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NANOTECHNOLOGY`S IMPLICATIONS IN MEDICINE AND PHARMACY

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Abstract

Nanotechnology is a multidisciplinary domain which brings the greatest scientific accomplishments in physics, chemistry, biology, mathematics and materials` science in order to apply newly acquired knowledge to further building at an atom`s level, and using molecules as bricks, nanomaterials with artificial intelligence, biocompatible structures, nanorobots most useful in medicine, chips with extremely high components` density and autoreplicable materials.

The applications founded upon nanotechnologies demand further exploration as they offer multiple advantages that must be implemented and, later on, turned into account.

The fast progress of the scientific communities in obtaining and characterizing their properties generates, at a global scale, novel ways to pursue in medicine, therefore leading to a decrease in the mortality rate and in some diseases` prevalence. Also, the transport and the release of drugs to target and the development, in the pharmaceutical domain and in the context of nanotechnology, ought to be regarded as science and technology for complex systems, at nanometric scale (10 – 1000 nm), as they are all made out of two components, the first of which is an active pharmacologic compound and, thereby, the whole system leads to a special function when it comes to treating, preventing and diagnosting various diseases, sometimes named „intelligent drug".

Keywords: nanotechnology, vesicular systems, lipidic nanosystems, niosomes, transferosomes, etosomes

INTRODUCTION

In the last years, both nano and biotechnologies are frequently used in almost all domains. A big part of the scientific community sees nanobiotechnology as being the key science at the millennium`s beginning, the one to completely revolutionize the XXIst century`s beginning, as it is the only one that could ensure a high quality of life, yet an easily sustainable one.

There is, still, an important number of scientists who believe that nanobiotechnology is a highly dangerous road to follow, as it is full of obstacles, a road which people do not understand well enough to properly use in order to reach the intended destination (Bangham A. D.,1972). Both nano and biotechnologies, in many domains, seem to offer the means to reach some goals, otherwise inaccessible. In the medical area, this includes

both improving the diagnosis techniques and the formulation – in the pharmaceutical sphere.

The challenge of developing novel therapeutic systems which improve the transport and, especially, the drug`s release must combine the formulation`s engineering with the extended competences of all knowledge in biology.

Based on these ideas and based on the advantages offered, a series of biocompatible structures have been developped that have recently changed their statute from a research subject of a laboratory to a strong industrial tool, as the distance in between their desired, ideal features and their feasibility strongly decreases (Bangham A. D.,1972).

MATERIAL AND METHOD

Due to the nano and biotechnologies` involvement in all domains of activity, as it was to expect, even in the medical domain and in the pharmaceutical industrial area, they brought real progress. Even concepts such as Nanomedicine and Nanobiopharmacy appeared.

Nanomedicine can be defined as one of nanotechnology`s application in health, in diagnosing and treating diseases in order to mentain the population`s general health state, using the gathered knowledge about the human body at a molecular level, as well as intruments (represented by complex structures) at the nanometric scale (in the metric measurement system, one nanometer is one biliard of a meter) (Baillie A.J et al., 1985, Barry B., 2006).

Mainly, the potential evolution of the research in the nanotechnology area, with applications in the medical and in the pharmaceutical spheres are as follows (Biju S.S. et al., 2006, Cevc G. 2003, Elka et al., 2001, Elka et al., 2007):

- creating and developing new drugs for the pharmaceutic industry – the obvious increase in the percentage of pharmaceutical products to use nanotechnology

- the increase in the ability to diagnose and treat chronic diseases, with high mortality rate and which affect the quality of life

- modeling the neuron – neuron interactions using modern nanobiotechnology

- developing the science and engineering of nanobiosystems, which will eventually lead to a better understanding of all living systems, developing new solutions for the proper health care, creating innovative, more suitable biocompatible materials; understanding the processes that take place inside the cell and inside the nervous system

- applying and understanding nanotechnologies in fields like biology, electronics, medicine and so on, areas that include artificial organs, prolongued life expectancy, creating new systems based not only on biological principles, but on the laws of physics and on the specific properties of various materials.

Therefore, one of the main directions for the further growth of nanomedicine is nanobiopharmaceutics that focuses upon developing new drug delivery systems (NDDS – new drug delivery system).

The ideal NDDS ought to fulfill two essential requirements: mainly, it should release the drug at a constant rate (the optimal ratio in between the dose and the organisms`s needs), as it should transport and channel the entity towards the target (Philips P.S., 2007, European Medical Research Councils 2005).

The long – term objective of all drug delivery systems lies in developing their ability to target specific receptors. Presently, the need for such transporters is the result of the demand to deliver the drug specifically to the organs affected by the disease, as therapies with high efficiency are required for the increase in the patient`s compliance, as it is most important so reduce the costs of health care services.

