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Review Article

Natural Rubber Latex on Medical Applications

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Abstract

In this review, latex from the Hevea Brasiliensis tree is presented as a material originating from nature, used to produce natural rubber, raw material for countless products for industry, as well as the manufacture of preservatives, and gloves, among others. Nowadays, its potential is expanding into various technological areas, one of which is biomedical, as described in this article. Latex has the possibility of being preserved using ammonium, which is a chemical of high health risk, but nowadays it is being substituted by acid systems excluding traditional chemicals. With these new preservation processes, the prospective use of latex for the design of biosensor scaffolds for drug release, and as membranes that can replace synthetic latex in patches for bioremediation in soft and bone tissues, synthetic muscles, membranes for biological micro laboratories, among others, is being studied to optimize its possibilities.

More Information

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Introduction

Natural rubber latex is considered a sustainable and renewable resource as it is obtained by tapping the liquid latex sap from trees without causing any harm. Through this tapping process, the renewable source of latex is able to flow. However, it is important to note that natural latex sap has certain limitations. It is highly influenced by temperature, becoming soft and sticky in hot conditions and brittle in cold environments. Additionally, in latex, Natural Rubber (NR) is contained within rubber particles, which are specialized organelles consisting of a hydrophobic NR core surrounded by a lipid monolayer and membrane-bound proteins. The resemblance in the fundamental carbon skeleton structure between NR and dolichols and polyprenols, commonly found in various organisms, implies a potential connection between the NR biosynthetic pathway and the polyisoprenoid biosynthetic pathway and that rubber transferase, which is the key enzyme in NR biosynthesis, belongs to the cis-prenyltransferase family [1]. Overall, this NRL has focused on the vulcanization process in which latex is converted into a firm and flexible product over a wide range of temperatures and applications, as well as biomedical options [2], still under research, and a broader consolidation of such materials is expected in a near future [3].

Over the past few decades, there has been remarkable advancement in the field of biomaterials, particularly in terms of their functionalities and applications. In order to achieve various functions such as tissue engineering, tissue repair, and controlled release of therapeutics, the development of biocompatible and biologically active materials has become crucial. The need to optimize manufacturing processes and the agility and performance of different medical treatments have made it possible for researchers with a multidisciplinary approach to continuously develop materials to improve people's quality of life [4]. However, it is a difficult task to find either synthetic or natural materials suitable for in vivo applications. Nature has provided us with the natural rubber latex from the rubber tree Hevea Brasiliensis, which is a colloidal system composed of 50% water, 30% - 45% rubber particles (cis-1,4-polyisoprene) and 4% - 5% non-rubber constituents (such as proteins, lipids, and carbohydrates in recent years, Natural Rubber Latex (NRL) has emerged as a promising biomaterial derived from renewable sources for various biomedical applications. This is primarily due to its angiogenic properties and the ability to create well-defined functional materials. NRL can be utilized in drug delivery systems (both oral and transdermal), as scaffolds for skin and bone regeneration, and as dressings for wound healing. The integration of drugs, nanoparticles, cells, and other substances into NRL and NR polymer chains provides a broad spectrum of potential applications, including the development of dressings with antimicrobial properties and sustained release systems [5].

Latex properties

Herculano, et al. [6] A biocompatible natural polymer has been proven to stimulate tissue repair by enhancing the vasculogenesis process, guiding and recruiting cells responsible for osteogenesis, and serving as a stable matrix for controlled drug release. The fabrication of medical devices using materials with these biological properties would be highly beneficial. Recently, a range of biomedical devices based on natural rubber latex has been developed to leverage its biological properties for enhanced tissue repair. Most of them were utilized to improve tissue repair in chronic wounds and critical bone defects, while others were employed in the development of drug-release systems for localized, sustained, and controlled therapeutic release. In some cases, it is possible that patients may show symptoms of allergy to the proteins present, which has led to the search for alternatives in the process of preservation and treatment of latex.

