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Nanotechnological applications of polymer-drug conjugate as oncological treatment

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Abstract. In recent years, the popular term "polymer-drug conjugate" has been introduced to describe new drug targets to combat diseases such as cancer. Due to its potential benefits in terms of human health, this concept has managed to gain attention in the pharmaceutical industry. These innovative developments involve detailed processes in materials science, as it is required to encapsulate different types of cells, as an active component within a material that releases the drug or conjugate directly on the tumor or in the affected area. Against this backdrop, the main objective of this work is to explore the state of participation of polymeric materials in medical and pharmaceutical sciences, in a context where recent cancer statistics are provided in some countries. From the review of the literature, it is evident the importance of the synthesis of new materials or polymeric conjugates, because these materials at the beginning have been used only as storage and delivery systems of drugs, but today they are used as direct treatment against diseases such as cancer, that is, as bioactive agents. Finally, it is possible to conclude that the conjugated polymer-proteins or polymer-drugs, currently on the market and others in the clinical research phase, these materials present physical properties such as biocompatibility and biodegradability, that is, compatibility with the living organism.

1. Introduction

In the middle of the 20th century, new pharmaceutical formulas began to be proposed based on the new knowledge generated by the study of the pharmacokinetics of the active pharmaceutical ingredient [1]. Since then, a drug is not only characterized by its action on the organism, that is, for its pharmacodynamics, but also for the effect that, through pharmacokinetic processes of absorption, distribution, metabolism and excretion, it exerts on the organism itself [2]. Biopharmacy emerged as a link between pharmacokinetics and pharmaceutical technology, deriving pharmaceutical research towards obtaining pharmaceutical forms that, in addition to developing the classically defined functions, achieve the release of the drug in the appropriate place in the organism and in such a way that ensures correct absorption in order to obtain a plasma concentration curve that is optimal in terms of effect and tolerance [3].

In the case of active pharmaceutical substances of rapid elimination [4], a pharmaceutical form is proposed that deliberately slows down the absorption of this substance, so that the resulting plasma concentration curves do not present toxic peaks and remain for a long time in the sector or band of

area of plasma concentration of effectiveness [5]. Likewise, there are new pharmaceutical forms whose main objective is to avoid the effect of first passage through the liver, using, for example, the skin as the place of administration, release and absorption of the drug [6].

In this order of ideas, it is found that, among the advances in the sciences of pharmacy, more advanced medicines are being sought, and new ways of introducing these into our body, for an area in constant development is the use of biopolymers as systems of transport of drugs or active principles for the diagnosis and treatment of cancer [6]. The idea arises from the consequences and difficulties generated by conventional antineoplastic chemotherapy, since these could be overcome or reduced by the use of "intelligent" biopolymers, which would allow the drug, when encapsulated, to be released in a controlled manner, only at the acid pH presented by the tumors, in a continuous manner, achieving high concentrations of the anti-tumor drug [7]. This allows, in turn, a decrease in the frequency of administration of antineoplastic drugs [8].

These findings indicate that, judging from the fact that the pharmaceutical industry is the main contributor or contributor to the development of new pharmacological targets for human health, it is necessary to continue researching on these issues, since society and humanity are facing increasing challenges in terms of health, public health policies, research on new pharmacological targets to relieve pain, among others. In this context, for the development of this research, the following questions arise: (a) What technologies are currently associated with the concept of polymer-pharmaceutical conjugate? (b) What is the polymer-pharmaceutical conjugates currently used? (c) What type of material is being used for the development and formulation of new pharmacological targets? Based on these questions, the main objective of this article is to fill a gap in the literature by providing an overview of the polymer-drug conjugates that are being investigated as pharmacological targets from the perspective of materials science and the industry environment.

In section 3, we answer the first research question, where the technology implemented by the pharmacological industry is described, being this the nanomedicine, making reference to nanotechnology. In sections 3.1 and 3.2, we give an answer to the question what types of materials are used for the development of these new products. In section 3.3, we present a description of a series of polymer-drug conjugate currently used. Finally, in section 4, conclusions and a final perspective are presented.

2. Methodology

For the development of the present research of literature review, it was chosen to elaborate a descriptive research, which has as purpose to present new pharmacological targets that help fight cancer as main treatment, it is provided a generality about polymeric materials as active agents and as transport agents of the active principle, some general characteristics of such materials, later on it is proceeded to make a description of materials found in the literature that serve for such purpose, according to researchers found in the literature, it is possible to evidence that the materials with better applications are the polymer-protein conjugates and polymer-drug conjugates.

The sources to execute the extraction of the information were the databases by subscription and of open access, of the Universidad Francisco de Paula Santander, San José de Cúcuta, Colombia, generating this way as result 82 articles used in the development of the review which are limited in a window of time from 1995 to 2019. The search was possible by executing the following search formulas: "polymer conjugate" + "cancer", "polymer" + "cancer", "polymer-protein conjugate" + "pharmacological target", "polymer" + "new materials" and "cancer". This search was carried out in an exploratory way in order to identify the supporting references.

