PHARMACEUTICAL COMPOSITION, PREPARATION AND USES THEREOF

FIELD OF THE INVENTION

The invention relates to a pharmaceutical composition comprising the combination of (i) a biocompatible nanoparticle and (ii) a compound of interest, to be administered to a subject in need of such a compound, wherein the nanoparticle potentiates the compound efficiency. The longest dimension of the biocompatible nanoparticle is typically between about 4 and about 500 nm, and its absolute surface charge value is of at least 10 mV (|10 mV|).

The invention also relates to such a composition for use for administering the compound of interest in a subject in need thereof, wherein the nanoparticle and the compound of interest are to be administered in said subject sequentially, typically between more than 5 minutes and about 72 hours one from each other.

The combined, and typically sequential, administration to the subject of the biocompatible nanoparticle and of the compound of interest maintains the pharmaceutical (i.e. therapeutic, prophylactic or diagnostic) benefit of said compound of interest for a reduced toxicity thereof in said subject, or increases its pharmaceutical benefit for an equivalent or reduced toxicity, when compared to the pharmaceutical benefit and toxicity induced by said compound when administered at the standard pharmaceutical dose.

The pharmaceutical composition of the invention typically allows a reduction of at least 10% of the administered compound pharmaceutical dose when compared to the standard pharmaceutical dose of said compound while maintaining the same pharmaceutical benefit for an equivalent toxicity, preferably a reduced toxicity, for the subject, or while increasing the pharmaceutical benefit for an equivalent or reduced toxicity for the subject.

BACKGROUND

In order to ensure safety and efficacy, therapeutic compounds are required to be selectively delivered to their target site at an optimal rate in the subject in need thereof.

Pharmacokinetics (pK) is a branch of pharmacology dedicated to the determination of the fate of substances administered externally to a living organism. This determination involves steps of measuring compound's concentrations in all major tissues over a long

enough period of time, preferably until the compound's elimination. Pharmacokinetics is necessary to efficiently describe the compound's behavior *in vivo*, including the mechanisms of its absorption and distribution as well as its chemical changes in the organism. The pK profile in the blood can be fitted using various programs to obtain key pK parameters that quantitatively describe how the body handles the compound. Important parameters include maximum concentration (C_{max}), half-life ($t_{1/2}$), clearance, area under curve (AUC), and mean resident time (MRT), i.e. the average time during which a compound stays in an organism. When a prolonged blood circulation of the compound formulation is observed, it is usually associated to an increased $t_{1/2}$, a reduced clearance, an increased AUC, and an increased MRT. pK data are often used in deciding the optimal dose and dose regimen for maintaining the desirable blood concentration in order to improve therapeutics' efficiency with minimal side effects. In addition, as well known by the skilled person, the blood concentration of a compound is correlated with both its efficacy and toxicity in most cases, typically for free drugs.

The physico-chemical properties of therapeutic as well as prophylactic compounds have an important impact on their pharmacokinetic and metabolic fate in the body. Therefore, selection of appropriate physico-chemical properties is key when designing such a compound. However, since the compound is not always endogenously provided by the organism itself and is usually externally administered, its biodistribution profile has to be optimized in order to fit with, and preferably optimize, the desired pharmacological action thereof.

Several approaches have been explored to optimize the delivery of a compound to its target site. A strategy is to design a therapeutic compound with stealth properties to prolong its blood half-life and consequently, to enhance its accumulation to the target site. One favorable approach is the covalent attachment of polyethylene glycol (PEG) to the therapeutic compound that has proved to increase the *in vivo* half-life ($t_{1/2}$) of the circulating compound, the level of the *in vivo* half-life increase varying depending partly on the nature of the compound and on that of the coating. Also, drug carriers such as liposomes, emulsions or micelles have been developed to enhance therapeutic efficacy of drugs by modifying their biodistribution profile in the subject's body.

However, lack of selectivity in the biodistribution of the therapeutic compounds still remains a concern. So far, poor pharmacokinetics and high toxicity are important causes of failure in therapeutic compounds development.

As an example, in the context of cancer treatment, intentional inhibition of essential functions of the body in order to kill cancer cells results in on-target or on-mechanism toxicity in normal cells, and clinicians have to rely on differences in dose–response and therapeutic compounds distribution between tumors and normal tissues to find a possible therapeutic window. Of note, hepatotoxicity remains a major reason for drug withdrawal from pharmaceutical development and clinical use due to direct and indirect mechanisms of drug-induced cell injury in the liver.

An approach proposed for nanoparticulate compounds such as drug carriers [*Critical Reviews in Therapeutic Drug Carrier Systems 11(1):31-59 1994*] is to pre-inject a decoy carrier to decrease, saturate, or even inactivate the phagocytic capacity of the reticuloendothelial system (RES). Impairment or blockade may also be associated with decreased plasma levels of opsonic molecules. Intravenous administration of certain agents, such as alkyl esters of fatty acids, dextran sulfate, salts of rare earth elements (e.g. $GdCl_3$), drug carriers, either empty or encapsulating clodronate, prior to administration of test particles, has been demonstrated to induce moderate to dramatic reduction in kupffer cells uptake.

For instance, authors in "*Biomimetic amplification of nanoparticle homing to tumors*" [*PNAS 2007*], reported the role of RES in the clearance of their nanoparticles "CREKA-SPIO". Initial experiments showed that intravenous (IV) injected "CREKA-SPIO" nanoparticles did not effectively accumulate in MDA-MB-435 breast cancer xenografts. In contrast, a high concentration of particles was seen in RES tissues. By depleting RES macrophages in the liver with liposomal clodronate, they found a 5-fold prolongation of their particle's half-life. However, clodronate agent induces the apoptosis of macrophages from liver and spleen, and this is considered as globally detrimental as macrophages depletion increases the risks associated to immunosupression and infection. In a second experiment, the authors tested liposomes coated with chelated Ni (II) as a potential decoy particle hypothesizing that iron oxide and Ni (II) would attract similar plasma opsonins, and that Ni-liposomes could therefore deplete them in the systemic circulation. Indeed, intravenous (IV) injected Ni-liposomes, whether administered 5 minutes or 48 hours before

the injection of CREKA-SPIO nanoparticles, allows a five-fold increase of the nanoparticles' blood half-life. However, high toxicity was observed causing deaths among tumor mice. Plain liposomes were also tested instead of Ni-liposomes. However, while reducing the toxicity when compared to said Ni-liposomes, plain liposomes were far less effective than them. Indeed, the blood half-life increase was only of a factor about 2.

