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Gel-based on Collagen-polyacrylate-MOF as an Adjuvant in Skin Wound Healing: A Case Study

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ABSTRACT

A case study was made with the participation of population of General Cepeda a municipality of Coahuila de Zaragoza State in México. People with chronicle wounds in the skin associated with diabetic neuropathy, a venous ulcer, and burns were invited to participate and signed an informed consent to use a gel-based on collagen-polyacrylate-MOF, which acted as an adjuvant in skin wound healing. The outstanding results of the study indicated that the gel-based on collagen-polyacrylate-MOF, enhances the healing process in short periods of use in patients (promoted by collagen), preventing the appearance of pathogens that hinders the healing (effect promoted by polyacrylate and MOFs).

According to the preview results, a further clinical study should be made with a major population.

Keywords: *Collagen, Polyacrylate, MOFs, Gel, Skin wound healing.*

1. Introduction

The repair, replacement and/or regeneration of damaged tissue such as bone, cartilage, and skin represent the fundamental goal of tissue engineering. In humans, the skin is considered one of the largest organs, that are responsible for controlling and regulating contact with the external world, protecting the organism from physical, chemical, and microbiological impacts, and, for the maintenance of temperature, electrolyte, and fluid balance [1].

The healing time of skin injuries varies depending on the extension and depth of the wound, and the clinic history of the patient. In this way, diabetes is an illness that not only causes hyperglycemia, but also, causes several affections such as kidney failure, cardiovascular disease, and peripheral arterial disease, among others [2]. In the specific case of skin, diabetes hinders the healing of skin injuries, located commonly in extremities as feet, due to the high risk of infections, and if the infections are not controlled can cause as the last option, the amputation of the member or a part of it. Diabetes causes dry and itchy skin, also the callus formation, the generation of venous, and diabetic ulcers promoted by neuropathy of diabetic feet [3].

Thus, diabetes turns these affectations from acute wounds, which normally take within 8 to 12 weeks to be cured, to chronic wounds that fail the normal progress of recovery, and these cannot be repaired for a normal process of healing [4]. The general treatments for ailments such as burns, venous and diabetic ulcers in diabetic patients include 1) to control their hyperglycemia, 2) the cleaning and the debridement (if necessary) of the damaged skin, 3) the use of wound dressings depending on the location, depth, amount of exudate and possible infection, and 4) the topical application of gels that contain endogenous growth factors to promote the skin healing [3]. For the last 40 years, the most typical skin wound dressings include synthetic foam dressings, hydrocolloids, iodine-contained gels, hydrogels, alginates, silicone meshes, vapor-permeable adhesive films, and silver/collagen-containing dressing [4]. The main roles of wound dressings are the promotion of healing, avoiding the wound dehydration, and

acting as a barrier against penetration of pathogenic bacteria [4]. In this sense, hydrogels are wound dressings commonly applied for the recovery of chronic wounds such as necrotic wounds, pressure ulcers, and burns. Some examples of hydrogels are Intrasite™, Nu-gel™, Aquaform™ polymers, sheet dressings, impregnated gauze, and water-based gels. Some disadvantages of hydrogels include exudate accumulation leading to bacterial proliferation [4].

Hence, it was formulated a water-based gel with bioactive agent such as collagen, and antibacterial agents such as sodium polyacrylate, and MOF (Metal-Organic Framework). It is well reported that collagen is a protein that promotes fibroblast proliferation and accelerates endothelial migration acting as an adjuvant in the skin healing process [4-5]. Claudio-Rizo et al [6] has found that hydrogels based on collagen and sodium polyacrylate are biocompatible, with both improved mechanical and antibacterial properties.

Also, MOFs can serve as antibacterial agents, and at the same time be biocompatible depending on their chemical composition [7]. Thus, Cabrera-Munguia et al [8] has synthesized a MOF called BHET-Al (comprised from bis hydroxyethyl terephthalate (BHET) and aluminum ions), this was dispersed on the water where a fibroblasts culture was incubated demonstrating to improve their metabolism indicating that BHET-Al does not present cytotoxic effects that decrease the breathing capacity of these cells. This disclosure article presents and discusses the favorable results of a water-based gel constituted with collagen, sodium polyacrylate, and MOF, when it was applied in a case study in diabetic patients with chronic wounds that include second-degree burns, venous and diabetic ulcers. This gel involves the combination of polymers, biopolymer, and MOF that interact with the wound bed promoting the healing of chronic wounds (Fig.1).