For example, Seiichi, et al. [7] showed that the condition for the removal of all proteins from natural rubber was set at 0.1 w/w% urea, 0.025 w/w% polar organic solvents in the presence of Sodium dodecyl sulfate, followed by centrifugation two or three times. The total nitrogen content and the amount of extractable proteins of the protein-free natural rubber were 0.000 w/w% and 0.0 µg/ml, respectively. This indicates that the proteins in the latex were only bound to the surface of the rubber particles by the physical interactions, but not by the chemical interactions. The tensile strength of the protein-free natural rubber (N% = 0.000w/w%) was significantly lower than that of the natural rubber, although the tensile strength of the deproteinized natural rubber (N% = 0.012 w/w%) was similar to that of the source rubber. Thus, the proteins and fatty acid ester groups were found to play an important role in the properties of natural rubber.

Improvements in the mechanical properties of deproteinized NRL have been achieved, but even with the presence of ammonium in the different samples, it is expected to continue towards a totally free NRL or with the minimum of chemical substances for biomedical applications., is the sample of Thuy T. Thi, et al. [8]. The mechanical properties of the were significantly improved, with tensile strength almost doubled compared to deproteinized natural rubber. The molecular weight distributions of the materials were studied and the results obtained were in full agreement with the thermo-mechanical analyses. This improvement in the thermal and mechanical properties of the materials demonstrated a viable combination between graft copolymerization and hydrogenation in and hydrogenation in the modification of NR.

In this summary, we outline the recent advancements in these areas. Specifically, this review presents several applications, discusses critical issues related to the use of natural rubber latex in biomedical applications, and emphasizes future opportunities for biomedical devices derived from natural rubber latex, with a focus on one of the most extensively explored materials, NRL:

*NRL membranes can be applied to dermal wounds, helping with healing.

*NRL serum has angiogenic, anti-inflammatory, antimicrobial, and osteogenic properties.

*NRL can also be used as an occlusive membrane for Guided Bone Regeneration (GBR) applications [9], biological aspects of NRL-AgNP (silver nanoparticles), cell viability, tissue reaction, and guided bone regeneration membrane are favorable for use in GBR procedures.

*NRL matrix-based biomedical devices can be used to release bioactive compounds, for example, the incorporation of Ibuprofen (IBF) on NRL [10]. The NRL membranes' incorporation of IBF was evaluated through physical-chemical, in vitro permeation, hemocompatibility, and molecular modeling assays. The in vitro release profile of IBF in acidic and basic media was analyzed over 96 hours. The drug permeation results indicated that the IBF-NRL membranes could be suitable for localized skin treatment. It was demonstrated that the IBF-NRL membrane exhibited significant potential as a new adhesive for treating inflammatory processes and injuries.

*NRL is a biocompatible polymer capable of stimulating the repair of adjacent tissues.

Preservation latex

Y. Tanaka, et al. explored the NRL and showed the most traditionally used conservant to preserve NRL recently collected for long periods is ammonia [11]. Incorporating ammonia in concentrations exceeding 0.35% by mass serves as a highly effective bactericide, whereas lower concentrations (0.005% by mass) can expedite bacteria growth. Elevating the pH through ammonia addition enhances the electrical charge density at the interface between rubber particles and the aqueous medium, consequently fostering heightened colloidal stability of NRL. To date, challenges have persisted in the development of tissues suitable for clinical utilization, particularly in tissue engineering applications like wound healing, skin replacement, and tissue grafts. These tissues require cytocompatibility, biological activity, and foremost, biodegradability. However, NRL-based biomaterials need to exhibit enhanced biodegradability, biomimicry, and the ability to sustain their structure and function for extended periods. Consequently, there is a demand for the development of novel NRL-based materials to create bioactive, biodegradable, and biomimetic biomaterials, particularly for integration into biofabrication technologies.

