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NANOTECHNOLOGY AND NANOMEDICINE: KEYS TO THE DEVELOPMENT OF CLINICAL TRIALS AND OBTAINING OF NEW DRUGS

Medical Science

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ABSTRACT

In modern medicine, nanotechnology has a good present and better future. Industry is developing nanodrugs mainly in cancer but also in other pathologies. It is betting by multicomponent biocompatible drug delivery platforms. This evolution will allow us realize new Clinical Trials and obtain personalized therapies with an optimal profile of efficacy. However, previosly it must be solved some technical problems with respect to safety and toxicity of nanomaterials used and its handling. Thus, regulatory agencies should establish laws and rules about use of these nanomaterials, as well as specific guidelines on all products currently used in nanomedicine.

KEYWORDS

Nanomedicine; Clinical Trials; Nanotechnology

1. Introduction

Nanotechnology applied to medicine or nanomedicine is a multidisciplinary science focused on the study, design, synthesis, development and application of functional materials and systems in medicine.

The objective of nanomedicine is the development of selective therapies aimed at prevention and / or treatment of multiple diseases (1). Nanostructures, used in nanodrugs, are characterized by having unique physical-chemical properties (surface properties, rheology, electrical conductivity or magnetism). These allow their application with different therapeutic purposes (2-4).

The nanostructures can be composed of different materials such as liposomes, polymers, micelles, nanocrystals, metal / metal oxides and other inorganic materials, proteins or carbon nanotubes (2,4-6) (Figure 1). These materials coud be modified with different markers to achieve greater selectivity (7). Size, structure, composition, biodegradation, and distribution in the organism are key on its functionality and applicability (1,7).

Nanoparticles (1-100 nm) improve the solubility, stability, bioavailability and toxicity of systemic treatments. They also improve the specific tissue or molecular selectivity, diagnosis, pharmacokinetic profile and / or tissue regeneration (7,8). Thus, nanomedicine could be applied to obtain information about heterogeneity of treatments and patients, allowing us to obtain individualized treatments (9,10). However, at present there are difficulties that prevent the clinical translation of the nanodrugs (11). Among its main technical applications have the release / bioavailability of drugs and tissue engineering, diagnosis, and therapeutic-diagnostics (theranostics) aimed at the treatment of pathologies such as cancer, cardiovascular, infectious or immunological diseases (1,8). Recent studies show important advances in administration of drugs in oncological therapy due to the development of nanomedicine (8).

However, this technology has some challenges such as an improved characterization, possible problems of toxicity, lack of specific guidelines from the regulatory bodies or efficiency consideration to establish a clearly position this technology.

Therefore, objective of this work was to demonstrate the degree of current development of nanomedicine, its present and future perspective, as well as the technical and regulatory challenges to be solved for the development of Clinical Trials in this area.

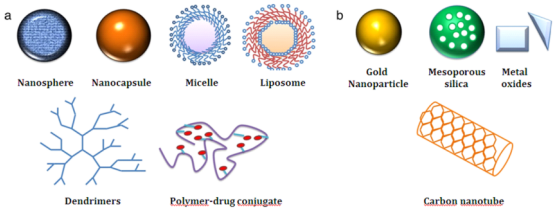
2. Socieconomic development of nanomedicine

According to the Joint Research Center, the United States (US) is the world leader in number of patent applications in the field of nanomedicine (53%), followed by Europe (25%). Although European countries lead biomedical publications in this field, they have a greater difficulty in transforming the results of research into commercial applicability. The high cost of production and commercialization of these innovative drugs together with the restrictions of the paying entities with respect to their use can pose a reimbursement problem for the industry, which could be reluctant to finance this type of research (10,12- 14).

However, in medium-long term, nanomedicine could generate great saving, both direct and indirect costs. By reducing adverse effects profile, the need for medical assistance (personnel costs and hospitalization costs) is reduced, period of work inactivity of patients is reduced, and the quality of life is improved.

Inclusion of new nanodrugs, in terms of cost-effectiveness, could suppose a profitable business to attract the investment of industry (13,15). At present, most of the nanodrugs to approve under clinical investigation are nanoformulations of commercialized drugs. In this way, approval by regulatory agencies is simpler at an more affordable cost (2,15). For the approval of a new drug, it must significantly improve the effectiveness with respect to existing drugs with the same indication and decrease the toxicity.

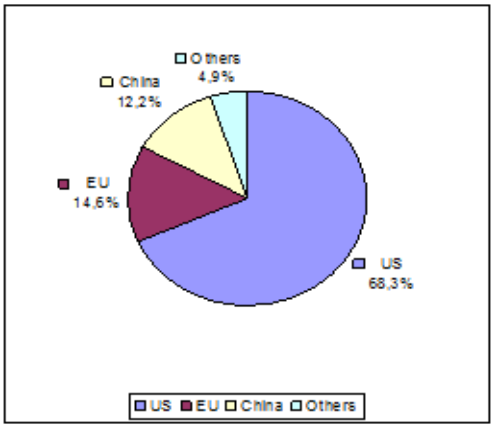
Figure 1. Organic (a) and inorganic (b) nanostructures for the transport and release of drugs (Rojas-Aguirre et al)



3. Present and future perspective of nanodrugs

Until 2015, only 13 nanodrugs were approved by the The Food and Drug Administration (FDA) of US to treat some type of specific pathology. However, in recent years, the commercialization of these drugs has increased, as well as a significant increase in the number of Clinical Trials that is taking in place. Currently, 104 Clinical Trials are active, of which 82 (78.8%) in oncology (78 neoplasms, 22 tumors) - 94.8% Phase I, II or I-II. This fact warns of a future increase in the clinical applications of this type of drugs (2,6,16-19). A 68.3% (56/82) of the studies are conducted in the US, 14.6% (12/82) in the EU, 12.2% (10/82) in China, and 4.9% (4/82) in other areas (Graph 1) (19).

