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BABT
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Review - Human and Animal Health

Alginate/Chitosan Associates a Platelet-rich in Fibrin Exudates as Drug Delivery Systems in Wounds: a Mini-Review

Carlos de Almeida Barbosa [1,5]
https://orcid.org/0000-0003-3674-7774

Rossana Baggio Simeoni [2,4]
https://orcid.org/0000-0002-9976-5809

Luize Kremer Gamba [2]
https://orcid.org/0000-0003-4415-6210

Victoria Stadler Tasca Ribeiro [2]
https://orcid.org/0000-0002-6767-3598

Marco André Cardoso[3]
https://orcid.org/ 0000-0002-3148-8366

Ricardo Correa Cunha [2,3]
https://orcid.org/ 0000-0003-4902-4006

Clayton Fernandes de Souza[1]
https://orcid.org 0000-0002-3968-4185

Júlio Cesar Francisco [2,4,5*]
https://orcid.org/0000-0003-1970-6399

Luiz Cesar Guarita-Souza [2]
https://orcid.org/0000-0003-2781-9705

Beatriz Luci Fernandes [1]
https://orcid.org/ 0000-0003-1751-7930

[1]Pontifícia Universidade Católica do Paraná, Escola de Ciência da Vida. Programa de Pós-graduação em Tecnologia em Saúde (PPGTS). Curitiba, Paraná, Brasil. [2]Pontifícia Universidade Católica do Paraná, Escola de Medicina, Programa de Pós-graduação em Ciências da Saúde (PPGCS). Curitiba, Paraná, Brasil; [3]Universidade Positivo, Curitiba, Paraná Brasil; [4]Instituto de Tecnologia do Paraná (TECPAR), Curitiba, Paraná, Brasil; [5]Unicuritiba - Centro Universitário Curitiba - Curitiba, Paraná, Brasil.

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*Correspondence: julio.apfr@gmail.com (J.C.F.).

HIGHLIGHTS

- Alginate/Chitosan is the second most abundant polysaccharide on earth.
- PRF (platelet-rich fibrin) potential to play adjunct roles in regenerative medicine.
- 3D printing grafts can increase wound healing capacity.
- Prospective of combining PRF with different biomaterials promotes tissue regeneration.

Abstract: The use of biopolymers and platelet-rich fibrin (PRF) is currently investigated as an excellent application biomaterial in the tissue engineering field. Natural biomaterials with application potential in tissue engineering and regenerative medicine are due to their characteristics in biocompatibility, biodegradability, and mechanical characteristic. Though, the basic knowledge of three-dimensional fibrin scaffold and chitosan/alginate processing technology combined with an understanding of the physical-chemical properties of this natural biomaterial is necessary for proper application in regenerative medicine and tissue engineering. This mini review summarizes the information on the composition of chitosan/alginate and PRF in medical area and discusses recent developments with a special focus on its use for the application of drug delivery. The most important advances and stimulating applications are studies in regenerative medicine and tissue engineering, for wound healing to treat burns, tumor treatment, nanoparticle carriers, and drug delivery systems.

Keywords: Drug delivery systems, chitosan/alginate, platelet-rich fibrin; Regeneration; Wound healing.

INTRODUCTION

Chronic wounds are a growing problem worldwide. Chronic wounds, such as non-healing pressure ulcers (NHPUs), venous ulcers (VUs), and diabetic foot ulcers (DFUs) exhibit a disturbance associated with the skin repair process, persisting for more than six weeks [1]. In the United States, the medical expenditure of treating chronic wounds exceeds $25 billion annually, with more than 6.5 million affected patients around the world [2].

In diabetic foot ulcers, 84% of patients with diabetic foot require an amputation which affects the quality of life of these patients [3].

In addition, the treatment of acute and chronic wounds is associated with the large use of local and systemic antibiotics collaborates to the high predominance of multidrug-resistant infections. This impacts a high cost of approximately R$ 96.8 billion with hospitalizations in Brazil [4].

However, innovations in natural or synthetic biomaterial treatment appear as a possibility for the treatment of diabetic ulcers [5]. Currently, autologous platelet-rich fibrin (PRF) exudate, has emerged as a promising adjuvant for the treatment therapeutic of diabetic foot ulcers in regenerative medicine, can easily be collected, rich in growth factors and cytokines such as IL6, IL8, IL4, and TGF-β, for future clinical applications does not imply any risk of rejection [6].

More recently have gained importance in the biomedical sectors marine biopolymers such as chitosan and alginate salts. This natural, abundant, and versatile polysaccharide is excellent in biodegradability and biocompatibility, non-toxicity, and low cost [6]. These properties allow them to become potential candidates for safe, inexpensive, and effective drug delivery [7].

Notably, the therapy for chronic wounds and diabetic ulcers is not satisfactory and includes of palliative care, vascular optimization, and prevention of infections [8]. The three-dimensional fibrin scaffold and chitosan/alginate associate could form the basis of a recent treatment, which could recover the body's normal healing processes [9].