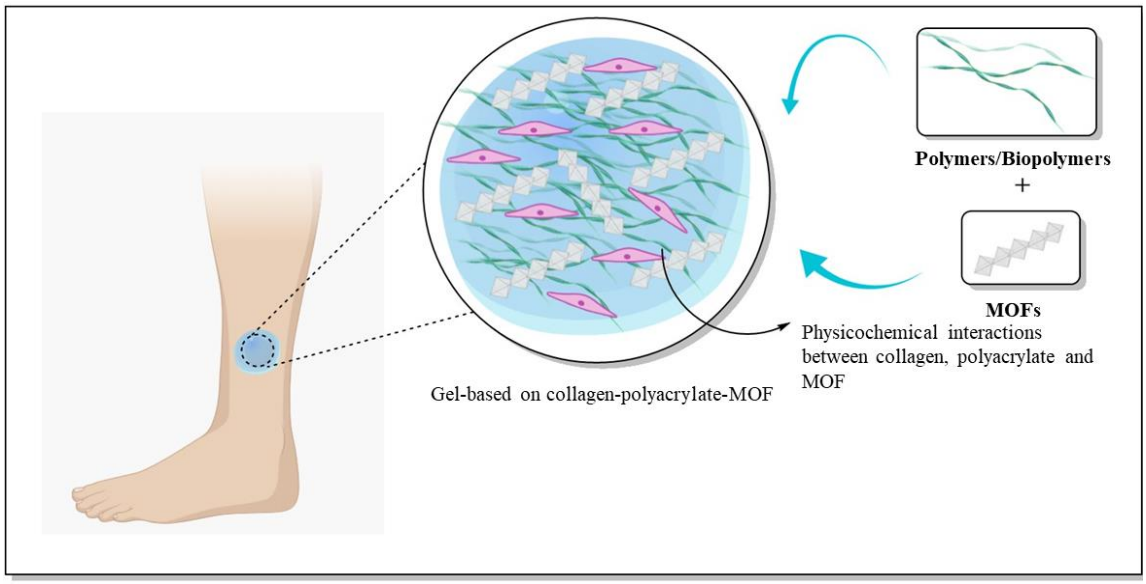

Fig.1. Application of gels based on collagen/sodium polyacrylate coupled with MOF

2. Objective of the Study

The objective of the case study was to evaluate the performance of a gel-based on collagen-polyacrylate-MOF applied on people of the affected population with chronicle skin wounds which are associated with diabetic neuropathy, venous ulcer, and burns.

3. Literature Review

In mammals, the skin is considered the hugest organ, but the skin consists of two organs: epidermis of ectoderm and dermis of mesoderm. While that the epidermis can be regenerated by cellular proliferation without the formation of scars, the dermis is mainly composed of collagen and elastic proteins supported by glycosaminoglycan (GAG). Thus, the dermis constitutes 95% of the skin thickness and is fundamental for flexibility and skin mobility.

Then, when the dermis is damaged, it can only be repaired by the fast arrangement of collagen that later is remodeled causing a scar, the deeper the injury is in the dermis, the more significant the scar will be, thus the skin appearance and the function will be compromised [9].

The cicatrization process (Fig.2) is understood as four interconnected phases that depend on the cellular activation that stimulates the growth, repair and tissue remodeling which favors the characteristics that keep the normal conditions of the tissue [10]

Hemostasia or coagulation phase

The coagulation begins immediately the skin injury has occurred and it last until the fifteen minutes. Its purpose is to avoid blood loss, as it serves to stop the hemorrhage with a blood clot, which is formed with the help of platelets and immunological cells; this action protects the vascular systems and the function of vital organs. In addition, the blood clot formation generates a fibrin blockage that serves as scaffolding for the cells that will participate in the next phases.

Inflammation phase

The inflammation phase begins after the coagulation, and it can last up to six days. The purpose of the inflammatory process is to isolate or destroy the infectious agents that threaten the tissue, and to remove the dead cells by means of phagocytes and monocytes. These immunological cells play a key role in the secretion of growth factors and cytokines that attract the necessary cells for the proliferation process (fibroblasts and keratinocytes).

Proliferation phase

The proliferation phase begins on the third day that the skin injury has occurred, and it has a duration of fifteen and twenty days. The aim of the proliferation phase is to form a protective layer against harmful agents. This phase involves several events such as the development of granulation tissue to generate a temporary extracellular matrix formed by fibroblasts (fibrillogenesis), the formation of new blood vessels (angiogenesis), and the formation of a new epidermis layer that consequently contracts the wound. This last phase is regulated by macrophages, fibroblasts, endothelial cells, and keratinocytes.

