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Function and Application of NanoParticles as Effulgent Probes in Biology

Dr. Hamed Mohamed Abubaker Malek, Dr. Moustfa Mohamed Hassan Eshtewi
Department of Physics Faculty of Science,Sebha University,Libya
Department of Physics Faculty of Science,Sirt University,Libya

ABSTRACT:
In Solid state science, one of the applications of certain effulgent nonmaterial's (effulgent materials are substances which convert an incident energy input into the emission of electromagnetic waves in the ultraviolet (UV), visible or infrared regions of the spectrum, over and above that due to black-body emission) has been in the field of biology, both for the development of biochips, contrast agents, tissue revealers. Therefore the use as a fluorescent biological probe appears as the most promising. A biological probe is an object attached to the targeted bimolecular that can easily be detected. It is divided into two parts, the part carrying the biological "function", and the detectable part. Detection can be done through different physical properties.

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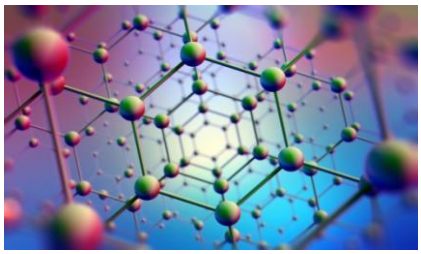
I. INTRODUCTION

Nanotechnology, although not a new concept, has gained significant momentum in recent years. The prefix "nano" means one-billionth. In the metric scale of linear measurements, a nanometer is one-billionth of a meter. Primarily in the material science standard, the term "nanotechnology" is now commonly used to refer to the fabrication of new materials with nanoscale of dimensions between 1 and 100 nm.1 However, with its development, the scope of this definition also expanded. Nanoparticles of different sizes have different biomedical purposes. In physics and electrical engineering, nanotechnology is associated with quantum behavior and the behavior of electrons and photons in nanoscale structures. Nanoparticles are interpreted the relationship among nanotechnology, chemistry, and biology.

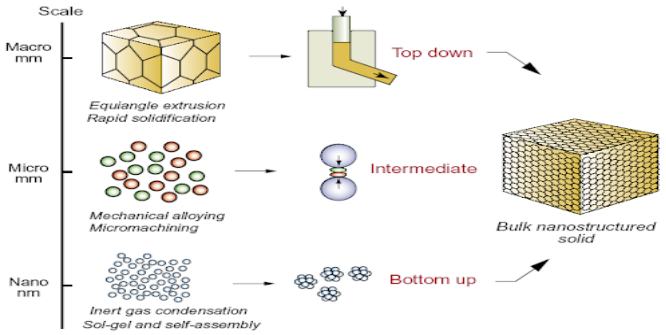


Fluorescent probes for biology many advances in the field of biology have been made thanks to development of these fluorescent biological markers. These markers can be from different natures, and we will recall here that of the main fluorescent entities used to create biological fluorescent probes. Organic fluorescent probes When Coons developed a technique for labeling antibodies with fluorescent organic molecules in the 1940s. He paved the way for development of immunofluorescence. This technique consists of labeling antibodies by fluorescent molecules, creating a marker targeting the corresponding antigen. The advances in molecular biology have enabled the creation of numerous probes fluorescent organics to mark virtually any region of a biological entity.

Likewise, with the development of fluorescence microscopy, fluorophores organic compounds that can be used in these markers have seen their number grow and their characteristics diversify. Of two fluorophores used Fluoresceine and Rhodamine B, a few hundred are currently available commercially. These organic fluorophores are essentially aromatic molecules, exhibiting a system of highly delocalized electrons giving them the properties of luminescence in the visible range. Good candidates as fluorophores for probes biologicals must be capable of being excited by a commercial source and their fluorescence must be easily detected. Thus, they must exhibit significant absorption at the length excitation wave, and emission intensity after excitation sufficient to allow detection. Organic fluorophores have absorption and emission spectra with broad bands, and absorption and emission maxima not far apart (low Stokes shift). The low Stokes shift often induces efficient detection at detriment of effective excitation, and a compromise between excitation and detection must useful.
Typically, organic fluorophores exhibit an extinction coefficient molar in the range of 5 to 200. 103 L.mol-1.cm-1, and a quantum yield varying from 0.05 to 1. The fluorophores used thus allow efficient labeling of cell tissues. However, in it observe a rapid decrease in fluorescence signal over time of these organic fluorophores (after a few seconds and up to a few minutes). This rapid decrease in luminescence is due to photo degradation of fluorophores in the presence of oxygen. This irreversible phenomenon prevents monitoring of individual biomolecules requiring intense excitations for long periods of time, and has led the scientific community to look for new, more photostable fluorophores.