This combination chitosan/alginate is considered a novel type of drug delivery system in different therapeutic applications. This mini-review summarizes the information on the composition of chitosan/alginate and PRF, the application of drug supply, in medicine, and debates recent innovations with a special focus on its use for tissue engineering. The most important advances and stimulating applications are studies in regenerative medicine and tissue engineering, for wound healing to treat burns, tumor treatment, nanoparticle carriers, and drug delivery systems.

Characteristic and formulation of platelet-rich fibrin

1. *Properties*

Platelet-rich fibrin (PRF) is an autologous blood-derived product that consists of a high concentration of leukocytes, cytokines, and glycoproteins such as thrombospondin obtained by centrifuged, according to the centrifugation force used [10]. Platelet activation and fibrin polymerization are instantaneous because it has no addition of anticoagulant or calcium thrombin/gluconate. It contains a complex composed of leukocytes, interleukin (IL)-1β, IL-4, and IL-6, cytokines, and glycoproteins such as thrombospondin, including the transformation of β-growth factor (TGF-β), and others that are involved in promoting tissue repair and regeneration [11].

The PRF has been widely used in various in several areas of regenerative medicine such as cartilage and tendon repair and has shown promising experimental and clinical effects in periodontal wound healing, especially in chronic wounds [12]. Recent review studies have shown actual clinical evidence of PRF in several areas, covering oral, maxillofacial, and orthopedic surgery and that contains all the constituents favorable for the healing process [13]. A review by Mohan and coauthors [14] suggested the presence of platelets and growth factors can convert an osteoconductive graft into an osteopromotive one in the field of dentistry.

2. *Preparation and preservation*

The method of preparation and isolation of PRF is very simple because it involves various protocols describing blood collected in 10 mL plastic sample tubes, speed, time, and temperature of centrifugation of whole blood which contains platelets, and leukocytes undergo spontaneous coagulation (figure 1). Through the blood clot that forms at the site of the injury, activated platelets and leukocytes are trapped in a fibrin-rich matrix [14].

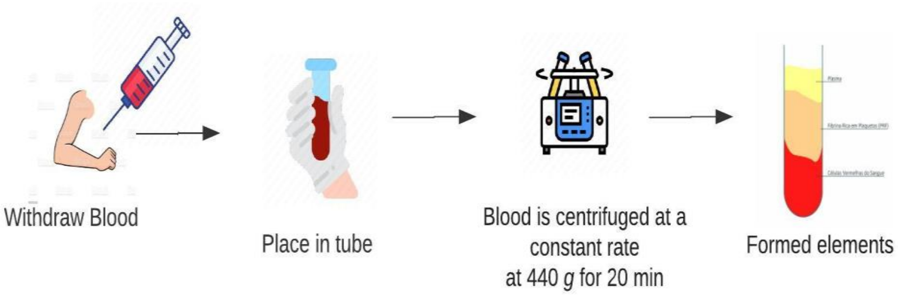

Figure 1. Preparation of platelet-rich fibrin (PRF)

Fujioka-Kobayashi and coauthors 2017 showed that an increase in the number of leukocytes and platelets can be influenced by increasing according to the centrifugation force used [15] Recently, the literature described various centrifugation protocols and these studies have shown that the centrifugal force (RCF) has the role of influencing the components and the bioactivity of PRF, thus acting on its therapeutic efficacy [16].

The PRF is usually used in an autologous fashion and fresh. However, studies demonstrated that its use lyophilized or freeze-dried can be packaged at room temperature for several months, easily reconstituted, and used when needed [17].

3. *Chitosan*

Chitosan is a natural alkaline polysaccharide acquired from marine crustaceans' chitin, produced chitosan by a deacetylation method. This is a bioactive biopolymer with a wide diversity of applications in both medical materials and biomedicine due to its characteristic such as antibacterial activity, non-toxicity, ease of modification, and biodegradability [18].

This is a linear polymer of beta-(1-4)-linked N-acetyl-2-amino-2-deoxy-d-glucose (acetylated) and 2-amino-2-deoxy-d-glucose with a combination of the partly polycationic and partly hydrophobic may present different biological activities that depend on different structural forms [19]. Thus, the physical-chemical properties such as excellent solubility, pH sensitivity, targeting, and mucosal adhesion of chitosan, and the molecular weight together with the deacetylation degree are the most important property of both chitin and chitosan [20].

The regenerative medicine applications of chitosan and chitin are due to the existence of their remarkable particularly such as biodegradability, biocompatibility, anti-tumor, antioxidant, bacteriostatic, low immunogenicity, antibacterial, and antifungal activities [21]. These characteristics have drawn attention to various applications in the textiles industry, chemicals, food, and medicine. In medicine the spatial effort for drug delivery, artificial skin, cartilage regeneration, and wound repair [22].