Maturation phase

The maturation is the last phase, where the tissue is remodeled, this means, the formation, organization, and resistance that the tissue gets when the new skin or scar is formed, by means of the skin contraction generated by fibroblasts and the organization of collagen packages. The duration of this phase depends entirely on the extension and characteristics of the injury.

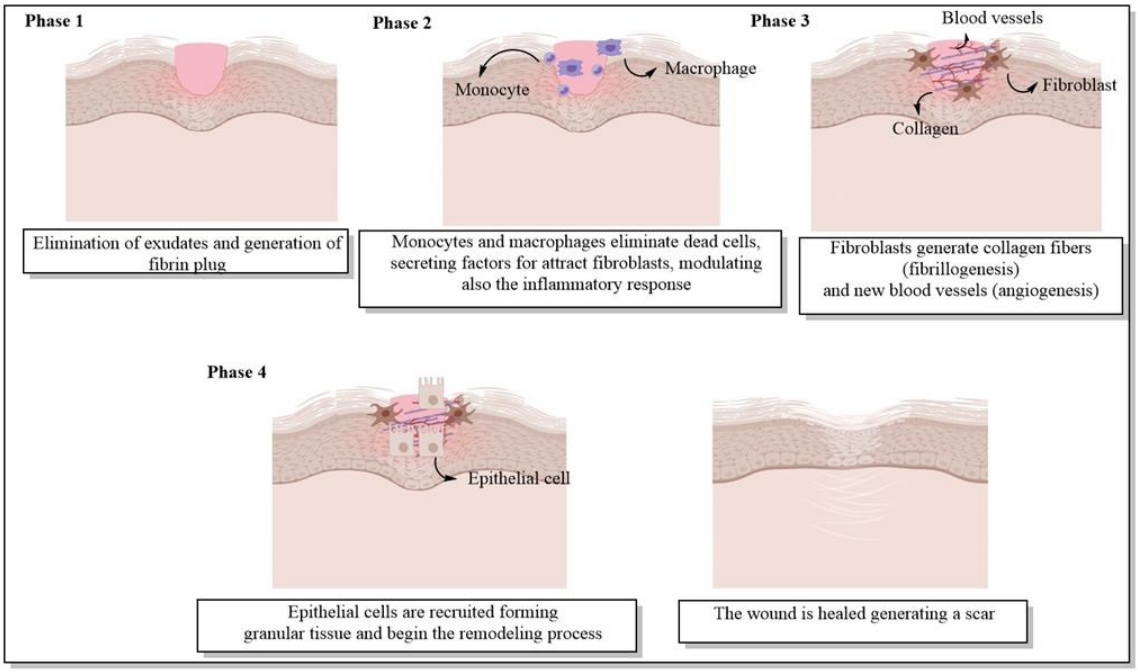

Fig.2. Phases of skin regeneration

4. Materials and Methods

4.1. Preparation of gel- based on collagen-polyacrylate-mof

The main components of the gel are type I collagen, which was extracted from the porcine dermis, the method applied was described somewhere else [6]. Another important ingredient is sodium polyacrylate which has demonstrated antimicrobial properties in a previous study [6]. Also, the gel contains a MOF with aluminum as a metallic center and BHET as ligand, showing biocompatibility properties for fibroblasts [8]. All these compounds were mixed with other typical ingredients contained in a cosmetic formula such as water, glycerin, natural oil, triethanolamine, among others, to prepare the gel-based on collagen-polyacrylate-MOF (Fig.3).

Fig.3. Gel-based on collagen-polyacrylate-MOF

4.2. Irritability test

The irritability test was performed according to the FEUM (Pharmacopoeia of the United Mexican States) [11]. The test was performed on approved animals for the ethics committee of the Faculty of Chemical Sciences of the

Autonomous University of Coahuila (Number protocol: P-FCQ-H-01-09-21-2). The experiments were carried out following the NOM-062-ZOO-1999 recommendations [12] for the care and use of laboratory animals, these recommendations are in concordance with the international guides.