Technological applications

Boratto, et al. [12] demonstrated that Natural Rubber Latex (NRL) derived from Hevea brasiliensis exhibits exceptional mechanical properties and serves as a biocompatible electrically insulating material. The study focused on a blend of NRL and Poly(3,4-ethylene dioxythiophene) poly(styrene sulfonate) (PEDOT:PSS), denoted as N/P, with varied volume ratios and curing temperatures to achieve an optimal balance of flexibility and conductivity. Low-temperature annealing at 60 °C dries, cures, and enhances the blend's tensile strength and conductivity within minutes. Among the various N/P concentrations tested, the membranes with an N/P ratio of 1/4 and those that underwent thermal curing exhibited the most promising conductive and flexible properties for bioelectronic applications. Furthermore, they displayed excellent interconnectivity between their electrical and mechanical properties, which can be attributed to the efficient percolation of the conductive polymeric chains during thermal curing. These membranes are able to withstand strains as high as 700%. The composition exhibited exceptional properties for bioelectronic devices that can operate under strains of up to 100% with no substantial variations in electrical resistance, for instance, strain gauges, electronic skin, or pliant conductors.

Green electrospinning is a promising, relatively new technology where a polymer (latex) is spun from an aqueous dispersion using a template polymer. Andrade, et al. [13] explore this clean and safe technology that can spin hydrophobic polymers using water as a medium. A systematic study examined the impact of the molar template polymer, Polyvinyl Alcohol (PVA), the total solids content of the initial dispersion, and the particle/template ratio. The polymer particles in this work consisted of a copolymer of methyl methacrylate-co-butyl acrylate (MMA/BA) that carried cross-linkable articles.

Prepared in 5 mL vials with magnetic stirring, the latex (containing 50 wt.% s.c.) was added dropwise to the PVA aqueous solution (with a concentration of 10 wt.%). This was done to adjust the final s.c. of all blends to 17 wt.%. Furthermore, a surfactant at 1wt%/wt% (Dowfax 2A1) was utilized to stabilize the polymer particles, resulting in a diameter of 107 nm ± 1 nm. Thus, it can be concluded that the initial complex dispersion's viscosity is influenced by the particle size distribution and surface chemistry of the polymer particles, which is determined by the presence of functional groups or the surfactant used. As a result, these factors significantly impact the resulting fiber morphology.

The first step involves exploring the manufacturing process for membranes through casting, as well as dressings and scaffolds through electrospinning [14]. Other techniques such as spraying, dipping, compression, extrusion, protein extraction, and blow spinning are also examined. The final section presents our perspectives for future research related to manufacturing biomaterials with optimal characteristics for biomedical applications and regenerative medicine. Nanocomposites composed of NR and chitin nanofibers displayed enhanced strength and tenacity with the addition of a small amount of fibers. In contrast, incorporating a smart polymer poly(vinyl alcohol)-isopropylacrylamide with deproteinized natural rubber during hydrogel production enhanced traction resistance and rupture elongation. Adding NR to the blend with polycaprolactone increased the tensile modulus, ultimate elasticity, and strain of electrospun mats. By using 10 wt% NR, elongation (238%) and swelling properties (202%) were further optimized [15].

Biomedical applications

The biodegradability of natural rubber latex is not significantly high compared to other polymers that are used for developing materials that have biomedical applications. This plays an important role in avoiding medical interventions needed to remove them. Herculano, et al. [16]. To enhance the biodegradability and subsequent absorption of natural rubber latex membranes, we can associate them with polylactic acid. This polymer is biodegradable, bio-reabsorbable, and biocompatible, making it widely studied in biomedical, pharmaceutical, and environmental fields. The membranes were prepared using various polymer mass ratios dissolved in dichloromethane. It was observed that the membrane properties were impacted by the different ratios of polymers. The infrared spectroscopy indicates no new chemical interactions were formed while the scanning electron microscopy showed a polymer network formed in membranes with the highest proportion of natural rubber latex mass. Increasing polylactic acid in the membranes improved material degradation by up to 130%, and no hemolytic effects were observed, making it a fascinating option for biomedical applications.

In the next decade, microfluidics innovation [17] may be possible to restore vision and reverse the effects of spinal cord injury or disease. Additionally, a lab-on-a-chip could allow for medical diagnoses without the need for a clinic or for instantaneous biological agent detection. Bioelectronics is the discipline resulting from the convergence of biology and electronics. Microfluidic devices are based on the replication of microchannels and chambers through casting. Nowadays, latex combines flexibility and transparency on polymeric platforms. Natural rubber is proposed as an alternative material for preparing microfluidic devices due to its advantages in terms of flexibility, eco-friendliness, and lower cost compared to other commonly used polymeric microfluidic materials. However, natural rubber faces challenges such as compounds leaching when in contact with fluids, low stretching resistance, and reduced transparency due to water absorption rate. To address these issues, we evaluated the essential mechanical, optical, and structural properties of natural rubber in centrifuged and pre-vulcanized rubber membranes, along with the application of a polymeric coating on the membrane surfaces.