WO2005086639 relates to methods of administering a desired agent selectively to a target site in a subject, typically in the context of ultrasound or X-ray exposure, or in the context of magnetic resonance imaging (MRI), as well as in the context of therapy. The aim of the described method is to improve or maintain the efficiency of the agent of interest while reducing the total dose of agents concretely administered thanks to concomitant administration of a decoy inactive carrier.

The described invention employs a probability-based approach. A non-targeted inactive agent ("inactive carrier") is co-administered (i.e. "substantially simultaneously") with a targeted agent of interest (present in an "active composition") exhibiting similar physical features, in order to facilitate the evasion of the RES system by the targeted agent of interest thereby allowing an improved uptake of the agent of interest at the desired site. This approach results in a lower exposure of patients to the agent of interest and, as a consequence, in a lower per dosage cost of said agent of interest. The active composition and the decoy inactive carrier are administered within five minutes of each other, preferably within 2 minutes of each other, or even less. This approach relies on the presence of a large excess of untargeted "carrier" or "decoy" vehicles and on the probability that this decoy carrier in excess will compete with the targeted agent of interest for an uptake by the reticuloendothelial system when supplied in the presence of vehicles that are targeted to a desired location. The half-life of particles captured by RES is dose dependent, i.e. the circulating half-life of particles increases as the dosage increases. The slower clearance associated to higher dosages is thought to favor the maintaining of a total agents high concentration allowing a decrease of the dose of the agent of interest which is to be administered. In other words, an increased half-life of total agents due to a global higher dosage thereof should be beneficial to the targeted agents, according to the authors of WO2005086639. The requirement involved by this approach is that the active agent and the inactive one behave similarly with regard to their clearance characteristics in the RES, whatever their respective compositions.

In this approach, the quasi-concomitant injection of the inactive agent and of the active one is required to increase the global amount of agents present in the blood and consequently to prolong their blood half-life. Such strategy, which expressly relies on a probability-based approach, necessarily requires the association of the active agent with a targeting agent in order to achieve its successful accumulation on the target site by conferring said active agent an advantage over the inactive one. In addition, due to the quasi-concomitant injection, a specific design of the inactive carrier may be required depending on the intended use of the active composition.

As apparent from the prior art and despite of a long medical need, the improvement of compounds (including therapeutic, prophylactic as well as diagnostic compounds) which cannot be efficiently used in patients due to their unacceptable toxicity or to their unfavorable pharmacokinetics parameters remains a concern.

SUMMARY

In one aspect, there is provided a use of a combination of (i) a biocompatible nanoparticle having a longest dimension of between about 4 nm and about 500 nm and an absolute surface charge value of at least 10 mV (|10 mV|) and of (ii) a pharmaceutical compound of interest in the manufacture of a medicament, for enhancing therapeutic efficiency of the pharmaceutical compound of interest, wherein the nanoparticle and pharmaceutical compound of interest are to be administered in the subject sequentially, and wherein the nanoparticle is to be administered to the subject between more than 5 minutes and about 72 hours before or after the pharmaceutical compound of interest.

In an embodiment, the disclosure relates to a pharmaceutical composition comprising the combination of (i) a biocompatible nanoparticle and of (ii) a pharmaceutical compound of interest, wherein the longest dimension of the biocompatible nanoparticle is between about 4 nm and about 500 nm, and the absolute surface charge value of the biocompatible nanoparticle is of at least 10 mV (|10 mV|) for use in a therapeutic, prophylactic or diagnostic method in a subject in need thereof, the therapeutic, prophylactic or diagnostic

method comprising a step of administering the pharmaceutical compound of interest to the subject and a distinct step of administering the nanoparticle, said nanoparticle being administered to the subject between more than 5 minutes and about 72 hours before or after the pharmaceutical compound of interest.

DETAILED DESCRIPTION

The present invention now allows optimization of the efficiency of a compound of interest (herein also simply identified as "the compound") whatever its intended use in the context of therapy, prophylaxis or diagnostic. The composition herein described which is a combination of (i) a biocompatible nanoparticle and of (ii) at least one compound of interest, optimize the at least one compound of interest pharmacokinetic parameters, and, as a consequence, now renders possible the development of therapeutic compounds which could not have been developed otherwise due for example to their unacceptable toxicity.

A typical composition of the invention (herein generally identified as "pharmaceutical composition") is a composition comprising the combination of (i) a biocompatible nanoparticle and (ii) at least one compound ("the compound of interest"), wherein the longest dimension of the biocompatible nanoparticle is typically between about 4 nm and about 500 nm, and the absolute surface charge value of the biocompatible nanoparticle is of at least 10 mV.

A preferred object of the invention is a pharmaceutical composition comprising the combination of (i) a biocompatible nanoparticle and of (ii) a pharmaceutical compound of

interest, wherein the longest dimension of the biocompatible nanoparticle is between about 4 nm and about 500 nm, and the absolute surface charge value of the biocompatible nanoparticle is of at least 10 mV (|10 mV|) for use for administering the pharmaceutical compound of interest in a subject in need thereof, wherein the nanoparticle and the compound of interest are to be administered in a subject in need of said compound of interest, between more than 5 minutes and about 72 hours one from each other.

The combined administration to the subject of the biocompatible nanoparticle and of the compound of interest, through the composition of the invention, typically allows (maintains) the same pharmaceutical (i.e. therapeutic, prophylactic or diagnostic) benefit of the compound for a reduced toxicity thereof for the subject, or increase the pharmaceutical benefit of the compound for an equivalent or reduced toxicity thereof for the subject (preferably a reduced toxicity), when compared to pharmaceutical benefit and toxicity induced by the standard pharmaceutical dose of said compound.

The pharmaceutical composition of the invention typically allows a reduction of at least 10%, preferably at least 15%, of the administered compound pharmaceutical (i.e. therapeutic, prophylactic or diagnostic) dose when compared to the standard pharmaceutical dose of said compound (i) while maintaining the same pharmaceutical benefit for an equivalent toxicity, preferably a reduced toxicity, for the subject or (ii) while increasing the pharmaceutical benefit for an equivalent or reduced toxicity for the subject.

As the shape of the particle can influence its "biocompatibility", particles having a quite homogeneous shape are herein preferred. For pharmacokinetic reasons, nanoparticles being essentially spherical, round or ovoid in shape are thus preferred. Such a shape also favors the nanoparticle interaction with or uptake by cells. Spherical or round shape is particularly preferred.