3. Nanomedicine as an anticarcinogenic treatment

Some authors refer to one of the applications that is arousing the greatest interest in the scientific community and is the treatment of cancer. The way of acting on this complex pathology has been very varied, including the use of encapsulated and genetically modified cells that express the cytochrome P450 enzyme, the vectorization of the therapeutic agent towards the tumor focus by means of the

continuous secretion of a complex formed by interleukin-2 and the crystallizable fragment region of a humanized antibody with great affinity for tumors or the inhibition of tumor angiogenesis, that is, the formation of blood vessels that nourish and irrigate the tumor mass. This last strategy has been tested both through the secretion of monoclonal antibodies that block proteins essential in the endothelial construction, by releasing endogenous antiangiogenic factors that inhibit and prevent the formation of vascular structures [9-14].

There are materials such as hydrogels, which are materials with an excellent potential for this application, since their physical characteristics: degree of hydration, porosity, crosslink density, mechanical resistance, among others, can be easily altered and controlled, in order to modify the speed of release of a given drug [15,16]. These materials have been used as vehicles to immobilize, encapsulate and release in a controlled manner a large number of substances with physiological activity, such as: antibiotics, anticoagulants, antineoplastic, antibodies, drug antagonists, contraceptives, among others. Many of the studies with hydrogels have focused on the release of relatively low molecular weight species, but lately there has been increased interest in macromolecular components such as proteins [17].

The microencapsulation of cells is a therapeutic strategy that allows the treatment of a large number of chronic diseases without the need for immunosuppressive agents [18]. To achieve this objective, it is necessary to immobilize cells secreting therapeutic products in properly designed microcapsules, so as to ensure the long-term functionality of the graft [19]. The advances made in this field over the last few years suggest that microencapsulation of cells could become a common therapeutic strategy in the near future [20]. Among the main therapeutic applications for microencapsulation are: cancer, central nervous system diseases such as Alzheimer's, Parkinson's, and Huntington's diseases, endocrine alterations such as dwarfism and hypoparathyroidism, development of bioartificial organs: diabetes, cirrhosis, and other diseases such as hemophilia and anemia [21-23].

The development of this emerging technology derives from the interest of the scientific community in providing a solution to a growing number of functional pathologies such as diabetes, cirrhosis, and diseases of the central nervous system (CNS). This interest started in the 1930s when a scientist named Bisceglie demonstrated how by introducing mouse tumor cells into polymeric membranes and transplanting them into the abdominal cavity of pigs, they were able to survive without being destroyed by the host's immune response [24]. The encapsulation of allografts and xenografts (grafts from subjects of the same or different species respectively), prior to their transplantation, significantly delayed the appearance of a rejection response. Years later, the concept of encapsulation was introduced as an immunoprotection measure to transplant cells and tissues without the requirement of immunosuppression [25]. Some applications of cell encapsulation and its function as a therapeutic application are: fibroblasts and myoblasts as therapeutic applications for cancer, metabolic and genetic diseases, renal cells for cancer and hemophilia, and hybridoma for cancer and antibody production.

3.1. Biodegradable polymers

Below, some polymers are presented as examples and their application in nanomedicine, as well as some inorganic compounds, such as in the treatment of brain tumors, since this area of the body is considered difficult to access, so they first turn to conventional treatments, then to new pharmaceutical targets, such as polymeric micelles, in which they introduce these polymers together with proteins or as coatings with bioactive material [26].

3.1.1. Poly-butyl acrylate. Biodegradable polymer that has been widely used in the preparation of nanoparticles. When circulating in the blood, nanoparticles are easily absorbed by organs rich in macrophages such as the liver and spleen, so they can be effective for applications in the brain, it is necessary to modify them chemically. Studies of these nanoparticles as delivery systems for the treatment of brain tumors include encapsulation of doxorubicin and gemcitabine [27,28].

3.1.2. Poly lactic-co-glycolic acid. Polymer often used in food and drugs. There are different types of poly lactic-co-glycolic acid (PLGA), depending on their composition lactic acid - glycolic acid, and synthesis parameters strongly influence the final properties of this. Due to its biodegradability and biocompatibility it is a potential candidate as a drug carrier in the brain. As for the studies with chemotherapeutics for the treatment of brain tumors, there are studies with 5-fluoracyl (5-FU) in a rat model with cells, in which the material was implanted intratumorally and it was possible to observe a decrease in the mortality of sick animals. These results are attributed to a sustained and local delivery of the medicine, since 5-FU is ineffective for this type of tumors. In another study, it was reported the use of PLGA - paclitaxel nanofibers with promising results in the treatment of recurrent gliomas [29-36].

3.2. Inorganic materials

Despite the advantages of using polymers as carriers or transport systems for drugs to the brain, there are some characteristics that still need to be optimized, such as the fact that they produce an immune response in most cases, and that the speed with which the polymer degrades is not yet perfectly controlled for all of them. For this reason, recent research has focused on the search for alternative materials, basically inorganic, which make it possible to overcome these limitations [37-41].