The irritability test is applied to find out the possible inflammatory reactions located on healthy skin and damaged skin of 6 common white rabbits *(Oryctolagus cuniculus)* with a weight in a range of 2 to 3.5 kilograms. One day before the test, the rabbits were shaved in the dorsal area avoiding mechanical irritation. The day of the probe, 4 square regions (4 cm x 4 cm) were delimited, in two of them (intercalated), an incision was made taking care to not injure the dermis or cause bleeding. In these 4 areas, 0.5 mL of gel was applied, and the regions were covered with a gauze, and this was attached with scotch tape. After 24 h and 72 h of exposition, the gauzes were removed from the shaved areas, and the resultant reactions were evaluated according to FEUM (Table 1)

Table 1. Resulting reactions in the irritability test

Cutaneous Reactions	
Erythema and formation of skin scar	Not erythema
	Very light erythema (barely noticeable)
	Well defined erythema
	Moderate to severe erythema
	Severe erythema to a light formation of crust
Edema formation	Not edema
	Very light edema (barely noticeable)
	Light edema (the area edges noticeable for defined elevation)
	Moderated edema (approximately 1 mm of elevation)
	Severe edema (a major elevation of 1 mm and an extension beyond the exposition area)

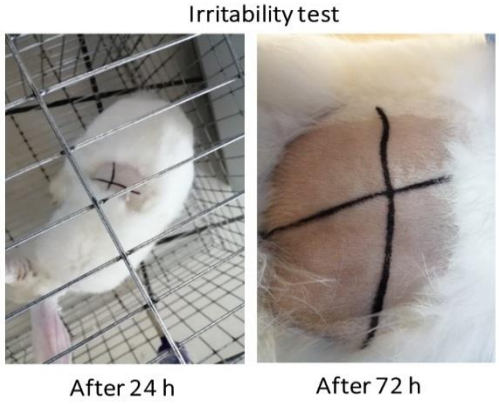

Fig.4. Appearance of a rabbit skin after 24h and 72 h of treatment

The results of the irritability test indicated that rabbit skins did not show any irritation sign or change on the skin after 24 h and 72 h, as is observed in fig.4. The irritability of the gel was analyzed to be cero points as MGA 515 of FEUM indicates, concluding that the gel formulation is not an irritating product for skin. This is very important since cosmetic products should not be irritants to be applied on human skin, thus, this gel product can be suitable for being used in persons, since the utilized feedstocks in the formulation do not cause dermal irritation.

4.3. Case study in people with chronic skin wounds

Since the irritability test of the gel does not show any kind of irritation, it was asked to the ethics committee of the Faculty of Chemical Sciences of the Autonomous University of Coahuila, to approve a case study to evaluate the efficacy of this gel to act as an adjuvant in the healing of chronic wounds such as second-degree burns, venous and diabetic ulcer in patients from the municipality of General Cepeda, Coahuila (Number protocol: P-FCQ-H-01-09-21-1). The study was carried out following the recommendations of NOM-012-SSA3-2012 [13], which establishes the criteria for the execution of research projects for human health, as well as international guidelines.

In this protocol was described the scope, procedures, and tracking of the cases. In concordance with this protocol, all the information related to the chemical composition of the gel was given to the volunteer patients, indicating the possible secondary effects. When the patient was agreed to participate in the case study, it was solicited to sign an informed consent that contain emergency numbers in case of severe irritation, the possible secondary effects such as allergies, unwanted inflammatory responses and zoonoses, and the instructions to follow to assure the suitable use and application of the gel.

The major recommendations were to not suspend their medical treatment against diabetes, and to have good hygiene on the affected area. The procedure to follow before the application of the gel was the cleaning of the affected area with antiseptic, if the wound shows fibrous tissue, this must be removed by debridement performed by a doctor or a nurse, to eliminate dead cells and avoid the formation of exudate that compromise the natural healing process of the skin.

After the appropriate cleaning of the wound, an amount of gel must be applied over the wound and 2 cm beyond the affected area, then the wound must be covered with sterile gauzes and a clean bandage to avoid the injury contamination, these processes should be periodically repeated 2 times at the day, preferably during the morning and before to go to bed.

After one week, the patients were visited to search for any kind of irritation in the affected area, fortunately, there was not any complaint or complication in the treated wounds. Since an acute wound can take from 1 to 3 weeks to be healed in patients without diabetes, this time was taken as a reference to visit the patients during 4 months of gel treatment. In this case study participated 12 persons, where 2 persons were affected by burns, 6 persons for diabetic ulcer, and 4 persons for venous ulcer; in all the cases the effect was the enhancement of the healing process in short time of use. Below some of the most relevant case studies of patients with wounds such as burns, diabetic and venous ulcers are discussed.

4.3.1. Burns

Typically, in non-diabetic persons, the healing time of a second-degree burn last from two to three weeks and often lefts scars. In diabetic persons, the healing of a second-degree burn is hindered by the susceptibility of the wound to be infected with bacteria such as streptococcus, proteus, pseudomonas, enterococcus, enterobacter, and the methicillin-resistant *Staphylococcus aureus* [14]. In Fig.5, it is shown a second-degree burn located in the right hand of a masculine patient of 51 years old, and its outstanding progress after 30 days, as it is observed there is not appreciated any scar in the affected area, and the generation of new tissue was promoted with the use of the gel.