In the spirit of the invention, the term "nanoparticle" refers to a product, in particular a synthetic product, with a size in the nanometer range, typically between about 1 nm and about 500 nm, preferably between about 4 nm and about 500 nm, between about 4 and about 400 nm, about 30 nm and about 300 nm, about 20 nm and about 300 nm, about 10 nm and about 300 nm, for example between about 4 nm and about 100 nm, for example

between about 10 nm, 15 nm or 20 nm and about 100 nm, or between about 100 nm and about 500 nm, typically between about 100 nm and about 300 nm.

The terms "size of the nanoparticle", "largest size of the nanoparticle" and "longest size of the nanoparticle" herein typically refer to the "longest or largest dimension of the nanoparticle" or "diameter of the nanoparticle" when spheroid or ovoid in shape. Transmission Electron Microscopy (TEM) or Cryo-TEM can be used to measure the size of the nanoparticle. As well, Dynamic Light Scattering (DLS) can be used to measure the hydrodynamic diameter of nanoparticles in solution. These two methods may further be used one after each other to compare size measures and confirm said size. A preferred method is DLS (Ref. International Standard ISO22412 Particle Size Analysis – Dynamic Light Scattering, International Organisation for Standardisation (ISO) 2008).

To be usable in the context of the invention, the absolute electrostatic surface charge (also herein identified as "charge" or "surface charge") of the biocompatible nanoparticle is to be higher than |10 mV| (absolute value). The surface charge of a nanoparticle is typically determined by zeta potential measurements in aqueous medium for a nanoparticles concentration between 0.2 and 10 g/L, for a pH between 6 and 8, and typically for electrolytes concentrations in the aqueous medium between 0.001 and 0.2 M, for example 0.01 M or 0.15 M.

Typically, the biocompatible nanoparticle of the present invention has an electronic surface charge of at least |10 mV|, i.e. below – 10 mV or above + 10 mV, for example below between – 12 mV or – 15 mV and – 20 mV or above between +12 mV or + 15 mV and + 20 mV, typically below – 15 mV or above + 15 mV. Preferably, the biocompatible nanoparticle of the present invention has an absolute electronic surface charge value ("absolute surface charge value") of more than 10 mV, said charge being even more preferably a negative charge.

So long as it is charged, the nanoparticle usable in the context of the invention can be either organic or inorganic. A mixture of organic and inorganic nanoparticles can further be used.

When organic, the nanoparticle can be a lipid-based nanoparticle (glycerolipid, phospholipid, sterol lipid, etc.), a protein-based nanoparticle also herein identified as

"protein-nanoparticle" (albumin for instance), a polymer-based nanoparticle ("polymeric nanoparticle"), a co-polymer-based nanoparticle ("co-polymeric nanoparticle"), a carbon-based nanoparticle, a virus-like nanoparticle (for example a viral vector).

The organic nanoparticle may further be a nanosphere (plain nanoparticle) or a nanocapsule (hollow nanoparticle) such as a liposome, a gel, a hydrogel, a micelle, a dendrimer, etc. A mixture of the herein described organic nanoparticles can also be used.

The polymer or co-polymer can be of natural or synthetic origin.

Examples of synthetic (artificial) and natural polymers or co-polymers usable in the context of the invention to prepare organic nanoparticles can be selected from polylactic acid (PLA), Poly (lactide-co-glycolic) acid (PLGA), Polyethyleneglycol (PEG), Polyglactin, Polylactide, Polyoxyethylene fatty acid esters, Polypropylene glycol, Polysorbate, Polyvinyl alcohol, Polyacrylamide, Polymethylmethacrylate, Polyalkylcyanoacrylate, Polylactate-co-glycolate,Poly(amido amine), Poly(ethyleneimine), alginate, cellulose and cellulose derivatives polymers, collagen, hyaluronic acid, polyglutamic acid (PGA), actin, polysaccharide, and gelatin.

When inorganic and when its longest dimension is typically below about 10 nm, for example below about 8 nm, below about 7 nm, typically comprised between about 7 nm and about 4 nm, for example below about 6 nm, below about 5 nm or below about 4 nm, the nanoparticle may be made of any inorganic material. The inorganic material may for example comprise metallic element from period 3, 4, 5, 6 of the Mendeleev's periodic table, including the lanthanides. When the longest dimension of the nanoparticle is typically below about 10 nm, the nanoparticles may assemble in larger structures. Assembling of nanoparticles in larger structure may typically be triggered by interactions between nanoparticles and a biocompatible polymer(s), protein(s), etc. Larger structure may also be obtained by trapping the nanoparticles in a carrier, typically a plain carrier such as gelatin structure (also herein identified as "gelatin nanoparticle") or a hollow carrier such as liposome. After *in vivo* administration, those larger structures may further release the nanoparticles.

When inorganic and when the longest dimension of said nanoparticle is typically of at least 10 nm, typically between 10 and 500 nm, the nanoparticle may comprise at least one of, or may consist in (i) one or more divalent metallic elements selected for example from Mg,

Ca, Ba and Sr, (ii) one or more trivalent metallic element selected for example from Fe and Al, and (iii) one or more tetravalent metallic element comprising Si.

In a particular embodiment, the inorganic material of the nanoparticle is selected from (i) one or more divalent metallic elements selected for example from Mg, Ca, Ba and Sr (ii) one or more trivalent metallic element selected for example from Fe and Al and (iii) one or more tetravalent metallic element comprising Si.

In a further particular embodiment, the inorganic material of the nanoparticle is selected from calcium carbonate ($CaCO_3$), magnesium carbonate ($MgCO_3$), magnesium hydroxide ($Mg(OH)_2$), iron hydroxide ($Fe(OH)_2$), iron oxyhydroxide (FeOOH), iron oxide (Fe_3O_4 or Fe_2O_3), aluminium oxide (Al_3O_4), aluminium hydroxide ($Al(OH)_3$), aluminium oxyhydroxide (AlOOH) and silicium oxide (SiO_2).

The nanoparticles used in the herein described compositions are to be biocompatible, i.e. compatible with living tissues. When required by their composition, the nanoparticles are thus to be coated with a biocompatible material to become usable. In a particular embodiment of the invention, the herein mentioned nanoparticle is thus covered with a biocompatible coating.

The biocompatible material can be an agent allowing interaction with a biological target. Such an agent will typically bring a positive or a negative charge on the nanoparticle's surface when the absolute charge of the nanoparticle is of at least 10 mV.