Among the most studied are oxides such as silicon, titanium, aluminum and zirconium. Their physicochemical characteristics are strongly related to the process of obtaining them. One way to make them biocompatible and selective is through the functionalization of their surface. The sol-gel process is an attractive method for the preparation of these types of oxides. Through the adequate control of the synthesis parameters we can obtain materials under design, which are highly selective. The materials obtained by this process, are usually used in catalytic processes, where properties such as surface area, porosity and particle size, also has a considerable impact on the selectivity of the catalyst. In addition, these nanostructured catalysts are stable for long periods of time [42-44].

3.3. Polymeric conjugates

The polymer conjugates are distinguished in two groups: polymer-protein conjugates and polymer-drug conjugates. Although the polymer-protein and polymer-drug conjugates are very similar, the objective or biological reason pursued in each case is different and so are the parameters to be taken into account for their construction [45]. Currently, polymer-protein conjugates are considered as oncological therapy of routine use in the clinic; the conjugate design of neocarzinostatin and poly styrene-comaleic acid (SMANCS) and the success of the PEGylation technique, that is, covalent bonding of polyethylene glycol (PEG) to a drug or therapeutic protein, have been responsible for this fact [46,47].

3.3.1. Poly styrene-comaleic acid. It is a protein conjugate of local administration, known in the market with the denomination Zinostatin Stimalamer ®, considered as the first polymer-protein conjugate that approached the pharmaceutical market, designed with the purpose of obtaining a conjugate of the anti-tumor protein neocarzinostatin, the conjugate is suitable for local administration in patients with hepatocellular carcinoma, using the femoral artery to access the tumor via the hepatic artery. The conjugation considerably increases the hydrophobicity of neocarzinostatin and therefore its lipid solubility, which allowed the administration of SMANCS in the contrast agent, thus increasing the plasma half-life, allowing the visualization of the tumor and improving the degree of tumor specificity. Preclinical studies with SMANCS showed that a large number of patients with hepatocarcinoma treated with this conjugate achieved a clear reduction in the size of the tumor (95% of cases) and a decrease in the levels of alpha-fetoprotein (86%) [48-51].

3.3.2. Covalent bonding of polyethylene glycol to a drug or therapeutic protein. Improving the therapeutic potential of proteins, the polyethylene glycol - asparaginase commercially known as Oncaspar ®, is the first anti-cancer conjugate PEG-protein to get the approval of the Food and Drug

Administration (FDA) in 1994. This conjugate is used for the treatment of acute lymphoblastic leukemia, where the native enzyme induces hypersensitivity reactions and has a relatively short plasma half-life (8-30 hours). Due to this, it is necessary to administer one dose daily for four weeks. However, the polymeric conjugate has a time of 0.5 to 14 days, which considerably decreases the frequency of doses to be taken by the patient. In addition, and consistently, the PEGylation of this enzyme decreases the hypersensitivity reactions [52-54].

3.3.3. Hydroxypropylmethacrylamide - doxorubicin. It is considered as the first anti-cancer conjugate to be clinically evaluated in 1994, it was demonstrated that Hydroxypropylmethacrylamide (HPMA) is a biocompatible polymeric carrier, non-toxic and non-immunogenic even at high doses, which establishes it as a suitable platform for the design of this type of systems. On the other hand, studies in phase 1 showed that the toxicity presented by the conjugate is up to five times less than that produced by free doxorubicin. It has been applied in studies to evaluate its reaction to the antitumor activity presented by chemo-resistant tumors (due to its different internalization mechanism) [55-58].

4. Conclusions

The natural polymers are a strategy that present a relevant traceability and background, these polymers are used in the microencapsulation of cells that are representative as an option for therapeutic development, and its role in the delivery of drugs and other active molecules against diseases such as cancer, metabolic diseases, genetic diseases, hemophilia, diabetes, Fabry disease, hypoparathyroidism, or procedures such as liver transplantation, among others. Biopolymers are used due to their unique properties; non-toxicity, water solubility, biocompatibility, biodegradability and high degree of functionality, which indicates a great advance in medicine. These new technologies are of great importance for the pharmaceutical sector and medicine, however, there are many challenges to be faced in this path, because these treatments are very recent and require great funding and above all, acceptance by patients and various phases of clinical experimentation.

The new clinical treatments against tumors or cancer, are promising, however, require the collaboration of nanomedicine to continue the generation of these treatments that are characterized by being less invasive, the polymers play an important role, since they serve as transport of multiple therapeutic agents directly to the cancer cells, these polymers are excited and driven by external actions such as temperature, pH, or others.

Polymers or polymer-protein or polymer-drug conjugates are present in the market, the increasing development and synthesis of new materials, are positioning themselves as effective anti-cancer therapies. However, there are still great challenges, but at the same time, there are opportunities that allow the development of these pharmaceutical technologies, because they are presented as pharmaceutical targets resulting in exploration and research stages and these results provide very interesting applications for the health sector.

Nanomedicine can generate a great change, especially in the relationship with new drugs such as the polymeric conjugates considered as therapeutic alternatives against cancer cells, at a molecular scale and even at a cellular level, so these advances are of great importance and are considered representative to treat a disease that today still has no cure.

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