II. SEMICONDUCTOR NANOPARTICLES

Semiconductor nanoparticles used in biosensing are generally compounds of metals with nonmetallic elements. Some semiconductor materials can become fluorescent in the form nanometric by quantum confinement effect. This is particularly the case with nanoparticles of CdE, where E represents S, Se, Te, when their dimension reaches sizes of the order of 2- 12 nm. Summaries to obtain well-dispersed objects, defined in size, shape and luminescence properties have been developed in particular by Bawendi's team, in a coordinating solvent medium, and improved by adding on the surface a layer of ZnS. Des progress made in understanding the surface chemistry of these nanoparticles, and the preparation of nanoparticles soluble in aqueous medium and biocompatible allowed to use these objects for biological applications. Semiconductor nanoparticles of the same material will see their properties optics change depending on their size. Indeed, the fluorescence properties come from the gap between valence and conduction levels, which increase with decreasing size. Thus, it is possible, from the same material, to modify its fluorescence properties by varying its size.



These semiconductor nanoparticles have proven to be an interesting alternative for the formation of fluorescent probes. Their optical properties can be compared to those of molecules fluorescent, and it has been shown that: Semiconductor nanoparticles emit on the order of 20 times more photons than organic molecules. However, their fluorescence properties are greatly reduced in aqueous media.

They exhibit a clearly more stable fluorescence signal than that of Organic fluorophores. Polymeric nanoparticles one of the options considered was therefore to develop polymeric systems having several organic fluorophores, in order to form fluorescent objects, of nanometric, and multiplying the properties of a single fluorophore. These systems would be then usable to form effulgent probes for labeling biomolecules individual. Different approaches have been used:

One of the approaches has been to develop polymeric beads and to graft the surface of these beads of organic fluorophores. The beads can then present fluorophores on the surface. This method therefore makes it possible to multiply the number of fluorophores at the same point, but these fluorophores, always subjected to the solvent can degrade quickly.

A second approach, requiring further syntheses, consists in incorporating fluorophores in a polymer bead. This was notably developed to train polystyrene beads containing organic fluorophores, but also beads of silica. In addition to the greater number of fluorophores present in the beads, this method protects fluorophores from their environment, and thus improves overall photostability of the system. This same approach was developed to encompass other effulgent objects, in particular lanthanide complexes, or even semiconductor nanoparticles.

The objects obtained by such an approach are generally of the order of a few hundred nanometers, which is quite large for biological probes nevertheless doped silica nanoparticles with an organic fluorophore, leading to 60 nm objects, which can be used as biological probes. Likewise, the Wiesner recently synthesized 30 nm silica nanoparticles, encompassing molecules of organic fluorophores, effulgent enough to be used as probes in biology.

A comparison of the brightness of these fluorescent silica beads to a molecule of Single organic fluorophore has shown that these nanoparticles are on the order of 20 times more effulgent, and 2 to 3 times more stable than the single fluorophore. Their luminosity is thus of the same order of magnitude as that of semiconductor nanoparticles, but their photostability needs to be improved. On the other hand, they present a size which is generally very well defined, and an easily modifiable surface for biofunctionalization.

Oxides doped with lanthanides

A second option was to synthesize materials in the form of nanoparticles. Strongly effulgent on a macroscopic scale. These non- effulgent materials intrinsically, must be doped either by defects or by interacting ions then with the crystal matrix, in order to be effulgent. Oxides doped with lanthanide ions are thus good phosphors, largely used in applications such as lighting or visualization devices. In indeed, lanthanides are characterized by fine emission lines, and long lifetimes (in the order of 0.1-1 ms). However, the excitation of these ions is relatively difficult. Their insertion into an oxide matrix, on the other hand, allows efficient excitation of the ions lanthanides by energy transfer.