An agent forming a positive charge on the nanoparticle's surface can be for example selected from aminopropyltriethoxisilane or polylysine. An agent forming a negative charge on the nanoparticle surface can be for example selected from a phosphate (for example a polyphosphate, a metaphosphate, a pyrophosphate, etc.), a carboxylate (for example citrate or dicarboxylic acid, in particular succinic acid) or a sulphate.

In a particular embodiment, as long as the absolute charge of the nanoparticle is of at least 10 mV (|10 mV|), the nanoparticle can be coated with a biocompatible material selected from an agent displaying a steric group. Such a group may be selected for example from polyethylene glycol (PEG); polyethylenoxide; polyvinylalcohol; polyacrylate; polyacrylamide (poly(N-isopropylacrylamide)); polycarbamide; a biopolymer; a polysaccharide such as dextran, xylan and cellulose; collagen; a switterionic compound such as polysulfobetain; etc.

The biocompatible coating may advantageously be a "full coating" (complete monolayer). This implies the presence of a very high density of biocompatible molecules creating an appropriate charge on the all surface of the nanoparticle.

The biocompatible coating may further comprise a labelling agent, typically an agent allowing the visualisation of a color using standard imaging equipment.

The combined administration of the biocompatible nanoparticle together with the compound of interest maintains the pharmaceutical (i.e. therapeutic, prophylactic or diagnostic), typically therapeutic, benefit of the compound of interest for a reduced toxicity, or increases the pharmaceutical benefit of the compound for an equivalent or reduced toxicity, for the subject, typically when administered in the subject in need of the compound of interest, between more than 5 minutes and about 72 hours one from each other, when compared to pharmaceutical benefit and toxicity induced by the standard pharmaceutical, typically therapeutic, dose of said compound.

In a particular embodiment, the combined administration of the biocompatible nanoparticle and of the compound of interest allows a reduction of at least 10%, preferably at least 15%, of the administered compound therapeutic dose, typically when administered in the subject in need of the compound of interest, between more than 5 minutes and about 72 hours one from each other, when compared to the standard therapeutic dose of said compound while maintaining the same therapeutic benefit for an equivalent toxicity or a reduced toxicity (preferably a reduced toxicity) of the compound for the subject; or while increasing the therapeutic benefit for an equivalent or reduced toxicity of the compound for the subject.

In a particular embodiment, nanoparticle(s) are administered with several compounds of interest, typically two compounds of interest.

The nanoparticle is preferably cleared from the subject to whom it has been administered typically within 1 hour and 6 weeks, for example 1 month (4 weeks), within 1 hour and 1 month, for example between 1 hour and 3 weeks, or between 1 hour and 2 weeks, or between 1 hour and 1 week, following its administration to a subject in need of the compound of interest.

The material constituting the nanoparticle (including its biocompatible coating when present) is important in determining the biopersistence of the nanoparticle. The

nanoparticle may be regarded as biodegradable (when constituted for example by a biodegradable polymer such as PLGA or PLA), dissolvable (iron oxide for example) or non biodegradable and non dissolvable. Biodegradable and dissolvable nanoparticles facilitate rapid nanoparticle clearance from the subject.

Different molecules or agents can be used according to the present teaching as the at least one compound of interest, typically as the at least one pharmaceutical compound of interest, administered in combination with a biocompatible nanoparticle as described hereinabove. This compound may be a therapeutic, a prophylactic or a diagnostic compound as previously explained. It can be an organic compound or an inorganic compound.

Examples of organic compound usable as the compound of interest can be selected from a biological compound, an antibody, an oligonucleotide, a synthesized peptide, a small molecule targeted therapeutic, a cytotoxic compound, and any corresponding prodrug or derivative thereof, etc.

In a particular embodiment, the compound of interest used in the context of the present invention is an organic compound preferably selected from a biological compound, a small molecule targeted therapeutic, and a cytotoxic compound. In another particular embodiment, the compound of interest is selected from an antibody, an oligonucleotide, and a synthesized peptide.

A biological compound is for instance an antibody, preferably a monoclonal antibody ("mAb"), such as infliximab, adalimumab, bevacizumab, rituximab, trastuzumab, ranibizumab, cetuximab, panatimumab; a protein or a recombinant protein such as enbrel (etanercept) or interferon beta-1a; a peptide or a recombinant peptide such as insulin glargine or betaseron; a vaccine such as prevnar 13 or gardasil; a biosimilar such as epogin; an enzyme or a recombinant enzyme such as replagal or creon; etc.

An oligonucleotide is for instance an antisense oligonucleotide, an aptamer, such as mipomersen sodium or pursennid, etc.

A synthesized or artificial peptide such as glatiramer acetate or leuprolide acetate.

A small molecule targeted therapeutic generally inhibits enzymatic domains on mutated, overexpressed, or otherwise critical protein (potential target in the context of cancer treatment) within the malignant cells. Some therapeutics agents include those that target cell division (for example a aurora-kinase inhibitor or a cyclin-dependent-kinase inhibitor), as well as other biological mechanisms such as protein turnover and chromatin modification (for example a histone-deacetylase inhibitor). Small molecules targeted therapeutics are for instance imatinib, rapamycin, gefitinib, erlotinib, sorafenib, sunitinib, nilotinib, dasatinib, lapatinib, bortezomib, atorvastatin, etc.

A cytotoxic compound is for instance a DNA-modifying agent, such as an anthracycline (for example doxorubicine, daunorubicine, etc.), an alkylating agent (for example melphalan or temozolomide), as well as a drug interfering very precisely with defined physiological mechanisms such as microtubule polymerization (for example taxol), or metabolite synthesis (for example methotrexate). An activable cytotoxic compound is typically used in the context of Photodynamic Therapy (for example photofrin), and is to be activated by an external source such as a laser source to produce its therapeutic effect. Other typical cytotoxic compounds are typically selected from chemotherapeutic agent as herein described or as known by the skilled oncologist.

A prodrug (for instance capecitabine or irinotecan) is metabolized in its active form *in vivo* to produce its expected therapeutic effect.

Examples of inorganic compound usable as the compound of interest can be selected from a transition metal coordination complex, a radiopharmaceutical compound, a nanoparticle, etc.

Transition metal coordination complexes offer potential advantages over the more common organic-based drugs, including a wide range of coordination numbers and geometries, accessible redox states, 'tune-ability' of the thermodynamics and kinetics of ligand substitution, as well as a wide structural diversity. Metal-based substances interact with cell molecular targets, affecting biochemical functions resulting in malignant cell destruction. Transition metal coordination complexes are typically cytotoxic agents (for instance, platinum coordination complexes: cisplatin, carboplatin, oxaloplatin, or ruthenium or gold coordination complexes) acting on DNA structures.

