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A New Frontier for Nanoparticulate Drug Delivery Systems to Improve Drug Targeting and Molecular Pharmacotherapy: Subcellular Bioavailability.

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Biopharmaceutics and pharmacokinetics have acquired a well-deserved place in medical and pharmaceutical research and practice of recent decades, contributing to the optimization of pharmaceutical formulation, ensuring bioequivalence, the safety and effectiveness of drug dosage forms in therapy.

New discoveries in molecular biology and genomics allow a diagnosis at the molecular level for more and more diseases.

This reality imposed to extend the notion of systemic bioavailability to the subcellular biophase bioavailability at the pharmacological site of action, both for the micromolecular drugs, as well as for macromolecular biologically active substances: protein or peptide drugs, DNA, oligonucleotides, small (short) interfering RNA (siRNA). There are tremendous works on the new biopharmaceuticals which will allow targeting of key biomarkers in the physiology and pathology of the cell as well as a more efficient targeting at the molecular level. The achievement of effective treatment at the molecular level can be fulfillment by specific and selective transport of the drug substance with the aid of a specialized nanoparticulate carrier, for safe and effective transport to the specific site of action in the cytosol and its organelles including nuclear targeting. These considerations justify efforts in research for the efficient cytosolic delivery either as systemic bioavailability fraction, or directly to specific site in biophase using nanoparticulate drug delivery systems (DDS). With the aid of these transport systems of drugs to cellular organelles it is possible the treatment of some of their diseases as well as direct treatment of genetic and metabolic diseases. The concentration of drug in biophase, at this time, cannot be measured. Assessment of drug amounts that have reached the individual organelles, i.e. the drug intracellular distribution, can be done using fluorescence based (confocal microscopy), Raman microspectroscopy and biochemical approaches. Therapeutic delivery of micromolecular drugs or macromolecular (siRNA) by in vitro studies, laboratory animals studies for therapeutic targeting, local delivery of drug loaded DDS by nanoparticulate vectors or some clinical studies were recently published [1-7].

Achieving such a goal is possible by giving some physicochemical properties for DDS able to overcome the physiological and intracellular barriers, by providing the desired bioavailability of the bioactive drug, its intracellular pharmacokinetics and its desired biological or pharmacological effect. Efficient intracellular targeting of drugs and drug delivery systems is a major challenge that should be overcome to enhance the therapeutic efficiency of intracellular-acting drugs. The most critical aspect for further advancement in therapy is a good formulation of the nanoparticulate DDS capable to protect the drug during transport, to avoid off targets effects, to prove enhanced and reproducible optimal subcellular bioavailability, specific gene silencing and efficient targeted delivery in vivo [8-11].

The efficient targeting to specific receptors in the body is based on biopharmaceutical properties of the transport system that ensures adequate bioavailability and pharmacokinetics in cytosol or the target organelles for the treatment of sickness. Current scientific research is focused in this case on the study of transport and bioavailability of the active substance inside the cell and the intracellular organelles. Preparation of the drug or gene carrier system should ensure stability of the drug substance incorporated during the transport to the target, low immunogenicity, good biocompatibility, selective targeting, and the efficient penetration of barriers, self-regulating drug release, without clinical side effects [12].

In most cases, cytosolic permeation of the drug/DDS by mechanisms of receptor mediated endocytosis, is a pre-requisite for its targeting to the organelle of interest, then in order to exert its activity, the drug must be released from the endosomes and lysosomes [13]. Nanopharmaceutical system internalization must be followed by endosomal escape, the transport in the cytosol and to cytosol assigned organelles including the uptake through the nuclear pore complex. Such properties are conferred nanoparticulate transport systems by functionalization, i.e., coupling with ligands that have specificity to receptors. They can be targeted to a specific cell population by the attachment of ligands, molecules that are mainly recognized by these cells facilitating the ligand-receptor internalization [14]. Drug delivery system involves technology designed to maximize therapeutic efficacy of drugs by controlling their biodistribution profile. The biodistribution profiles of carrier systems are determined by their physicochemical and biochemical properties. For nanoparticles-mediated gene delivery in order to improve the ability of translocation to the nucleus to increase gene transfection efficiency, is desired to overcome extracellular and intracellular transfection barriers, the blood-stream, the cellular membrane, endosomes, and the nuclear membrane. Future research will focus primarily on specialized transport to the cell organelles using nanoparticulate drug delivery systems for transport of drug substances.

The term targeting implies that the molecule is able to selectively accumulate at an intended site of action and that the selective accumulation is associated with its specific action (targeted therapy in cancer) [15,16]. Methods can be classified into two key approaches - active and passive for targeting drugs by means of designing innovative nanosystems. Specific transport in certain cell organelles involves specific target recognition in which the cargo is to be released. Selective

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accumulation are associated with the concept of bioavailability and biodistribution that are related to the physico-chemical properties of the molecule and of the drug delivery system and their influence on the systemic and organ (organelle) pharmacokinetics and bioavailability.

The use of nanoparticulate DDS for the transfer of DNA or RNA to somatic cells in order to obtain a therapeutic effect, by either correcting genetic defects, over-expressing proteins that are therapeutically useful, or inhibiting the production of harmful proteins, is another research direction (gene therapy) based on the subcellular bioavailability [17]. The RNAi represents a new approach for producing gene-specific inhibition and knockouts, and alongside recombinant protein and monoclonal antibody for designing new therapeutics entities to treat several pathologies such as cancer and metabolic diseases, viral and respiratory infections, brain and skin diseases, dominant genetic disorders, and autoimmune disease [18-20]. It is known that defects in the structure or function of proteins are responsible for many diseases because proteins are involved in physiological cellular processes. Current drug therapy aims specifically to inactive proteins while in gene therapy using RNAi is stopped the protein function by degradation of mRNA and consecutive translation in proteins [21].

Nanotechnology can improve the bioavailability of many promising and currently available drugs and thereby increase their effectiveness. Development of novel drug delivery systems by which the distribution to the target tissue is selectively increased compared with that to the tissue where toxicity may occur, can overcome the difficulties of conventional and prolonged release dosage forms to realize a therapeutic concentration in biophase. Intracellular pharmacokinetics and intracellular pharmacokinetic-pharmacodynamic models should be developed for better control of the interaction with subcellular targets.

It is expected that future research to bring progress in intracellular targeting using nanopharmaceutical systems to achieve an improvement of pharmacotherapy at the molecular level. The further development of nanomedicines will likely include a personalized medicine approach as an integral part of the clinical development strategy to identify subgroups of that particularly benefit from therapy. Elucidation of the active transport mechanisms and the ability to harness these with nanomedicines could provide a step forward in the treatment of cancer and other diseases.

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