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Wound Healing Dressing and Some Composites Such as Zeolite, TiO_2, Chitosan and PLGA: A Review

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***Abstract*—**The development of Drugs Delivery System (DDS) has been widely investigated in the last decades. In this paper, first a general overview of traditional and modern wound dressing is presented. This is followed by a review of what scientists have done in the medical environment, focusing on the possibility to develop a new alternative for DDS through transdermal pathway, aiming to treat melanoma skin cancer.

***Keywords*—**Cancer Therapy, Dressing Polymers, Melanoma, wound healing.

I. Introduction

IN the last decades, new technologies for Drugs Delivery System (DDS), have been investigated, aiming to achieve a rapidly healing and sometimes as a new alternative for some treatments such: ulcer wounds, diabetic feet and chemotherapy.

In this study, we have done a bibliography review in the wound healing dressing focusing on the therapy and new pathways, less invasive than traditional chemotherapy treatment, for melanoma skin cancer.

It is proven that patients, when are undergoing the traditional chemotherapy treatment, have lower immune defences due to the chemicals and several reactions which can occur in the body of the patient along the treatment. Most of these chemicals provoke death of health cells, as consequence, harming the health of the patient.

Hereafter, we have done a review containing some fundamentals concepts in wound dressing and last but not least in some composites such as Poly(lactide-co-glycoide) (PGLA), Titanium dioxide (TiO_2), Chitosan (CS) and Zeolite.
Procedure for Paper Submission

II. Wound Dressing

In the pharmaceutical and medical worldwide market, wound dressing form an important segment. Rapid healing should be achieved at reasonable cost with a minimal inconvenient to the patient. In the past the primary function was to prevent harmful bacteria entering into the wound and at the same time to keep the wound dry by allowing the evaporation of wound exudates.

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It is important to note that different wound dressings must be made for different applications, for example: providing low bacteria load, avoid moist environment around the wound, transferring drugs to the skin surface and last but not least effective oxygen circulation to aid regenerating cells and tissues. The wound dressing can be classified into the following guidelines:

A. Traditional Dressing

It does not provide a moist wound environment and is mainly made by cotton wool, synthetic or natural gauzes and bandages. Gauze dressing needs to be changed frequently to prevent maceration of the healthy underlying tissue [1]. Gauze dressing can cause patient discomfort, since it tends to become more adherent to the wound as the fluid production diminishes and are very painful to remove [2].

B. Modern Wound Dressing

These dressings were developed as an important improvement to the traditional wound healing agent described above. The main purpose is to create and retain moist environment around the wound aiming to facilitate the wound healing. Modern wound dressing are mainly classified according to the materials in which they are made from, including: Hydrogel dressing, Hydrocolloid dressing, Semi-Permeable Adhesive Film dressing, Biological dressing and Foam dressing.

- Hydrogel Dressings are based on synthetic polymers such polyvinylpyrrolidine and poly (methacrylates), insoluble and made from sweallable hydrophilic materials. There is no need for a secondary dressing due to their flexible nature, it can be cut and replaced around the wound. However, when applied to the wound as a gel, hydrogel dressing needs to be changed frequently and requires a secondary covering such as gauze [3]. The gels are used as primary dressing whereas the hydrogel films may be used as primary or secondary dressing. Hydrogel has higher patient acceptability, since it cools the surface of the wound, promotes moist healing and are nonreactive with biological tissues [4]. In the other hand, hydrogel dressing have low mechanical strength and therefore are difficult to handle. In addition, it contains significant amounts of water (70-90%), as a result they cannot absorb much exudate, may cause fluid accumulation, which can lead to bacteria proliferation, producing a foul smell in infected wounds and skin maceration. Hydrogel dressing should be used only for light to moderately exuding wounds [5]