Radiopharmaceutical compounds emit radiations for diagnosis purposes or in order to selectively destroy malignant cells. Typical radiopharmaceuticals may contain for example strontium-89, thallium-201, techtenium-99, samarium-83, etc.

Nanoparticle may be selected typically from a metal oxide nanoparticle (see WO 2009/147214 and WO 2007/118884 for example), a metallic nanoparticle (gold, platinum or silver nanoparticle for instance), a metal sulfide nanoparticle (Bi_2S_3 for instance), and any mixture thereof (for example a gold nanoparticle covered with hafnium oxide material). The nanoparticle is for example a nanoparticle which can be activated *via* an external source such as a electromagnetic radiation source, a ultrasound source, or a magnetic source, etc.

The compound of interest, which is administered in combination with a biocompatible nanoparticle as described hereinabove (typically sequentially administered as herein described), may be encapsulated in a carrier or grafted (or bound) to such a carrier according to means known by the skilled person. A typical carrier is for example a liposome (such as DOXIL or ThermoDox which uses thermosensitive lipid), micelle, polymeric (or "polymer") carrier, hydrogel, gel, co-polymeric carrier, protein carrier, inorganic carrier.

The pharmaceutical composition of the invention (defined by the combination of the compound of interest and of the nanoparticle) can be used in many fields, particularly in human or veterinary medicine. This composition is typically for use in an animal, preferably in a mammal (for example in the context of veterinary medicine), even more preferably in a human being whatever its age or sex.

The pharmaceutical compositions of the invention can be used in cardiovascular diseases, Central Nervous System (CNS) diseases, gastrointestinal diseases, genetic disorders, hematological disorders, hormonal disorders, immunology, infectious diseases, metabolic disorders, musculoskeletal disorders, oncology, respiratory diseases, toxicology, etc. In a preferred embodiment, the pharmaceutical composition is used in cardiovascular diseases, CNS diseases, oncology, infectious diseases, metabolic disorders.

In the context of the present invention, the nanoparticle and the compound(s) ("compound(s) of interest") are advantageously to be administered in a subject in need of said compound, between more than 5 minutes and about 72 hours one from each other, typically between more than 5 minutes and about 24 hours, preferably between more than 5 minutes or 30 minutes and about 12 hours, in order to optimize the compound pharmaceutical efficacy.

In the present invention, when the nanoparticle and the compound(s) ("compound(s) of interest") are advantageously to be administered in a subject in need of said compound, between more than 5 minutes and about 72 hours one from each other, the absolute surface charge value of the biocompatible nanoparticle is of at least 10 mV (|10 mV|).

In a particular embodiment of the present invention, when the nanoparticle and the compound(s) ("compound(s) of interest") are advantageously to be administered in a subject in need of said compound, between more than 5 minutes and about 24 hours one from each other, the absolute surface charge value of the biocompatible nanoparticle is advantageously of at least 15 mV (|15 mV|).

In another particular embodiment of the present invention, when the nanoparticle and the compound(s) ("compound(s) of interest") are advantageously to be administered in a subject in need of said compound, between more than 5 minutes and about 12 hours one from each other, the absolute surface charge value of the biocompatible nanoparticle is advantageously of at least 20 mV (|20 mV|).

Also herein described is a method for treating a subject suffering of a disease such as those herein mentioned, wherein said method comprises administering to said subject a pharmaceutical composition of the invention, typically administering a biocompatible nanoparticle and at least one compound of interest as herein described. Anyone of the nanoparticle or at least one compound of interest can be administered first to the subject as long as the biocompatible nanoparticle and the compound are administered between more than 5 minutes and about 72 hours from each other. Administration of any of said nanoparticle or at least one compound of interest can be a single administration of each, repeated administrations of each, for example several consecutive administrations of each.

The biocompatible nanoparticle may be administered once and the at least one compound of interest may be administered more than once and vice versa.

In a particular embodiment, the biocompatible nanoparticle is at least administered at the beginning of a protocol comprising several administrations of a compound interest, i.e. at least at the first administration of said compound of interest and before or after the administration thereof.

In another particular embodiment, the biocompatible nanoparticle is not administered at the beginning of a protocol comprising several administrations of a compound interest and is not administered before the second or third administration of said compound of interest, and before or after the administration thereof.

In the context of these last two embodiments, the biocompatible nanoparticle can also be administered together (before or after as previously explained) with the compound of interest during part or all of the subsequent administrations of said compound of interest.

In a particular embodiment, the nanoparticle of the invention is administered to the subject before administration to said subject of the at least one compound of interest, typically between more than 5 minutes and about 72 hours before administration of the at least one compound of interest.

In this context, the term "nanoparticle" can more particularly refer to a product, in particular a synthetic product, with a size between about 4 nm and about 100 nm, for example between about 10 nm, 15 nm or 20 nm and about 100 nm. An example of compound interest to be used with such nanoparticles is an organic compound, typically a biological compound. It is advantageously selected from an antibody, an oligonucleotide, a synthesized peptide, a small molecule targeted therapeutic, and a cytotoxic compound and is preferably an antibody, a small molecule targeted therapeutic and/or a cytotoxic compound. The term "nanoparticle" can otherwise refer to a product, in particular a synthetic product, with a size between about 100 nm and about 500 nm, typically between about 100 nm and about 300 nm. An example of compound interest to be used with such nanoparticles is an inorganic compound, typically selected from a metallic nanoparticle, a metal oxide nanoparticle, a metal sulfide nanoparticle and any mixture thereof or any compound of interest encapsulated in a carrier or grafted to such a carrier.

The biocompatible nanoparticle of the pharmaceutical composition of the invention can be administered by any route such as intra venous (IV), intra-arterial, and/or intra peritoneal. A preferred route of administration is the intra venous route.

The compound(s) of interest of the pharmaceutical composition of the invention can be administered by different routes such as subcutaneous, intra venous (IV), intra-dermic, intra-arterial, airways (inhalation), intra peritoneal, intra muscular and/or oral route (*per os*).

The following examples illustrate the invention without limiting its scope.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Schematic view of possible routes for therapeutic compounds removal from blood circulation depending on the compound's size (longest dimension).

