three steps mentioned, the second one is generally not well-controlled and takes a length of time (from 24 h to weeks depending on the targeted thickness) before a silica shell becomes thick enough to stabilize the particles in alcohol for the subsequent and extensive growth of silica.

There is a need to provide method for preparing a SERS particle that overcomes, or at least ameliorates, one or more of the disadvantages described above.

Summary

The present disclosure provides ~~According to a first aspect, there is provided~~ a method of preparing a surface enhanced Raman spectroscopy (SERS) particle comprising the step of encapsulating a plurality of Raman molecules on the surface of a metallic core with a biocompatible protective shell at an elevated temperature selected to decrease the encapsulation time more than one-fold relative to an encapsulation performed at 20°C.

In a first aspect, there is provided a method of preparing a surface enhanced Raman spectroscopy (SERS) particle comprising the steps of: forming a core-shell particle by encapsulating a plurality of Raman molecules on the surface of a metallic core with a biocompatible protective shell at an elevated temperature from 30°C to 95°C; and increasing the thickness of said biocompatible protective shell by adding an aqueous solution of a coating precursor under alkaline conditions to said core-shell particle.

Advantageously, the disclosed process, due to the use of an encapsulation temperature of at least 30°C, may result in the encapsulation of the Raman molecules by the biocompatible protective shell in a shorter period of time as compared to a process which was carried out at room temperature, which is typically carried out at a temperature of about 20°C to about 25°C. Advantageously, this may aid in substantially preventing the dissociation of the Raman molecules from the particle.

Even more advantageously, the use of the higher encapsulation temperature may result in a particle with an enhanced SERS intensity as compared to another particle having a shell of the same thickness but when made at room temperature.

The process may further comprise the step of increasing the thickness of the shell. The increasing step

may comprise the step of adding an aqueous solution of a coating precursor under alkaline conditions. Advantageously, the use of an aqueous solution during the increasing step may result in a particle with enhanced SERS intensity as compared to a prior art process which uses an alcoholic solution to obtain the shell on the particle. Accordingly, the increasing step may optionally exclude the use of an alcohol.

According to a second aspect, there is provided ~~The present disclosure provides~~ a particle prepared from the method as disclosed above~~of any one of claims 1 to 20~~ comprising a metallic core having a plurality of Raman molecules extending from the surface of the metallic core and a biocompatible protective shell encapsulating the Raman molecules.

According to an embodiment ~~second aspect~~, there is provided a particle prepared from the method as disclosed above ~~of any one of claims 1 to 20~~ comprising a metallic core having a plurality of Raman molecules extending from the surface of the metallic core and a biocompatible protective shell encapsulating the Raman molecules, wherein said particle has a Surface-Enhanced Raman Scattering (SERS) signal that is stable for at least one week.

Definitions

The following words and terms used herein shall have the meaning indicated:

The term "nanoparticle", as used herein relates to the average dimension of a nanoparticle having a size of less than about 1000 nm, particularly less than about 500 nm, more particularly less than about 100 nm. The average dimension may be between about 10 nm to about 100 nm. The nanoparticles may not be exactly spherical and the dimension of the nanoparticle may refer to the equivalent diameter of the nanoparticles relative to a spherical nanoparticle.

Claims

1. A method of preparing a surface enhanced Raman spectroscopy (SERS) particle comprising the steps of: forming a core-shell particle by encapsulating a plurality of Raman molecules on the surface of a metallic core with a biocompatible protective shell at an elevated temperature from 30°C to 95°C ~~selected to decrease the encapsulation time more than one-fold relative to an encapsulation performed at 20°C~~; and increasing the thickness of said biocompatible protective shell by adding an aqueous solution of a coating precursor under alkaline conditions to said core-shell particle.

2. The method as claimed in claim 1, wherein said encapsulating step comprises the step of adding said metallic core to a solution comprising said Raman molecules, an organo coupling agent and a silica precursor ~~under conditions to cause said Raman molecules to extend from the surface of said metallic core~~.

3. The method as claimed in claim 2, wherein said shell comprises silica.

4. The method as claimed in claim 2 or 3, wherein said organo coupling agent comprises amino functional groups and hydroxyl functional groups.