- Hydrocolloid Dressings are wound management products obtained from colloidal materials combined with other materials such as adhesives and elastomers. Hydrocolloid dressings are among the most widely used in medical market, due to its transparency capacity allowing wound observation and the dressing combines vapour permeability with absorbency and comfortability [6]. They can be used in chronic and acute wounds, as they do not cause pain on removal. Patients using hydrocolloid dressing experienced less pain were able to carry out their normal daily activity and require less analgesia [7]. In the presence of wound exudate, a change in the physical state occurs with the formation of a gel covering the wound; dressing becomes gradually more permeable to fluid and air as the gels form. [8]
- Semi-Permeable Adhesive Film Dressings have limited ability to absorb sufficient quantities of wound exudate. They require regular changing, may lead to bacteria proliferation, risk of infection and skin maceration. They are only suitable for relatively shallow wounds [9]
- Biological Dressings are made from biomaterials, are biodegradable, can play an active part in normal wound healing and new tissues formation [10]. They usually combine polymers such elastin, alginates, collagen [11], chitosan [12] and hyaluronic acid. In some cases they can be incorporated with some active compounds such as antimicrobial agents. Biological dressing may produce freeze-dried collagen bio matrices with the ability to pick up inflammatory cells containing phagocytised bacteria, debrides and fluids [13].
- Foam Dressings sometimes can have adhesive borders, and basically consist on polyurethane foam film or porous polyurethane foam [14]. In addition, they are convenient to wear, maintain the moisture around the wound sites and provide thermal insulation. The open porous structure provides a higher moisture vapour transmission rate. They can be used for minimal and moderate drainage to heavily exuding wounds [15].

III. Drug Delivery Dressing

Transdermal drugs delivery should enhance the drug absorption and alleviate skin disorder by promoting a prolonged delivery time to the target body site, as well increase the skin hydration to overcome the low skin permeability when the drugs are administrated through this rote. It is highly challenging to develop biomedical drugs with maximum therapeutic efficiency, an optimal bio stability and bioavailability. In addition, when drugs are delivered through transdermal route, it alleviates the discomfort and the physical pain, as well promoting convenience for the patient and compliance for the drug treatment [16]. The skin offers a readily accessible and large area surface for drugs absorption.

Polymers used as controlled releasing dressing are very promising, due to its potential advantages. Controlled release drugs generally provide a prolonged action of the drug activity by releasing for a long period of time, the polymeric dosage form without the need for a frequent dressing change [17]

Synthetic, semi-synthetic and natural derived polymers are useful, since they can avoid high systemic doses by releasing local concentration of antibiotics, drugs, anti-inflammatory, etc… [18]. Once the polymers have exerted their main desireeffect, they can be easily washed off the wound surface and therefore they are biodegradable.

The polymeric dressings employed for controlled drugs delivery to wounds include:

- Polymeric Biomaterials: Chitosan [19], collagen [20], hyaluronic acid [21].
- Hydrogels: Hydrocolloid, polyurethane-foam [22], poly (lactide-co-glycolide) [23], poly(vinil alcohol) [24].

The release drug rate is determined by the rate of diffusion of exudates dissolution into polymer matrix.

IV. Composites

A. Poly(lactide-co-glycoide) (PGLA)

In the last years, PLGA has been used for medical applications, generating tremendous interest in this field due to its excellent biodegradability and biocompatibility [25] they are natural polymers or synthetic in origin.

Controlled-release dosage forms could be employed in order to avoid the inconvenient surgical insertion. It has been proven by several authors that PGLA is degraded *in vivo*, either in enzymatically or non-enzymatically or both. When producing a matrix by Poly(lactide-co-glycoide, it is toxicologically safe and has a good rate of biocompatibility, and further is eliminated by the normal metabolic pathways [25]. This polymer can be used for parenteral or either transdermal administration, once used for this purposes, it must meet several safe requirements such as: suitable biodegradation kinetics, processing easily, mechanical properties, drug compatibility and last but not least biocompatibility.

When working with polymers, we have to consider that the melting point and the degree of crystallinity are directed related to the molecular weight of the polymer. Subsequently the mechanical strength, capacity to undergo hydrolysis, swelling behaviour and the biodegradation rate are directed influenced by the crystallinity of the PLGA polymer [25].