The NRL is used for Transdermal Drug Delivery System (TDDS) [18], transdermal drug delivery is a painless and non-invasive technique that utilizes a skin patch or other device to administer medications. The drug seamlessly penetrates through the skin layers and reaches the circulatory system, ultimately targeting specific organs for treatment. Despite the advancements in Transdermal Drug Delivery Systems (TDDS) and the development of devices that can deliver drugs with different origins (lipophilic, hydrophilic, and amphiphilic), dosage levels still fall short when compared to traditional delivery methods. Using NR as a matrix, this type of system can be created, but it remains a potential research avenue.

Camargo, et al. [19] proposed the use of a centrifugation process to reduce the leaching of natural rubber membrane compounds, and vulcanization to enhance the mechanical resistance of the polymeric membrane devices. A polymer coating was applied to prevent leaching and water absorption while maintaining transparency and preventing an increase in surface hydrophobicity. Once the centrifugation, vulcanization, and coating processes have improved the properties of the rubber, this polymer will emerge as an alternative, flexible, and cost-effective material for Natural Rubber Microfluidic technology/devices (NRMDs), used in optical and electrochemical applications on microreactors for the synthesis process.

Nowadays, the advent of soft lithography to fabricate devices in the elastomer Polydimethylsiloxane (PDMS) catalyzed microfluidic research growth in the last few years [20]. "Many modern laboratories solely rely on PDMS due to its low technology and investment requirements for micrometer-scale resolution structuring. However, PDMS has several limitations and is inept for mass production. Currently, available fabrication methods have restricted microfluidic devices to quasi-2D planar formats." Several groups have utilized 3D printing to create printed 3D microfluidic reactors and in situ reagents. However, most individuals lack the capability to achieve this. The resolution and price of consumer-grade 3D printers have significantly decreased, making them suitable for microfluidic device fabrication. Direct printing expedites device prototyping and provides scientists with an easily accessible tool to express their creativity, similar to how the introduction of PDMS soft lithography did 15 years ago. So is necessary to develop new proposals for materials, among these, the Natural rubber latex, but, with process optimization, degradation behavior, and physic-mechanical properties like PDMS.

Novelties in latex processes

Nowadays, J. C. Rodríguez Urbina [21] has shown two novel methods for liquid latex preservation and stabilization methods in an acid medium free of ammonia or other dangerous chemicals. The first method used dodecyl benzene sulfonic acid to both stabilize and preserve the liquid latex, and the second used ethoxylated tridecyl alcohol to stabilize and hydrofluoric acid to preserve the colloidal suspension, with the novel stabilizers and preservatives, the shelf life of liquid latex increases from a few months to a few years.

This product, based on Latex Ammonia-free, opens possibilities for medical applications because this is a potential adhesive without toxicity for approaching medicals and biological. Osswald, et al. [22] have shown, NRL-based ammonia-free adhesives as primary materials with bio-additives, specifically cellulose, and collagen, to enhance their mechanical property provide the industry with an adhesive safe to handle. Latex-based adhesives are in the development stage as there exists various grades of ammonia-free natural rubber latex, such as Betapreno, Gammapreno, Epsilonpreno, and Thetapreno, all of which offer a wide variety of chemical bond types. Also, the mentioned Alfapreno grades are only two formulations using cellulose and collagen, which opens the doors to a variety of future adhesive blends that have the ability to provide a wide range of sustainable adhesives with comparable strength to solvent-based adhesives.

Conclusion

This has been an interesting compilation of processes and advances in natural rubber latex, in which important achievements are elucidated, as well as an invitation to make the most of the knowledge achieved in recent years and to take natural resources, in this case, NRL, as a promising and fertile source for both medical processes and advanced materials for human beings.

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