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Review

Nanopharmacy: Inorganic nanoscale devices as vectors and active compounds

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ABSTRACT

In this review we would like to aim at pharmaceuticals engineered on the nanoscale, i.e. pharmaceuticals where the nanomaterial plays the pivotal therapeutic role or adds additional functionality to the previous compound. Those cases would be considered as nanopharmaceuticals. The development of inorganic systems is opening the pharmaceutical nanotechnology novel horizons for diagnosis, imaging and therapy mainly because of their nanometer-size and their high surface area to volume ratios which allow for specific functions that are not possible in the micrometer-size particles. This review will focus on pharmaceutical forms that are based on inorganic nanoparticles where the nanosize of the inorganic component provides unique characteristics to the pharmaceutical form. Several examples of these systems that are either in pre-clinical investigation and under examination by the Food and Drug Administration (FDA) or that have been already approved by the FDA and are in clinical practice today like Gastromark®, NanoTherm®, Colloidal Gold for Lateral Flow tests, HfO-NPs, BioVant™ will be described and reviewed.

Contents

1. The era of Nanoscience

Nanotechnologies are nowadays gaining in commercial use. After almost thirty years of basic and applied research, the number of commercial products advertised as containing nanoparticles (NPs) is increasing rapidly. Within all the fields to which nanotechnology can be applied, the medical field is one of the prominent directions which attract continuous investment and financial support. Nanomedicine could be defined as the application of nanotechnology to health care [1] [2] or more concretely, the use of nanoscale or nanostructured materials in medicine that according to their structure have unique medical effects [3]. Nanomedicine involves nanomaterials in a submicron size range of a few to a few hundreds of nanometers which are on purpose designed to

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result in new medical effects due to their unique physico-chemical properties that differ from their macroscopic counterparts. These materials also require novel manufacturing and characterization techniques. Different applications of Nanomedicine within the health care include the use of NPs (i) as active pharmaceutical ingredient (API), where the main role is played by the nanomaterial, i.e. for the purpose of therapy, diagnostics, imaging; (ii) as vectors (a solid carrier that introduces the active ingredient into a recipient or host organism) or with an *enabling* function. In the latest application, the NPs add a new functionality to the pre-existing product, e.g. NPs for target delivery or as biomaterials.

Based on the definition of Nanomedicine and that of Pharmacy (science concerned with the preparation, dispensing and effective use of pharmaceuticals), in this review we would referred to Nanopharmacy as an interdisciplinary science concerned with the preparation, dispensing and effective use of nanoscale-based pharmaceuticals, i.e. active compounds used in the treatment, cure, prevention or diagnosis of diseases. A proposed definition describes nanopharmacy as "*decreasing the particle size of sparingly soluble drugs down to nanometric regime and conjugation with appropriate excipients*" [4]. However, in this review we would like to aim at pharmaceuticals engineered on the nanoscale, i.e. pharmaceuticals where the nanomaterial plays the pivotal therapeutic role or adds additional functionality to the previous compound. Those cases would be considered as nanopharmaceuticals. The most common nanopharmaceutical forms today are organic platforms that include polymeric NPs and dendrimers, liposomes and other lipid assemblies, and engineered viral NPs mostly for drug/gene delivery applications [5]. Nevertheless, the development of inorganic systems is opening the pharmaceutical nanotechnology novel horizons for diagnosis, imaging and therapy mainly because of their nanometer-size and their *high surface* area to *volume ratios* which allow for specific functions that are not possible in the micrometer-size particles [6,7].

This review will focus on pharmaceutical preparations that are based on inorganic NPs where the nanosize of the inorganic component provides unique characteristics to the pharmaceutical form. Several examples of these systems that are either in pre-clinical investigation and under examination by the Food and Drug Administration (FDA) or that have been already approved by the FDA and are in clinical practice today like Gastromark®, NanoTherm®, Colloidal Gold for Lateral Flow tests, will be described and reviewed.