Figure 2: Schematic representation of the treatments' schedule for the pharmaceutical composition comprising (i) the biocompatible nanoparticles of example 3 and (ii) the Dox-NP® in MDA-MB-231-lucD3H2LN xenografts.

Figure 3: Tumor re-growth delay of the pharmaceutical composition comprising the biocompatible nanoparticles of example 3 and the Dox-NP® in MDA-MB-231-lucD3H2LN xenografts (mean RTV ± SD).

EXAMPLES

Example 1: Synthesis n°1 of liposomes as biocompatible nanoparticles

Liposomes are prepared using the lipidic film re-hydration method:

a) Lipids are solubilized in chloroform. Chloroform is finally evaporated under a nitrogen flow. Re-hydration of the lipidic film with HEPES 20 mM and NaCl 140 mM at pH 7.4 is performed at 50°C, so that the lipidic concentration is 5 mM.

The following lipidic composition was used to prepare charged liposomes: DPPC (DiPalmitoylPhosphatidylCholine): 86% mol; MPPC

(MonoPalmitoylPhosphatidylcholine): 10% mol; DSPE-PEG (DiStearylPhosphatidylEthanolamine-[methoxy(PolyElthyleneGlycol)-2000]): 4% mol.

b) Freeze-thaws cycles are then performed 6 times, by successively plunging the sample into liquid nitrogen and into a water bath regulated at 50°C.

c) A thermobarrel extruder (LIPEX™ Extruder, Northern Lipids) was used to calibrate the size of the liposomes under controlled temperature and pressure. In all cases, extrusion was performed at 50°C, under a pressure of 10 bars.

Size distribution of the as-prepared liposomes was determined by dynamic light scattering (DLS) using a Zetasizer NanoZS (Malvern instrument) with a 633 nm HeNe laser at an angle of 90°C. The liposomes suspension was diluted 100 times in HEPES 20 mM and NaCl 140 mM at pH 7.4. Liposome size (i.e. hydrodynamic diameter) was equal to about 170 nm with a polydispersity index (PDI) equal to about 0.1.

As understandable by the skilled person, the desired surface charge was obtained thanks to the selected lipidic composition, and its value was confirmed by zeta potential measurement using a Zetasizer NanoZS (Malvern instrument).

The liposomes were diluted 100 times in water and the pH of the resulting suspension was adjusted to pH 7.4. The liposome surface charge was equal to about – 14 mV at pH 7.4.

Example 2: method allowing a reduction of at least 10% of the dose of therapeutic compound to be administered in a subject for an equivalent therapeutic efficacy thereof in the subject.

A pharmaceutical composition according to claim 1 comprising a biocompatible nanoparticle and an activable oxide nanoparticle for anti-cancer therapy (used as "the compound" or "pharmaceutical compound") which can generate electron and/or high energy photon when exposed to ionizing radiations such as X-rays, is administered in nude mice bearing a xenografted tumor in the following manner:

a) administering to each nude mice (by intra venous injection) the biocompatible nanoparticles;

b) between more than 5 minutes and 72 hours following step a), administering (by intra venous injection) the therapeutic compound in each mice of step a) at a lower dose (10%) when compared to the dose currently used;

c) measuring the therapeutic compound concentration in blood or plasma samples of each mice to obtain the pharmacokinetic parameters of the therapeutic compound, said

concentration being measured once or preferably several times between 1 minute and 24 hours following the therapeutic compound administration;

d) assessing any clinical sign of toxicity after the administration of the pharmaceutical composition; and

e) measuring the tumor accumulation of the therapeutic compound 24 hours after its intravenous (IV) administration.

Example 3: Synthesis n°2 of liposomes as biocompatible nanoparticles

Liposomes are prepared using the lipid film re-hydration method:

a) Lipids are solubilized in chloroform. Chloroform is finally evaporated under a nitrogen flow. Re-hydration of the lipid film with HEPES 20 mM and NaCl 140 mM at pH 7.4 is performed at 60°C, so that the lipid concentration is 25 mM.

The following lipid composition was used to prepare charged liposomes: DPPC (DiPalmitoylPhosphatidylCholine) 62% mol; HSPC (Hydrogenated Soybean PhosphatidylCholine) 20% mol; CHOL (Cholesterol) 16% mol; POPS (1-Palmitoyl-2-Oleoyl PhosphatidylSerine) 1% mol; DSPE-PEG (DiStearylPhosphatidylEthanolamine-[methoxy(PolyElthyleneGlycol)-2000]) 1% mol.

b) Freeze-thaw cycles are then performed 6 times, by successively plunging the sample into liquid nitrogen and into a water bath regulated at 60°C.

c) A thermobarrel extruder (LIPEXTM Extruder, Northern Lipids) was used to calibrate the size of the liposomes under controlled temperature and pressure. In all cases, extrusion was performed at 60°C, under a pressure of 5 bars, with a 0.1µm pores size polyvinylidene fluoride (PVDF) membrane.

Size distribution of the as-prepared liposomes was determined by dynamic light scattering (DLS) using a Zetasizer NanoZS (Malvern instrument) with a 633 nm HeNe laser at an angle of 90°C. The liposomes suspension was diluted 100 times in HEPES 20 mM and NaCl 140 mM at pH 7.4. Liposome size (i.e. hydrodynamic diameter) was equal to about 145 nm with a polydispersity index (PDI) equal to about 0.1.

As understandable by the skilled person, the desired surface charge was obtained thanks to the selected lipidic composition, and its value was confirmed by zeta potential measurement using a Zetasizer NanoZS (Malvern instrument).

The liposomes were diluted 100 times in a sodium chloride solution at 1mM and the pH of the resulting suspension was adjusted to pH 7.4. The liposomes surface charge was equal to about – 25 mV at pH 7.4, NaCl 1mM.

Example 4: Tumor re-growth delay of the pharmaceutical composition comprising the biocompatible nanoparticles suspension of example 3 and the Dox-NP® in MDA-MB-231-lucD3H2LN xenografts (Figures 2 and 3)

This study was performed to investigate the efficacy of the pharmaceutical composition comprising (i) the biocompatible nanoparticle from example 3 and (ii) Dox-NP® (Liposomal Encapsulated Doxorubicin) as the therapeutic compound of interest, in MDA-MB-231-luc-D3H2LN tumor model xenografted on NMRI nude mice.

The human breast adenocarcinoma MDA-MB-231-luc-D3H2LN cell line was purchased at Caliper Life Science (Villepinte, France). The cells were cultured in Minimum Essential Medium with Earl's Balanced Salts Solution MEM/EBSS medium supplemented with 10% fetal bovine serum, 1% non-essential amino acids, 1% L-glutamine, and 1% sodium pyruvate (Gibco).