Graph 1. Nanotechnology. Origin of Clinical Trials



However, there are also formulations that are being developed for other indications such as infectious diseases, autoimmune diseases, metabolic disorders, dental, ophthalmic, neurological or psychiatric diseases (6,19). The current trend is to investigate new agents using liposomes, micelles, highlighting the introduction of formulations with dendrimers. However, many of new nanodrugs still present in its formulations a synthetic polymeric component (2,16,17). Most drugs have effects related to controlled release or increased release of the drug, achieving an increase in efficacy and safety. In addition, nanoformulations based on other types of nanoparticles (nanocrystals, inorganic nanoparticles and others) almost universally use surface coatings composed of antifouling polymers (2). Another clear trend is the movement away from relatively simple nanoparticles to complex and multicomponent drug delivery platforms. Thus, nanoformulations increase the chances of success from the therapeutic point of view by the follow:

1. They can concentrate a large amount of drugs, which could allow reduce the number of doses in a treatment. As well as store two different drugs in a single system enabling the administration of combinated therapies (20).
2. Nanosystems can be functionalized on their surface with molecules that selectively recognize target cells and with polymers that optimize their pharmacokinetic characteristics (21).
3. Nanocarriers can be designed to overcome or avoid resistance to drugs that they transport (22).
4. Multifunctional platforms can be designed to diagnose and treat a tumor process simultaneously (23).

An example of a specific nanodrug that is being investigated is SGT-53 (SynerGene Therapeutics), which contains an anti-transferrin antibody fragment that binds with a transfer of the glycoprotein receptor to cancer cells (2). This agent is in Phase 1-2 Clinical Trial for treatment of solid tumors, glioblastoma and metastatic pancreatic cancer (19).

4. Technical and regulatory challenges

Nanodrugs have been one of the main focuses of the pharmaceutical industry in the last decade. However, they present certain problems to be solved, such as the characterization of new nanomaterials with respect to their safety and toxicity (2). These nanodrugs can interact with many types of cells, organs and tissues (18). They can influence the effects of coagulation complement activation, compatibility of the immune system, activation of phagocytes, among others (24). Some formulations of nanodrugs also rise a challenge regarding the precise control of drug release, distribution and biodegradation (some nanoparticles do not biodegrade easily), so that their successful translation to the clinic is highly challenging (18,25). Because of this, the demand for drugs based on highly biocompatible nanomaterials is increasing. Nanodrugs must be tested to demonstrate an optimal benefit-risk ratio and obtain regulatory approval (24). In addition to general toxicity studies, in order to characterize the individual components of nanodrugs, *in vitro* and *in vivo* assays coud be useful to characterize biological activity and toxicity (24).

Regarding the development of nanomaterials, it is necessary to establish characterization standards, which have not been defined despite several attempts (2,24,26), as well as greater collaboration between regulatory agencies. On the other hand, we can not make a general statement about the safety of the nanodrugs because they incorporate a variety of nanoparticles and very heterogeneous materials (3). FDA has published guidelines regarding the importance of the characterization of nanomaterials and includes emerging standards for this purpose (2,27). These efforts are likely to allow better data regarding the toxicity of theses nanomaterials (2). But currently the information available is very limited.

Therefore, it is essential to: a) Deeping in knowledge of the physicochemical properties of existing nanodrugs, and serve as a basis for improving future ones. b) Standardize analytical techniques for the complete characterization of the nanosystems from the physicochemical and biological point of view. c) Monitoring the use of nanodrugs in the clinic to determine the degree of success of these therapies. On the other hand, FDA recommends to industry communicate the product development plan as soon as possible to adapt it to the specific regulation and address the scientific issues considered relevant.

5. Conclusions

In conclusion, nanotechnology has a good present and future in modern medicine. It will allow us personalized therapies with an optimal profile of efficacy, safety and diagnosis in the same treatment. Despite high cost of production of these drugs, the pharmaceutical industry continues developing a lot of Clinical Trials with very promising results and aimed at improving the health and quality of life of patients.

In order to guarantee its success, rational design and the systematic study of this technology are fundamental, and to determine its chances of success. For this, it is necessary to advance in the understanding and characterization of the main physicochemical attributes, characterization methods and behavior *in vivo* and *in vitro-in vivo* for the translation of nanomedicine with safety and efficacy.

Betting on this technology, it will mean in the coming years an improvement in the efficiency of treatments compared to conventional therapies. Therefore, regulatory agencies, paying entities and the pharmaceutical industry are engaged in a negotiating effort that allows patients to benefit of this technology in a sustainable manner.

Regulatory agencies should establish lay for safety and toxicity of the recommended use nanomaterials, as well as specific guidelines on all products currently used in nanomedicine.

This paper provides an up-to-date perspective on the emerging field of nanomedicine, and its industrial, health and regulatory development. And finally highlight that despite the difficulties they are currently being carried out an increasing number of Clinical Trials.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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