2. Physical, biochemical and biological properties of inorganic nanoparticles

2.1. Iron oxide nanoparticles (FeO-NPs)

FeO-NPs are commonly composed of an inorganic magnetic core and a biocompatible surface coating that provides chemical stability under physiological conditions, dispersibility in aqueous solution, and reduced toxicity [8–10]. Inorganic cores of 4–15 nm size made up of iron oxides such as magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3) dominate the field of biomedical applications due to their superior stability and the lower toxicity compared to other metal oxides [11,12]. FeO-NPs can naturally be broken down within the Fe-metabolism in the spleen and liver and due to their small size are more difficult to recognize by the immune system [13–15]. When the particle has only one magnetic domain (like in case of small NPs) thermal excitations can flip the direction of magnetization in relation to the particle axis at temperatures higher than the so called blocking temperature. Thus, superparamagnetic NPs (SPIOs) show no magnetism above the blocking temperature in the absence of an external magnetic field, as their respective magnetizations are randomly oriented. This is termed the superparamagnetic state [16]. A magnetic field can effectively magnetize the particles, as the magnetic moments of the particles are oriented in this field. When the field is removed the magnetization disappears completely, unlike in larger particles or bulk material in which residual magnetism (also known as remanence) can be observed. Depending on the sort of magnetic field applied, SPIOs exhibit different properties useful for medical applications, i.e. (i) as heat-producing agents for treatment or (ii) as contrast agents for imaging. (i) When exposed to varying magnetic fields created by alternating currents (AC) SPIOs heat up. The underlying heating mechanisms by which the field energy is converted into thermal energy depends on the magnetic properties of the particles and thus on their size [17]. Hysteresis heating under AC magnetic fields can only be observed in ferro- or ferri-magnetic materials, but not in superparamagnetic particles [17]. The heat originated by SPIOs is produced because the magnetic moments align under the influence of the magnetic field (but the particles as a whole do not physically rotate) and relax to their equilibrium orientation when the field is turned off. This effect is referred to as Néel relaxation [17]. During cyclic alignment energy is dissipated. In contrast, heating by physical rotation of the particle as a whole is referred to as Brownian rotation and possible in both cases [17]. SPIOs show remarkably higher specific absorption rates (SAR [W/g], the measure of the heat generating capacity of the magnetic substance in the alternating magnetic field) than larger particles. Thus, by applying the right quantity of field energy and for the right time heat can be efficiently produced to cause thermal-mediated cell death. This makes SPIOs a good alternative for clinical applications of hyperthermia, in particular for cancer therapy [18]. (ii) When exposed to static magnetic fields SPIOs are magnetized, which creates a local magnetic field gradient. This finally leads to improved signals for the visibility of the internal structure where the NPs are accumulated. Diagnostic imaging in principle depends on the signal contrast between normal and pathologic tissue: the higher the signal contrast, the more advantageous the conditions for resolving anatomic structures and pathologic changes. In general, contrast agents can mark selective regions such as the gastrointestinal tract, for example to enhance the distinction from other adjacent organs and tissues [20]. In essence, MR image contrast is mainly due to distinct spin relaxation times of different types of tissue and the local proton density. The spin is a fundamental quantum mechanical property, which has no classical analogue and is therefore not exactly illustrative. As a basic concept, the spin can be perceived as a vector that points in a respective direction. Within the MRI scanner a strong, static magnetic field causes the nuclear spins of hydrogen protons to precess around an axis parallel to the magnetic field lines. The precessing spins are like small magnets that orientate themselves on the sides of a cone parallel or antiparallel to the field lines. For energetic reasons, nuclei with parallel orientation predominate and create a constant magnetization. The precession frequency of the spins (Larmor frequency) depends on the strength of the applied field, and because the field is applied with a spatial gradient, the precession frequency of the spins depends on their position within the field. A transverse radio frequency (RF, an electromagnetic wave) pulse, tuned to the protons Larmor frequency of a certain layer within the magnetic gradient field, is used to deflect the spins, and thereby the magnetization is tilted. The magnetization can be decomposed into a component along field lines of the static magnetic field (longitudinal magnetization), and a perpendicular component (transverse magnetization). After the perturbation through the RF pulse both the longitudinal and the transverse magnetization relax independently to their state of equilibrium by spin–lattice and spin–spin interaction, respectively. The realignment of the magnetic moments induces small voltages in