NMRI nude mice, 6-7 weeks (20-25g) were ordered from Janvier Labs (France). Mice were subjected to a total body irradiation of 3Gy with the Cesium-137 irradiation device one day before the inoculation of the cancer cells for xenograft.

MDA-MB-231-luc-D3H2LN tumors were obtained by subcutaneous injection of 4.10^6 cells in 50 µL in the lower right flank of the mouse. The tumor were grown until reaching a volume around about 100 mm^3. Tumor diameter was measured using a digital caliper and the tumor volume in mm^3 was calculated using the formula:

$$\text{Tumor volume } (mm^3) = \frac{\text{length (mm) x (width)}^2\ (mm^2)}{2}$$

Mice were randomized into separated cages and identified by a number (pawn tattoo). Four groups were treated as illustrated on figure 2.

- Group 1: sterile glucose 5% (control (vehicle) group)

Four (4) mice were intravenously (IV) injected with a sterile glucose 5% solution on day 1, day 7 and day 14. Each time (day), two injections of glucose 5% were performed. The first injection of glucose 5% solution was performed 4 hours before the second injection.

- Group 2: Biocompatible nanoparticles from example 3 (control group)

Four (4) mice were intravenously (IV) injected with a sterile glucose 5% solution and the biocompatible nanoparticles from example 3 (10 ml/kg) on day 1, day 7 and day 14. Each time (day), the injection of biocompatible nanoparticles from example 3 was performed 4 hours before injection of the glucose 5% solution.

- Group 3: Dox-NP® (3mg/kg doxorubicin) (treatment group)

Five (5) mice were intravenously (IV) injected with a sterile glucose 5% solution and Dox-NP® (3mg/kg doxorubicin) on day 1, day 7 and day 14. Each time (day), the injection of sterile glucose 5% solution was performed 4 hours before the injection of Dox-NP® (3mg/kg doxorubicin).

- Group 4: pharmaceutical composition, i.e. the combination of (i) the biocompatible nanoparticles from example 3 and of (ii) Dox-NP® (3mg/kg doxorubicin) (treatment group)

Five (5) mice were intravenously (IV) injected with the biocompatible nanoparticles from example 3 (10 ml/kg) and with the Dox-NP® (3mg/kg doxorubicin) on day 1, day 7 and day 14. Each time (day), the injection of biocompatible nanoparticles from example 3 was performed 4 hours before the injection of Dox-NP® (3mg/kg doxorubicin).

The Dox-NP® (Avanti Polar lipids – Liposomal formulation of 2 mg/ml doxorubicin HCl at pH 6.5-6.8, in 10mM histidine buffer, with 10% w/v sucrose) was injected without additional dilution at a volume required to obtain 3mg/kg of injected doxorubicin.

The biocompatible nanoparticles suspension from example 3 was used without any additional dilution.

The Dox-NP® and the biocompatible nanoparticles from example 3 were administrated by intravenous injection (IV) via lateral tail vein with a 100U (0.3ml) insulin syringe (TERUMO, France).

Mice were followed up for clinical signs, body weight and tumor size.

The tumor volume was estimated from two dimensional tumor volume measurements with a digital caliper using the following formula:

$$\text{Tumor volume } (mm^3) = \frac{\text{length (mm) x (width)}^2\ (mm^2)}{2}$$

In each group, the relative tumor volume (RTV) was expressed as Vt/V_0 ratio (Vt being the tumor volume on a given day during the treatment and V_0 being the tumor volume at the beginning of the treatment).

The treatment efficacy was determined using the specific growth delay (SGD) over two doubling time (one doubling time being the amount of time it takes for the tumor to double in volume) and the optimal percent T/C value (% T/C).

The SGD was calculated over two doubling time as follows:

$$SGD = \frac{\text{T4d treated} - \text{T4d control}}{\text{T4d control}}$$

with T4d being the time required for the tumor to double twice in volume (mean RTV from 100 mm^3 up to 400 mm^3).

The Percent T/C value ("% T/C") was calculated by dividing the median of the relative tumor volume of treated groups (groups 2, 3, 4) versus control group (group 1) at days 1, 3, 7, 10, 13, 15, 18, 21 and 24, and by multiplying the result of said division by 100 (see Table 2). The lowest % T/C values obtained within 2 weeks following treatment injection (with or without biocompatible nanoparticles as used in the context of the present invention) correspond to the optimal %T/C values.

Figure 3 shows the mean relative tumor volume (mean RTV) for all groups as obtained (in the conditions previously described) after IV injections of:

- vehicle (sterile glucose 5%) on day 1, 7 and 14 (group 1);
- biocompatible nanoparticles from example 3, 4 hours prior each vehicle (sterile glucose 5%) injection on day 1, 7 and 14 (group 2);
- Dox-NP® (3mg/kg doxorubicin) on day 1, 7 and 14 (group 3); or
- biocompatible nanoparticles from example 3, 4 hours prior the Dox-NP® (3mg/kg doxorubicin) injection on day 1, 7 and 14 (group 4).

As shown on figure 3, a marked tumor growth inhibition is observed after the first injection of the pharmaceutical composition comprising the combination of (i) the biocompatible

nanoparticles from example 3 and (ii) the Dox-NP® (3mg/kg doxorubicin), when compared to the Dox-NP® (3mg/kg doxorubicin) alone.

The time required (expressed in days) for each tumor to double twice in volume (T4d) was calculated (as a measure of the duration of the treatment effects). T4d for the pharmaceutical composition was estimated to about 31 days versus about 14 days for the Dox-NP® alone (table 1). In addition the Specific Growth Delay (SGD) estimated from the tumors growth over two doubling time (starting from a mean RTV of 100 mm^3 up to 400 mm^3) was equal to about 2 for the pharmaceutical composition versus about 0 for the Dox-NP® alone (table 1).

Table 1:

Groups	T4d (in days) between 100 and 400 mm^3 (mean RTV)	SGD
Group 1: vehicle (control group)	11	-
Group 2: Biocompatible nanoparticles from example 3	11	0
Group 3: Dox-NP® alone (3mg/Kg)	14	0
Group 4: Pharmaceutical composition comprising (i) the biocompatible nanoparticle from example 3 and (ii) Dox-NP® (3mg/Kg)	31	2

Table 1: Time for the tumor to double twice in volume (T4d) and Specific Growth Delay (SGD) estimated from the tumors growth over two doubling time. Td4 represents the number of days to reach two doubling time (mean RTV from 100 mm^3 up to 400 mm^3). The control group is the vehicle (glucose 5%) alone (-).