On the other hand, there is an imperative need for the further development of transport means for the new classes of pharmaceutical products, which is not accomplished only by using the classical research methods, as nanotechnology is essential for reaching this here`s objective. Such transporters can be successfully used when dealing with low soluble pharmaceutical forms.

This targeted transport system`s main feature is its high therapeutic efficiency as it improves the pharmacological properties of all drugs used not only in cancer therapy, but also when dealing with affections that need high potency medication. Therefore, by introducing transporter nanoparticles for pharmaceutical substances, there is a tendency towards maximizing the bioavailability considering both the targeted organ and the actual moment in which the drug is released. The recorded progress is quite important, especially because each year, due to the low bioavailability, more than 65 billiard $ are lost (Baillie A.J et al,1985).

The conventional forms of dosage, including the extended release ones, are not entirely capable of fulfilling none of a NDDS properties. So far, none of the available drug release systems behaves in an ideal fashion, but research in this domain is in progress. Recently, various transport systems and technologies have been studied with the sole purpose of controlling the drug`s release rate and to improve the efficiency and the selectivity of the formulation. During the last decade, micro and nanospheres, polymeric micelles, hydrogel materials and nanocapsules

proved efficient in improving the specific targets of drugs, in lowering their systemic toxicity, as they improve the treatment`s rate and they protect the active substances against any biochemical degradation (Bangham A. D.,1972).

VESICULAR TRANSPORT AND TARGET DELIVERY SYSTEMS

Almost 75 years ago, Paul Ehrlich introduced the concept of the „magic bullet", as he offered the vectorised transport mechanism for therapeutic products directly to the affected cells (Freitas R., 1996-2010). Vesicular systems, such as liposomes, niosomes, sphingosomes, transferosomes and pharmacosomes, are used to improve the therapeutic index of all drugs, both for the new ones and for the ones which already exist (Freitas R., 2014-2015, Gautam A. et al., 2012).These distinct systems are used on a large scale, in gene – delivery, in treating cerebral tumors and in issues regarding the stability and the permeability of drugs. As drug vectors, they allow administering some active compounds that, in any other conditions, raise various problems such as: low therapeutic index, low specificity, numerous side effects, low stability (proteins) and the inaccessibility of the target (DNA) (Gautam A. et al., 2012). Hydrophilic drugs can be kept in the internal compartment which contains water, while the loaded amphiphilic, lipophilic and hydrophilic substances are able to interract with the lipidic bilayers through hydrophobic/electrostatic interractions (Freitas R., 2014).

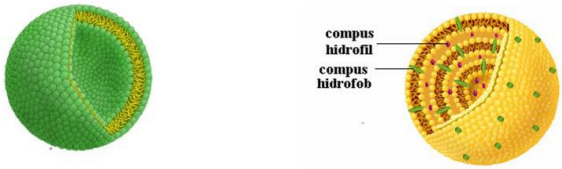


Fig.1. Structure of lipidic unilamelar vesicles (left) and multilamelar (right) and the manner to incorporate bioproducts

The main problems when researching transport systems and their drug release rate are the premises for new studies. They include kowledge about incorporating and releasing drugs, in the formulation`s stability, in its biocompatibility, biodistribution and the target release, as well as its functionality. More, when it is exclusively used as transporter, the side effects of the residual material are to also be considered. Therefore, biodegradable nanoparticles, with limited life, are the ones to consider.

The main objectives of nanopharmacy in transport and in drug release include: ●High specificity of the transport and of the encapsulated material`s release;

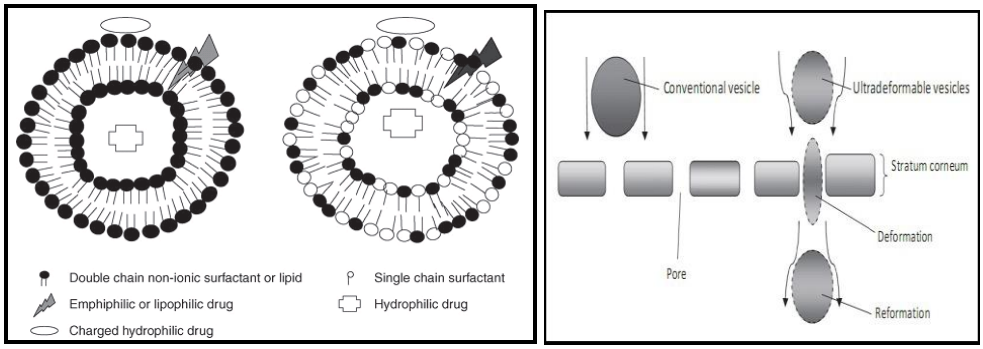
- The diminishing of the toxicity, while mentaining the therapeutic effect;
- High safety and great biocompatibility;
- The fast development of new, safer drugs.

Usually, vesicles are made out of phospholipids and, when needed, tensioactive agents. The presence of a tensioactive agent in the composition of the lipidic vesicles modifies the elasticity of the vesicular wall as well as the transport fashion of the encapsulated material.