The use of such effulgent oxides in biology has so far been little discussed, oxides doped with lanthanide ions not having been synthesized in well crystallized form at nanoscale only relatively recently. However, some work has showed that their use as effulgent probes in biology was promising, from made of the diversity of possible luminescence colors, their photostability, and the times long lifetimes (of the order of a millisecond). It had studied the biofunctionalization of lanthanum phosphate nanoparticles codoped with cerium and 7nm in size terbium, but no application to the system. The Tillation also demonstrated the possibility of using oxide nanoparticles of gadolinium doped with terbium 3-8 nm in size for biological applications as biochips or as tracers. However, cell applications are still few: the first works of Doat et al. on particles of bioapatite doped with europium internalized in cells have so far little impact. Even, the detection of a effulgent nanoparticle of small size has not yet been established. We were therefore interested in one of these oxides doped with lanthanides effulgent, namely yttrium vanadate doped with europium. Synthesis and optical properties of this oxide doped with different lanthanides have been extensively studied at laboratory, as well as its applications as a effulgent transparent material.

Its application as a fluorescent biological probe will be described here. To be used as fluorescent biological probes, the nanoparticles of yttrium vanadate doped with europiums must have a particular affinity with biomolecules. We are thus interested in the different biological systems allowing specific recognition between two biomolecules.

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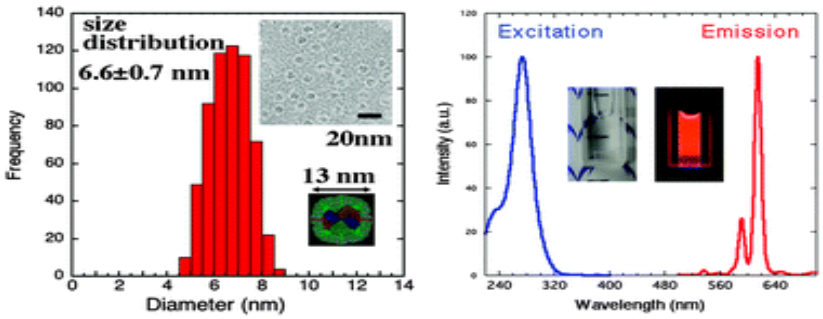
III. SYNTHESIS OF NANOPARTICLES DOPED WITH YTTRIUM VANADATE

Luminescent europium (Eu) and dysprosium (Dy) doped yttrium–vanadate (Y–V) nanoparticles (NPs) were synthesized in the cavity of the protein, apoferritin. Y–V NPs were synthesized by incubating a solution of apoferritin with Y3+ and VO3− ions in the presence of ethylene diamine-*N*-*N*′-diacetic acid (EDDA). The procedure of the synthesis developed by Huignard in the laboratory will be here remembered. The critical parameter for the formation of the orthovanadate phase during this synthesis is the pH value, which we will discuss next. During the synthesis by precipitation of metal salts developed by Huignard, yttrium and europium nitrates were used as sources of Y3 + and Eu3 + ions, and sodium orthovanadate as a source of VO4 ions3-. A 0.1 M aqueous solution of Na3VO4 is freshly prepared. His pH is measured, and adjusted if necessary to a value between 12.6 and 13. A volume of solution of Y1-x Eux (NO3) 3 to 0.1 M in ions (Y3 + + Eu3 +) is added drop by peristaltic pump into the Na3VO4 solution with stirring. A Milky white precipitate appears as soon as the Y1-x Eux (NO3) 3 solution is added. The addition continues until the pH reaches a value of 8-9. The solution contains many counter-ions, the presence of which is harmful stabilization of particles in solution. It is then purified by three centrifugations at 11,000 g for 20 minutes each followed by a redispersion by syndication. 128 Dialysis against deionizer water for 16 hours is then carried out, in order to obtain a solution with a conductivity of less than 100 S.cm2. The final solution is very diffusing and flocculates after a few days.