The PLGA polymer is biodegraded into glycolic and lactic acid [26]. Glycolic acid enters the tricarboxylic acid cycle or it is excreted in the kidney and eventually eliminated as water and carbon dioxide [25]. Lactic acid enters the tricarboxilic acid cycle and is metabolized, further it is eliminated from the body as carbon dioxide and water.

Rajeev [27] states that PGLA polymers are easy to formulate into drugs carrying device and have been approved by the FDA for drugs delivery approaches. By adjusting the GLA composition, drug loading, micro particle size, molecular weight, porosity and others factors, we can achieve various drug release profiles. These polymers are also used as graft materials for artificial organs, and recently as supporting scaffolds in tissue engineering. Its toxicity and safety have been tested in several studies and are currently being used in human contraceptives implants, resorbable sutures, bone

implants and screws. Further, local delivery drugs also prevent the loss of the therapeutic agent to other areas, thereby minimizing the doze and the cost of the therapy. The transdermal drug delivery system should overcome the low skin permeability when the drugs are administrated through transdermal route, as well to promote greater and prolonged delivery time to the target body sites.

B. Titanium Dioxide (TiO_2)

Titanium dioxide is frequently used in the pharmaceutical and cosmetic industries. It is an important product for nanotechnology because of its photo catalysis, anticorrosion and high stability. TiO_2 is considered very safe. We must take into consideration that the maximum amount and concentration of TiO_2 that can be added is restricted, since high levels of TiO_2 in the skin surface can cause irritation of the skin and the viscosity becomes excessive.

The use of nanoparticles of TiO_2 should be avoided after UV irradiation, since these nano particles may pass through the skin and penetrate into the tissue and may be a risk to human health. It can be easily activated by photo-energy to produce free radicals, such as hydroxyl radical, these radicals are known to induce DNA damages, apoptosis of cells *in vitro* and cytoskeletal dysfunction in macrophages.

The penetration of TiO_2 nanomaterials into transdermal route is time-dependent. After 60 consecutive days, all test nanopigments can pass through the skin layer and enter into various organs. It is proven that topical application of nano TiO_2 for a prolonged period can cause dermal toxicity, most likely associated with oxidative stress, free radical generation and collagens depletion that can lead to skin aging. Furthermore, recent researches have indicated the hazardous effects of TiO_2 on living cells, such as skin cancer cells, human skin fibroblasts [28] and cutaneous injury [29] under UV irradiation.

Jianhong [30] reported the capacity of penetration profile of nano-TiO_2 across porcine ear skin *in vivo*. The ability of TiO_2 nanoparticle of penetrate the skin was related on its size because only 4 nm TiO_2 reached the deeper layer of epidermis (basal cell layer). Particles of smaller size have a higher penetration capacity and can reach deeper layer of the skin and may cause severe pathological changes in the skin ultrastructure.

Protein tyrosine nitration is a prevalent post-translational modification which occurs as a result of nitrates and oxidative stress, it has been found in a several cutaneous pathological events such as: cutaneous inflammation, systemic sclerosis, contact hypersensitivity and thermal injury. In humans, the sweat state, nitrite can be found in concentration up to 15μM on the skin surface, its presence can strongly enhanced the UV-induced death fibroblast due to the nitrite photo decomposed production. The higher concentration of nitrite in the skin surface combined with protein tyrosine nitration and TiO_2 – photo catalytic effect, may be involved in the toxicity of nano TiO_2 to the skin.

C. Chitosan (CS)

Chitosan is a natural polymer, biodegradable, non-toxic, biocompatible and safe. Chitosan must be dissolved in the media with acid pH, and using 1-3% aqueous acetic acid solution to solubilize CS. A higher degree of deacetylation (> 65%) can increase the charge density and eventually improve the drug transportation. It is relatively reactive and can be produced in various forms such as: fiber, paste, powder, etc… CS is muco adhesive and has a positive charge [31], is biocompatible with living tissues since it does not cause rejection and allergic reactions, it has been wildly used for health application once that it posses antimicrobial activity, good coagulation and immunostimulating ability, it can also absorb toxic metals like lead, mercury, cadmium, etc… [32].