More, their composition influences the physical and the chemical features such as: size, electric charge, thermodinamic state and the bilayer`s elasticity.

These features have a significant effect in the vesicles` behavior as transport systems of drug substances (Cevc G.et al., 2010, Honeywell et al., 2005).

Figure 2 shows the structural difference between the rigid lipidic vesicles and the elastic ones, as well as their penetration mechanism through the skin.



A **B**

Fig. 2. Structural representation of rigid vesicle (left) in comparison to an elastic vesicle (A) (Honeywell-Nguyen P. L 2005), considering the transdermal transportation (B) (Stamatin I. 2008)

In order to allow the release of the drug to its target, a number of lipidic vesicular transport systems (such as liposomes that are either rigid or deformable: transferosomes, etosomes, niosomes).

Vesicular systems, as nanometric phospholipidic structures, have the advantage to be small, flexible and biocompatible, therefore being capable of passing through the small veins and through the endotelial wall, without causing coagulation.

Nowadays, other materials exist, inclusding various nanometric copolymers and dendrimers which modify the encapsulated or the adsorbed drug`s distribution throughout the body.

Through their phospholipidic nature, they are not only a powerful transport system for the encapsulated material, but also an important source of phosphatidyl choline, which, in turn, is a heat source with an important anti – aging role.

The advantages of using lipidic nanosystems:

- they have a versatile structure, which can be easily adapted either through formulation or through preparation, in order to offer the needed properties for a specific application;
- they can be used to include numerous lipophilic drugs into the double – lipid layer, as they are to include hydrophilic substances into the aqueous compartment of amphiphilic ones;
- they are biologically inert as they are completely biodegradable, as the phospholipids out of their structure are the natural components of the cell`s membrane;
- through encapsulation in the double lipidic layers or in the aqueous compartments, the drugs are protected from the destructive action of external environmental factors (air, light) or internal ones (enzymes or inhibitors that are present in the biological mediums);
- they offer new possibilities of releasing therapeutic agents which are encapsulated to the specific target, into the body (organ, tissue, cell), as they have the same evolution as the lipidic nanosystem because they are released only when the target was reached;
- as drug vectors, they allow administering active compounds with problematic pathways of administration: low therapeutic index, low specificity, numerous side effects, low stability (proteins), inaccessibility of the target (DNA);
- they improve bioavailability (Stamatin I. 2008, Kumar et al., 2012)

Deformable lipidic nanosystems also show a series of specific advantages:

- **Niosomes:** a better compliance towards lipophilic systems, are osmotically stable and active, they increase the entrapped drug`s stability, their manipulation and the surfactants` storage do not need any special conditions; they increase the transdermic penetration for the encapsulated substance; they can be used not only for parental administration, but also for oral topical administration as well; they also protect the drug`s molecules` degradation, when passing through the gastro – intestinal tract (M. Reza Mozafari and Kianoush Khosravi-Darani 2007, M. R. Mozafari 2007).
- **Transferosomes:** are able to pass through pores that are less of one tenth their size, which allows them the breach through the skin; their preparation and the characterization methods are simple; they can

ensure the transdermic transport both for lighter molecules and for the ones with big molecular mass; they depend on certain compositions and certain administration way; they facilitate a specific therapy and minimize the side effects (Ciutan M. 2008).

- **Etosomes:** etosomes make the transdermic transport easier; their composition is sure and the toxicologic profile of the etosomal component is well documented; they have a great compliance of the patient as the etosomal drug is administered in a semi – solide state (cream, gel); they are quite simple to obtain, with no need of complicated technical investitions to produce etosomes; the etosomal system is passive, non – invasive and available for immediate merchandizing (Upadhyay N. et al., 2011, William W. et. Al., 2004).

Disadvantages:

- rather expensive production process
- difficult storage which lasts for short periods of time
- accentuated tropism for liver and spleen, after intravenous administration
- they are not an universal drug carrier and they only present specific advantages for some pharmaceutical and cosmetical applications (Venkateswarlu I. et al., 2011).

CONCLUSIONS

Using nanotechnologies in medicine and, more exactly, in the transport and in the targeted release of biocompounds is evolving.

For decades, all pharmaceutical fundamental sciences used nanoparticles in order to diminish the administered compounds` toxicity and side effects. So far, only the advantages of using these transport and release systems for bioactive compounds were considered, and the disadvantages were not sufficiently investigated, for these transport systems can pose risks for the patient.

Still, so far the scientific paradigm for the possible nanoparticles` reactivity is lacking and we have gathered rather few information about the interractions in between nanoparticles and living organisms.

In order to further develop, implement and turn in account sure nanoparticle systems for both the transport and the targeted release of drugs, a clear conceptual understanding of the possible biological responses to nanomaterials is most required.

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