characterizations & Biomedical Applications/ Springer *2022* https:// doi.org /10.1007/978-981-19-5338-5	Application of Chitosan Based nanocomposites in Tissue Engineering and regenerative medicine	Tailin Rieg, Angelo Oliveira Silva, Ricardo Sousa Cunha, Karina Luzia Andrade, Dachamir Hotza, Ricardo Antonio Francisco Machado
Rubber Technology: Manufacture, Processing, Properties and Applications/ Elsevier *Submitted in 2021*	Rubbers in biomedical applications	Karina Luzia Andrade, Heloisa Ramlow, Juliana Ferreira Floriano, Daniela Bresolin, Emanoelle Diz Acosta, Ricardo Antonio Francisco Machado, Fabricio Luiz Faita
Tópicos em Preparação e Caracterização de Materiais Poliméricos/ Editora UFPR *Accepted in July 2021 - *According to the notice, the publisher has up to two years to publish the book*	Eletrofiação: Andaimes nanofibrosos poliméricos para aplicações na engenharia de tecidos	Karina Luzia Andrade, Mariana Ferreira Ávila, Emanoelle Diz Acosta, Fabrício Luiz Faita, Ricardo Antonio Francisco Machado
Tópicos em Preparação e Caracterização de Materiais Poliméricos/ Editora UFPR *Accepted in July 2021 - *According to the notice, the publisher has up to two years to publish the book*	Monocamadas automontadas poliméricas e filmes finos poliméricos: Propriedades e aplicações biomédicas	Karina Luzia Andrade; Valdir Aniceto Perreira Junior; Carolina Carnicel; Ana Cláudia Tasinaffo Alves; Genilza da Silva Mello
Tópicos em Preparação e Caracterização de Materiais Poliméricos/ Editora UFPR *Accepted in July 2021 - *According to the notice, the publisher has up to two years to publish the book*	Suspensões poliméricas para recobrimento de material particulado em leito móvel.	Mariana Ferreira Ávila; Karina Luzia Andrade; Raul Favaro Nascimento

Table 25 - Relevant scientific productions developed during the Ph.D. period – Articles.

Journal	Title	Authors
Surfaces and Interfaces *2022* https://doi.org/10.1016/j.surfin.2022.102129	Wettability tuning of natural rubber/polyvinylpyrrolidone electrospun nonwoven mats	Karina Luzia Andrade, Fabrício Luiz Faita, Rodney Marcelo do Nascimento, Ricardo Sousa Cunha, Daniela Bresolin, Emanoelle Diz Acosta, Ricardo Antonio Francisco Machado
Polímeros: Ciência e Tecnologia *2022* https://doi.org/10.1590/0104-1428.20210114	Latex and natural rubber: Recent advances for biomedical applications	Karina Luzia Andrade, Heloisa Ramlow, Juliana Daniela Bresolin, Emanoelle Diz Acosta, Ricardo Antonio Francisco Machado, Emanoelle Diz Acosta, Fabrício Luiz Faita, Ricardo Antonio Francisco Machado
Brazilian Journal of Chemical Engineering *Submitted – August 2022*	Latex and natural rubber: Processing techniques for biomedical applications	Karina Luzia Andrade, Heloisa Ramlow, Juliana Ferreira Floriano, Emanoelle Diz Acosta, Fabrício Luiz Faita, Ricardo Antonio Francisco Machado
Journal of Luminescence *2022* https://doi.org/10.1016/j.jlumin.2021.118498	Strongly polarized light from highly aligned electrospun luminescent natural rubber fibers.	Fabricio Luiz Faita; Patricia Tuzimoto; Giliandro Farias, Karina Luzia Andrade; Deuber L.S. Agostini, Aldo E. Job; André A. Vieira; Hugo Gallardo; João Canejo, Maria H. Godinho; Ivan H. Bechtold
Journal of the Textile Institute *2020* https://doi.org/10.1080/00405000.2020.1785071	Smart textiles: an overview of recent progress on chromic textiles	Heloisa Ramlow; Karina Luzia Andrade; Ana Paula Serafini Immich

Table 26 - Relevant scientific productions developed during the Ph.D. period – Conference papers.

Event	Title	Authors
XX Brazil MRS Meeting – SBPMat *2022*	Surface analysis of electrospun nonwoven mats from natural rubber and polyvinylpyrrolidone: Experimental measurements and theoretical modeling	Karina Luzia Andrade, Fabrício Luiz Faita, Rodney Marcelo do Nascimento, Ricardo Sousa Cunha, Heloisa Ramlow, Emanoelle Diz Acosta, Ricardo Antonio Francisco Machado
XX Brazil MRS Meeting – SBPMat *2022*	Characterization of PAN-PMMA/polysilazane-derived ceramic fiber mat with electromagnetic reflection loss in C-band 5G	Heloisa Ramlow, Karina Luzia Andrade, Cintia Marangoni1 Ricardo Antonio Francisco Machado
23° Congresso Brasileiro de Engenharia Química (COBEQ) *2021*	Obtenção de microfibras de borracha natural e poli(ε-caprolactona) pela técnica de eletrofiação para aplicação em lesão de pele	Karina Luzia Andrade, Rayane Helen de Andrade Alves e Silva; Ricardo Sousa Cunha; Aline Maria de Borba; Emanoelle Diz Acosta; Fabricio Luiz Faita; Ricardo Antonio Francisco Machado
23° Congresso Brasileiro de Engenharia Química (COBEQ) *2021*	Análise de superfície de fibras eletrofiadas a partir de blendas poliméricas de BN:PVP e PCL:PVP	Karina Luzia Andrade; Ricardo Sousa Cunha; Daniela Bresolin; Emanoelle Diz Acosta; Fabricio Luiz Faita; Ricardo Antonio Francisco Machado
15° Congresso Brasileiro de Polímeros (CBPol) *2019*	Potencialidade de uma membrana plana comercial de PVDF aplicada à recuperação de água do efluente do tingimento têxtil contendo corante disperso no processo de destilação por membrana	Heloisa Ramlow; Karina Luzia Andrade, Cintia Marangoni, Ricardo Antonio Francisco Machado
Europe-Africa Regional Conference of the Polymer Processing Society (PPS2019) *2019*	Smart polymeric materials applied to industry 4.0: A review on electrochromic textiles.	Heloisa Ramlow; Karina Luzia Andrade; Cintia Marangoni; Ricardo Antonio Francisco Machado