In order to prepare micro/nanoparticles of chitosan we can use several methods such as: sieving methods [33], reverse micellar method [34], ionic gelation [35], emulsion-droplet coalescence method [36], coacervation/precipitation [37], emulsion cross-linking [38], spray drying [39].

In the last few years some alternative treatments for cancer therapy has been developed as Neutron Capture Therapy (NCT). Gadopentetic acid-loaded with CS nanoparticles indicate that these nanoparticles are useful against cultured cancer cells *in vitro* [40]. Gadolinium (GdNCT) appears to be promising method on cancer treatment when loaded with CS nanoparticle, every methods of NCT has its advantages and disadvantages.

Tokumitsu et al. [41] demonstrated the potential usefulness of Gd-NCT for cancer therapy using CS nano particles as a novel device in subcutaneous B16F10 melanoma cancer. The nano particles have been incorporated with 1200mg of natural gadolinium, administered intratumorally twice in mice-bearing; 8h later was performed the second gadolinium administration and thermal neutron irradiation for the tumor site, with the fluency of $6.32X10^{12}$neutron/cm^2. The tumor growth was significantly suppressed after irradiation in the solution-administered group. Nanoparticles indicate

D. Zeolite

Zeolite has been recently considered for medical use, due to their stability in biological environment and properties. Natural zeolites, are rock-forming, mico porous silicate minerals, are solid inorganic crystalline materials comprised of silicon, oxygen and aluminium. In the biomedical applications they can be used in wound healing treatment [42], drug delivery systems (DDS) [43] and magnetic resonance imaging [44].

There are many studies that have reported the capacity of zeolite to be applied as adjuvant in anticancer therapy, based on results obtained in various tumor cells [45]. It has anticarcinogenic, antibacterial and antimetastatic effect [46]. In addition, it is a powerful natural antioxidant and immunostimulator [47].

Zeolite acts as inhibitor of monocarboxylate transponter 1 (MCT1), when combined with α-cyano-4-hydroxycinnamic acid. MCT1 is protein upregulated in skin cancer and thus a potential target for cancer therapy.

Malignant cells are the result of stimulated oncogenes, caused by protein kinase, in the mutation of DNA. The activated zeolite inhibits protein kinase B(c-Act) to other kinase, preventing in this manner, the creation of malignant cells [47].

Clinoptilolite is a mineral of the natural zeolite, having very strong antioxidantives properties, that could affect an oxidative stress in cancer. It is very well known that zeolite can act in the healing process in superficial skin wounds as acute skin problems (post-operative wounds treatments) and chronic skin problems (allergic reaction, skin infection and decubitus ulcers) [48].

V. Conclusion

This bibliography review has been made to establish a start line for the development of a PhD thesis, focusing the melanoma skin cancer therapy through transdermal DDS. In conclusion, we can state that, for this application, we could use modern wound dressing, namely Hydrocolloid dressing, which is the most widely used in the medical market, due to its properties such as vapour permeability with absorbency and comfortability for the patient, avoiding pain on removal. In addition, regarding the cancer therapy, it is important to develop controlled release drugs, providing a prolonged action of the drug activity for a long period of time.

Hydrocolloid dressing based on PLGA could be an emerging alternative, once combined with chitosan and zeolite. Studies in both composites CS and zeolite have reported that the first one has antimicrobial activity, good coagulation and immunostimulating ability. Gadolinium loaded with CS appears to be promising in subcutaneous B16F10, melanoma cancer. The second one has very strong anti-oxidative properties that could affect an oxidative stress in cancer. On the other hand, we point out that TiO_2, should be avoided after UV irradiation, as the particles of smaller size have a higher penetration capacity and may pass through the skin, penetrating into the tissues and may be a risk to human health. When used for prolonged period, it can cause dermal toxicity, free radicals generation and oxidative stress that can lead to skin aging.

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