4. *Alginate*

Just like chitosan, alginate is an anionic linear biopolymer obtained from brown algae Phaeophyta species and used in various sectors of medicine because of its mucoadhesive and biocompatibility behavior and non-immunogenic properties [23]. These natural polymers derived from carbohydrates form polysaccharides and have been widely used in medicines or drug delivery systems as well as in the food sector [24].

It exhibits relevant characteristics such as non-toxicity, biocompatibility, biodegradability, non-immunogenicity, affordability, and high absorption capacity are fundamental in regenerative medicine.

Alginate has been employed in the clinic by increasing the absorption of wound exudates because of its mucoadhesive, biocompatibility, and hemostatic properties, minimizing bacterial infections [25].

For application to the wound, sodium alginate-based scaffolds have distinct formulations, as well as hydrogels, films, foams, nanofibers, and topical preparations integrating the wound hydrated to promote better healing [26,27]. Among the various formulations, the hydrogels are used for drug delivery by ionic crosslinking with cations or by acid precipitation, which can occur by external or internal gelation because of their biodegradability and biocompatibility and their similar physical structure to the natural extra-cellular matrix (ECM) with the human body [28,29].

Bioinks are natural or synthetic polymers. Natural biopolymers have emerged as an important material biome for the care of acute and chronic wound healing in the development of 3D scaffolding in tissue engineering. Thus, among natural polymers, alginate has been extensively utilized as a bioink due to its fast-fit gelation character according to physiological conditions without composing adverse products [30].

5. *Bioprinting is an innovative technology for drugs delivery*

Since the 1980s, Charles Hull has developed the 1st 3D structures printer using computer-aided design (CAD) capable of creating solid objects through the layer-by-layer deposition of bioink. Thus, three-dimensional bioprinting 3D is an emerging research area with various finalities in the production of functional tissues and organs [31].

More recently, is a novel 3D biofabrication method, and constructs include la-ser-assisted bioprinting (LaBP), inkjet bioprinting/droplet bioprinting, and extrusion-based bioprinting [32,33].

The recent advances in research in bioprinting and 3D printing describe the applications of the biopolymer, focusing on the advantages and future of the use of drug delivery systems in the pharmaceutical industry. The mini-review includes both chitosan/alginate and PRF biomaterials used either isolated or in combination used as 3D fabrication (Table 1).

Table 1. summary of outstanding recent bioinks studies for drug delivery.

Natural biomaterial-based bioinks						
Bioprinter composition	**Material**	**Target tissue**	**Bioprinting technique**	**Printed geometries**	**Application**	**Reference**
Alginate	Hydrogels	Skin	Extrusion Printing	Honeycomb-like construct	Wound dressing	35
Chitosan	Hydrogels	Tissue	Extrusion Printing	Square grid	Tissue engineering applications	36
Chitosan-alginate	Hydrogels	Gastrointestinal tract	Extrusion Printing	Grid	Gastrointestinal tract	37
Chitosan-alginate	Hydrogels	Skin	Extrusion Printing		Wound dressing	38
Collagen	Extracellular matrix	Cornea	Extrusion Printing	Grid	Corneal stroma tissue	39
Fibrinogen	Extracellular matrix	Skin	Extrusion Printing	Square grid	Epidermis	40
Platelet-rich fibrin	Hydrogels	Periodontitis	Extrusion Printing	Meshed tubes	Antibacterial	41

The promotion of new computational models is a field of interest that can be applied to the experimental optimization of drug delivery.

6. *Biomedical applications of chitosan/alginate blends*

Recently, chitosan/alginate blends formulations with a unique set of properties have attracted plenty of attention with immense potential for applicability in tissue engineering [42]. Several studies related to drug release systems using chitosan have been published in cardiovascular diseases, as well as for viral diseases that are in the in vitro development phase [43].

However, all types of biomaterials used in the medical field need to be previously analyzed for any adverse biological effects, regarding inflammatory, allergic, coagulation/hemolysis responses, and carcinogenic responses. In this way, the biocompatibility of hydrogels is a particular property that must be initially tested before being addressed for any biomedical applications [44].

The biopolymer chitosan/alginate blends combine the intrinsic characteristics of the scaffolds structure and those of the biocompatible polysaccharides, signifying that they are appropriate for biomedical applications. The development of hydrogels to reproduce the extracellular matrix (MEC) in the body allowed its various applications in the biomedical area, such as the release of drugs and scaffolding for tissue engineering [45].

Here we consider the latest uses of hydrogels in the field of regenerative medicine and its biomedical applications.

CONCLUSION

Several publications suggest that the application of PRF and chitosan/alginate isolates accelerates the healing process in chronic diabetic wounds. Clinical and experimental studies using PRF or chitosan/alginate after a cutaneous wound in rats have described promising results in the quality of scar tissue in recent years.

Lastly, we note that clinical trials and experimental studies have intensively explored both biomaterials as a matrix for promising three-dimensional scaffolding migration, stimulating inflammatory cells, macrophages, and fibroblasts or targeted drug delivery in regenerative medicine and tissue engineering.

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