unacceptable variability. Moreover, the extend of exposure of those "stealth" DDS has been related with more adverse events. DOXIL, a PEGylated liposomal formulation comprising doxorubicin, was for instance found to produce serious adverse events, such as the hand-foot syndrome or mucositis. The hydrophilic coating of the liposomes was questioned as perhaps facilitating their accumulation in eccrine sweat gland in palms and planta [Pegylated liposomal doxorubicin-related palmar-plantar erythrodysesthesia ('hand-foot' syndrome). D. Lorusso et al. Annals of Oncology. 2007; 18, 1159-1164].

WO2005/063305 relates to an assembly comprising a gas-filled microvesicle (with a size typically of at least 0.5 μm) and a component (with a size about below 100 nm) associated to said microvesicle. The resulting assembly is to be used as a pharmaceutically active component in diagnostically and/or therapeutically active formulations. The two components, i.e. the gas-filled microvesicle and the microvesicle associated component, are administered simultaneously typically for enhancing the imaging in the field of ultrasound contrast imaging, including targeted ultrasound imaging, ultrasound-mediated drug delivery and other imaging techniques.

As apparent from the prior art and despite of a long medical need, the safe and efficient delivery of pharmaceutical compounds (including therapeutic, prophylactic as well as diagnostic compounds) to their target site(s) remains a concern. There is a clear need to improve the compound's efficacy and safety, or in other words the pharmaceutic compound's transport and release, in order for said compound to reach its target site in a subject in the necessary and sufficient quantity to get the desired diagnostic, therapeutic or prophylactic effect.

**SUMMARY**

In one aspect, there is provided the use of a pharmaceutical composition comprising the combination of (i) at least one biocompatible nanoparticle and of (ii) at least one carrier comprising at least one pharmaceutical compound, 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|, and wherein the carrier is devoid of any surface sterically stabilizing agent, in the manufacture of a medicament for use in a therapeutic, prophylactic or diagnostic method in a subject in need of said at least one pharmaceutical compound, wherein the subject is to be administered with the at least one carrier comprising at least one pharmaceutical compound and the at least one biocompatible nanoparticle, and wherein said at least one biocompatible

nanoparticle is to be administered to the subject between more than 5 minutes and about 72 hours before or after the at least one carrier comprising at least one pharmaceutical compound, and wherein the biocompatible nanoparticle is not used as such as a pharmaceutical compound.

## 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) at least one biocompatible nanoparticle and of (ii) at least one carrier comprising at least one compound of interest, optimize the at least one compound of interest's pharmacokinetic parameters, and, as a consequence, now renders possible the development of pharmaceutic compounds which could not have been developed otherwise due for example to their unacceptable toxicity. Typically, the biocompatible nanoparticle is

## CLAIMS

1. Use of a pharmaceutical composition comprising the combination of (i) at least one biocompatible nanoparticle and of (ii) at least one carrier comprising at least one pharmaceutical compound, 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|, and wherein the carrier is devoid of any surface sterically stabilizing agent, in the manufacture of a medicament for use in a therapeutic, prophylactic or diagnostic method in a subject in need of said at least one pharmaceutical compound, wherein the subject is to be administered with the at least one carrier comprising at least one pharmaceutical compound and the at least one biocompatible nanoparticle, and wherein said at least one biocompatible nanoparticle is to be administered to the subject between more than 5 minutes and about 72 hours before or after the at least one carrier comprising at least one pharmaceutical compound, and wherein the biocompatible nanoparticle is not used as such as a pharmaceutical compound.

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 an 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 claim 1, wherein the carrier is a plain carrier.

10. The use according to claim 1, wherein the carrier is a hollow carrier.

11. The use according to anyone of claims 1 to 10, wherein the carrier's surface is devoid of any hydrophilic polymer.

12. The use according to anyone of claims 1 to 11, wherein the carrier's surface is devoid of any polyethylene glycol (PEG) polymer.

13. The use according to anyone of claims 1 to 12, wherein the at least one biocompatible nanoparticle and the at least one carrier comprising the pharmaceutical compound(s) are to be administered in combination, to thereby maintain the therapeutic benefit of said pharmaceutical compound(s) for a reduced toxicity, or increase the therapeutic benefit of said pharmaceutical compound(s) for an equivalent or reduced toxicity, for the subject, when compared to therapeutic benefit and toxicity induced by the standard therapeutic dose(s) of said compound(s) in the absence of any biocompatible nanoparticle and/or carrier.

14. The use according to anyone of claims 1 to 13, wherein the at least one biocompatible nanoparticle and the at least one carrier comprising the pharmaceutical compound(s) are to be administered in combination, to thereby allow a reduction of at least 10% of the administered pharmaceutical compound(s) therapeutic dose(s) when compared to the standard therapeutic dose(s) of said compound(s) 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 in the absence of any biocompatible nanoparticle and/or carrier.

15. The use according to anyone of claims 1 to 14, wherein the at least one 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 at least one pharmaceutical compound referred to in claim 1.

16. The use according to anyone of claims 1 to 15, wherein the pharmaceutical compound is selected from a small molecule, in particular a targeted small molecule, a cytotoxic compound and a transition metal coordination complex.

17. The use according to anyone of claims 1 to 16, wherein the pharmaceutical compound is encapsulated in the carrier, impregnated in the carrier or bound to the carrier.

18. The use according to anyone of claims 1 to 17, wherein the pharmaceutical compound is released from the carrier by temporal-controlled diffusion, carrier erosion and/or carrier degradation.

19. The use according to anyone of claims 1 to 17, wherein the pharmaceutical compound is released from the carrier in response to an intracellular or an extracellular stimulus.

20. The use according to anyone of claims 1 to 17, wherein the pharmaceutical compound is released from the carrier when said carrier is exposed to electromagnetic radiations, ultrasounds and a magnetic field.