The concentration of orthovanadates in the suspension is determined by measurements absorbance, the principle of which is described in the appendix. This measurement carried out after purification shows a solid phase formation yield close to 100%.

pH during synthesis

The pH value during the synthesis of yttrium orthovanadate was optimized by Loon at 12.5 <pH <13 to promote precipitation of the orthovanadate phase pure yttrium. Indeed, Huignard observed the irreversible formation of yttrium hydroxide when the initial pH is greater than 13 and the formation of a brown precipitate when it is below pH 12.5, which he attributed to the formation of yttrium polyvanadates. The addition of nitrates was in this case carried out all at once.

However, when slowly adding yttrium and europium salts to a solution of sodium orthovanadate initially at 12.5 <pH <13, we observed a decrease slow pH, followed when pH <8 by a sharp decrease in pH. This decrease the sudden drop in pH is accompanied by the formation of a slightly yellow precipitate. This phenomenon can be understood from the work of Ropp and Caroll concerning the stability of vanadates in solution and can be summarized by chemical equations following:

When introducing yttrium salts in solution at 12.5 <pH <13

$$Y^{3+} + 3OH^- \rightarrow Y(OH)_3(\downarrow)$$

$$Y(OH)_3(\downarrow) \rightarrow Y^{3+} + 3OH^-$$

$$Y^{3+} + VO_4^{3-} \rightarrow YVO_4(\downarrow)$$

$$3VO_4^{3-} + 3H^+ \rightarrow V_3O_9^{3-} + 3OH^-$$

$$Y^{3+} + V_3O_9^{3-} \rightarrow YV_3O_9(\downarrow)$$

Visualization of the crystallinity of nanoparticles

The crystallinity of the objects can be visualized on an electron microscopy image in transmission, in high resolution. The high resolution makes it possible to obtain a level of resolution of the image of the order of a few angstroms (2 Å) by precise adjustments of the alignment and astigmatism of the optics of the microscope, which makes it possible to distinguish crystal structures by diffraction of crystal planes. Such a shot was taken at Irradiated Solids Laboratory at Ecole Polytechnique.

IV. CONCLUSION

In this part, we are interested in the deposition of a layer of thin polysiloxanes at the surface of nanoparticles from solutions alkoxysilanes. A low layer thickness is necessary for application in biology, in order not to work with objects of too large size, which would disturb this biological system studied. After discussing the parameters to be controlled during the deposition reaction, we have adapted this method to coating of Y1-xEuxVO4 particles with a layer of unfunctionalized polysiloxanes. The deposited layer has a thickness of about 10 nm, with slow kinetics. This thickness could not be reduced by the experiments envisaged. We then modified the operating conditions in order to deposit on the surface nanoparticles a thinner layer. We then used functionalized trialkoxysilanes, and worked under conditions accelerating the kinetics of condensation of trialkoxysilanes. Under such conditions, the amount of trialkoxysilanes deposited on the surface of the particles is much lower, of the order of a few monolayers. Thus, an in-depth study of the characterization of the functionalization with glycidoxy propyl tri methoxy silane has shown that 8 functions are grafted per nm2.

In the case of functionalization with amino propyl tri ethoxy silane, the deposit was more efficient (23 to 53 amino propyl tri ethoxy silane / nm2), and led to the formation of a layer 1 to 3 nm thick. We have therefore shown through this work that it is possible to functionalize the nanoparticles with guanidine retaining a colloidal state. The modification of the particle surface is confirmed by surface potential measurements. However, we do not yet have a precise measurement of the number of guanidine deposited by nanoparticle.

Electrophysiology measurements have shown that these functionalized nanoparticles with guanidine have a blocking action on the potential-dependent sodium channels. Moreover, fluorescence imaging shows that the nanoparticles react exclusively with sodium channels.

The nanoparticles functionalized with guanidine therefore form a mime of toxin, reacting specifically with potential-dependent sodium channels by blocking their activity. The localization of sodium channels in cardiomyocytes by fluorescence of nanoparticles attached to these channels is then possible.

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