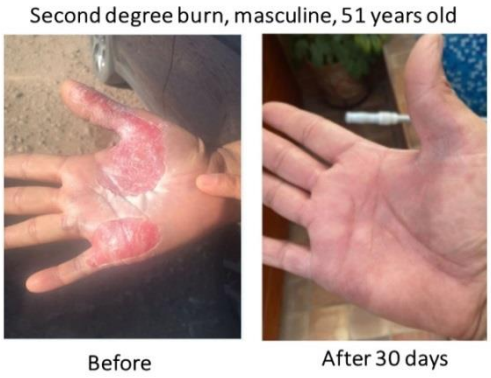

Fig.5. Case 010, second degree burn

4.3.2. Diabetic ulcer

The common healing time for a diabetic foot ulcer is around six months, and if the infections are not attended can lead to the amputation of the member or a part of it [15].

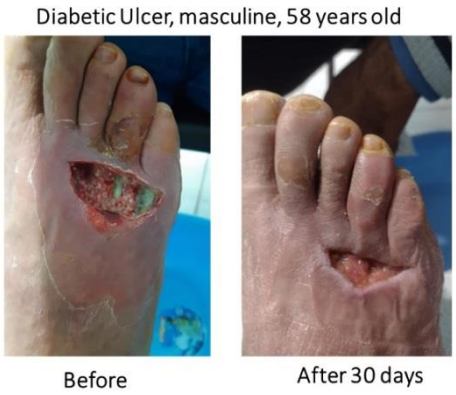

Fig.6. Case 011, diabetic ulcer

Fig.6 shows a diabetic ulcer in a masculine patient of 58 years old, where is clearly appreciated that at the beginning the foot ulcer is located below the toes, and the depth of the injury was not only affecting dermis and epidermis, but also connective tissue. Only after 30 days of the gel treatment, the decreased of the length and depth of the wound are clear, and also an improvement in the tissue regeneration.

4.3.3. Venous ulcer

The time that takes the recovery of a venous ulcer is around eight months, but the more complicated problem is its recurrence after healing [16]. Fig.7 exhibits a venous ulcer of a feminine patient of 67 years old, the left image

shows that the venous ulcer is located in the right foot, presenting a purple-colored area around the wound, and also the presence of fibrinous tissue and crust that should be removed. Then, after 30 days of gel treatment is noticeable the decrease of the venous ulcer depth, and the recovery of the natural rose-colored skin around the wound, it is an indication that new tissue is being formed in the wound, indicating that the gel is helping in the healing process.

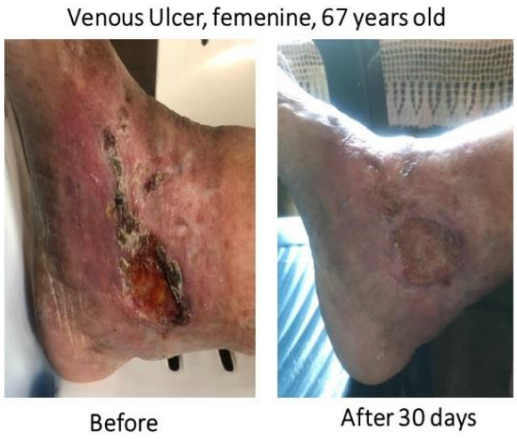

Fig.7. Case 007, venous ulcer

All the people that took part in the case study were taken their diabetes or hypertension medication during the study. As it is observed in the upper images the gel-based on the collagen-polyacrylate-MOF act as an adjuvant agent in the healing process of chronicle wounds, being the most notorious changes after 30 days of gel application.

5. Conclusion

The results of the case study, on people with damaged skin caused by burns, diabetic and venous ulcers, after 1 month of application of the gel, indicated that collagen, sodium polyacrylate, and MOF act synergistically in the healing of chronic wounds. Since collagen act as a promoter of fibroblasts metabolism in the inflammatory phase, sodium polyacrylate, and MOFs avoid possible infections due to their antimicrobial properties; thus, this gel has a potential application as an adjuvant in the healing process of chronic wounds in diabetic persons, then as future work, it is proposed the collaboration with the hospital of the Autonomous University of Coahuila to carry out a deeper clinical study.

6. Acknowledgements

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Declarations

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Competing Interests Statement

The authors declare no competing financial, professional and personal interests.

Ethical Approval

Based on institutional guidelines.

Consent for publication

Authors declare that they consented for the publication of this research work.

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