Furthermore, the percent T/C (%T/C) (calculated until the day of sacrifice of group 1) decrease faster for the pharmaceutical composition than for Dox-NP® alone. This demonstrates a marked impact of the pharmaceutical composition. The optimal %T/C of 25 observed at day 24 was indeed obtained for the pharmaceutical composition, i.e. the combination of (i) the biocompatible nanoparticles from example 3 and (ii) the Dox-NP®

(3mg/kg doxorubicin), whereas the optimal %T/C of 38 observed at day 21 was obtained for the group Dox-NP® alone (Table 2).

Table 2:

Days	Group 2: biocompatible nanoparticles alone	Group 3: Dox-NP® alone (3mg/kg)	Group 4: Pharmaceutical composition comprising (i) the biocompatible nanoparticle and (ii) Dox-NP® (3mg/Kg)
1	100	100	100
3	104	126	121
7	90	106	80
10	87	76	60
13	103	80	55
15	98	74	45
18	98	56	43
21	87	38	33
24	98	40	25

Table 2: percent T/C (%T/C) is calculated by dividing the median of the relative tumor volume of treated groups (groups 2, 3, 4) versus control group (group 1) at days 1, 3, 7, 10, 13, 15, 18, 21 and 24, and by multiplying the result of said division by 100. Control group is group 1 (vehicle sterile glucose 5% alone). %T/C is calculated until day 24 which correspond to the day of sacrifice of group 1 (control group). Optimal %T/C is indicated for each group in gray boxes.

Overall, those result showed an advantageous tumor growth delay when using the pharmaceutical composition of the present invention [corresponding to the combination of (i) the biocompatible nanoparticles from example 3 and of (ii) the Dox-NP® (3mg/kg doxorubicin)], which is not observed when the Dox-NP® (3mg/kg doxorubicin) is used alone (i.e. in the absence of the biocompatible nanoparticles used in the context of the

present invention). This tumor growth delay was observed when the biocompatible nanoparticles from example 3 and the compound of interest (the Dox-NP®) were administered sequentially, the biocompatible nanoparticle being administered to the subjects 4 hours before the Dox-NP®.

Inventors are reproducing this experiment to confirm that the same result is observed so long as the compound of interest and the biocompatible nanoparticles are administered in the subject between more than 5 minutes and about 72 hours, one from each other.

CLAIMS

1. Use of a combination of (i) a biocompatible nanoparticle having a longest dimension of between about 4 nm and about 500 nm and an absolute surface charge value of at least 10 mV (|10 mV|) and of (ii) a pharmaceutical compound of interest in the manufacture of a medicament, for enhancing therapeutic efficiency of the pharmaceutical compound of interest, wherein the nanoparticle and pharmaceutical compound of interest are to be administered in the subject sequentially, and wherein said nanoparticle is to be administered to the subject between more than 5 minutes and about 72 hours before or after the pharmaceutical compound of interest.

2. The use according to claim 1, wherein the nanoparticle has an absolute surface charge value of more than |10 mV|, said charge being a negative charge.

3. The use according to claim 1 or 2, wherein the nanoparticle is an organic nanoparticle.

4. The use according to claim 3, wherein the nanoparticle is selected from a lipid-based nanoparticle, a protein-based nanoparticle, a polymer-based nanoparticle, a co-polymer-based nanoparticle, a carbon-based nanoparticle, and a virus-like nanoparticle.

5. The use according to claim 1 or 2, wherein the nanoparticle is any inorganic nanoparticle and the longest dimension of said nanoparticle is below about 7 nm.

6. The use according to claim 1 or 2, wherein the nanoparticle is an inorganic nanoparticle, the longest dimension of said nanoparticle is of at least 10 nm, and the inorganic material of the nanoparticle is selected from (i) one or more divalent

metallic elements selected for example from Mg, Ca, Ba and Sr, (ii) one or more trivalent metallic element selected for example from Fe and Al, and (iii) one or more tetravalent metallic element comprising Si.

7. The use according to claim 6, wherein the inorganic material is selected from calcium carbonate ($CaCO_3$), magnesium carbonate ($MgCO_3$), magnesium hydroxide ($Mg(OH)_2$), iron hydroxide ($Fe(OH)_2$), iron oxyhydroxide (FeOOH), iron oxide (Fe_3O_4 or Fe_2O_3), aluminium oxide (Al_3O_4), aluminium hydroxide ($Al(OH)_3$), aluminium oxyhydroxide (AlOOH) and silicium oxide (SiO_2).

8. The use according to anyone of claims 1 to 7, wherein the nanoparticle is further covered with a biocompatible coating.

9. The use according to anyone of claims 1 to 8, wherein the sequential administration of the biocompatible nanoparticle and of the compound maintains the therapeutic benefit of the compound for a reduced toxicity, or increases the therapeutic benefit of the compound for an equivalent or reduced toxicity, for the subject, when compared to therapeutic benefit and toxicity induced by the standard therapeutic dose of said compound.

10. The use according to anyone of claims 1 to 8, wherein the sequential administration of the biocompatible nanoparticle and of the compound allows a reduction of at least 10% of the administered compound therapeutic dose when compared to the standard therapeutic dose of said compound while maintaining the same therapeutic benefit for an equivalent toxicity or a reduced toxicity for the subject or while increasing the therapeutic benefit for an equivalent or reduced toxicity for the subject.

11. The use according to anyone of claims 1 to 10, wherein the nanoparticle is cleared from the subject to whom it has been administered within one hour and six weeks after its administration to a subject in need of the pharmaceutical compound of interest referred to in claim 1.

12. The use according to anyone of claims 1 to 11, wherein the compound is an organic compound preferably selected from a biological compound, a small molecule targeted therapeutic, and a cytotoxic compound.

13. The use according to claim 12, wherein the compound is selected from an antibody, an oligonucleotide, and a synthesized peptide.

14. The use according to anyone of claims 1 to 11, wherein the compound is an inorganic compound selected from a metallic nanoparticle, a metal oxide nanoparticle, a metal sulfide nanoparticle and any mixture thereof.

15. The use according to anyone of claims 1 to 14, wherein the compound of interest is encapsulated in a carrier.

16. The use according to anyone of claims 1 to 14, wherein the compound of interest is bound to a carrier.