5. The method as claimed in claim ~~4~~3, wherein said hydroxyl functional groups adsorbs said Raman molecules on the surface of said metallic core and cross-links with said silica precursor to form said silica shell.

6. The method as claimed in any one of the preceding claims, wherein said elevated temperature is selected from the group consisting of ~~30°C to 95°C,~~ 30°C to 40°C, 30°C to 50°C, 30°C to 60°C, 30°C to 70°C, 30°C to

80°C, 30°C to 90°C, 40°C to 95°C, 50°C to 95°C, 60°C to 95°C, 70°C to 95°C, 80°C to 95°C and 90°C to 95°C.

~~7. The method as claimed in any one of the preceding claims, wherein the encapsulation time is decreased at least two-fold, at least three-fold, at least four-fold, at least five-fold, at least six-fold, at least seven-fold, at least eight-fold, at least nine-fold, at least ten-fold, at least eleven-fold or at least twelve-fold, relative to an encapsulation performed at 20°C.~~

~~8.~~7. The method as claimed in any one of the preceding claims, wherein said encapsulating step is undertaken for a period of time from 4 hours to 45 hours.

~~9. The method as claimed in any one of the preceding claims, further comprising the step of increasing the thickness of said silica shell.~~

~~10. The method as claimed in claim 9, wherein said increasing step comprises the step of adding an aqueous solution of a coating precursor under alkaline conditions.~~

~~11.~~8. The method as claimed in claim ~~10~~1, wherein said aqueous solution further comprises a catalyst selected from the group consisting of ammonia, 2-aminoethanethiol, ethanolamine, 2-(dimethylamino)ethanethiol, 2-(ethylthio)ethylamine and propylamine.

~~12.~~9. The method as claimed in claim ~~10 or claim 11~~1, wherein said aqueous solution is substantially free of an alcohol.

~~13.~~10. The method as claimed in ~~any one of~~ claim~~s~~ ~~10 to 12~~1, wherein said coating precursor is selected from a silane compound.

~~14.~~11. The method as claimed in ~~any one of~~ claim~~s~~ ~~10 to 13~~1, wherein said alkaline conditions is selected from a pH in the range of 7 to 10.

~~15.~~12. The method as claimed in ~~any one of~~ claim~~s~~ ~~10 to 14~~1, wherein said increasing step is undertaken for a period of time from at least 2 hours.

~~16.~~13. The method as claimed in any one of the preceding claims, wherein said metallic core comprises a transition metal.

~~17.~~14. The method as claimed in any one of the preceding claims, wherein said metallic core has a cross-sectional diameter selected from 50 to 1000 nm.

~~18.~~15. The method as claimed in any one of the preceding claims, wherein said Raman molecule is selected from the group consisting of a near infrared (NIR)-SERS active organic dye which belongs to the tricarbocyanine library (CyNAMLA), 4-(4-Aminophenylazo)phenylarsonic acid monosodium salt, arsenazo I, basic fuchsin, Chicago sky blue, direct red 81, disperse orange 3, HABA (2-(4-hydroxyphenylazo)-benzoic acid), erythrosin B, trypan blue, ponceau S, ponceau SS, 3,3'-diethylthiatricarbocyanine, 1,5-difluoro-2,4-dinitrobenzene, cresyl violet, 2-naphthalenethiol, crystal violet, pyrazole, p-dimethylaminoazobenzene and mixtures thereof.

~~19.~~16. The method as claimed in ~~any one of~~ claim~~s~~ ~~9 to~~ 1~~8~~, wherein the thickness of said silica shell before said increasing step is selected from 2 nm to 10 nm.

~~20.~~17. The method as claimed in ~~any one of~~ claim~~s~~ ~~9 to~~ 1~~9~~, wherein the thickness of said silica layer after said increasing step is selected from 10 nm to 1100 nm.

~~21.~~18. A particle prepared from the method of any one of claims 1 to 17~~20~~ comprising a metallic core having a plurality of Raman molecules extending from the surface of the metallic core and a biocompatible protective shell encapsulating the Raman molecules~~, wherein said particle has a Surface Enhanced Raman Scattering (SERS) signal that is stable for at least one week~~.

~~22.~~19. The particle as claimed in claim ~~21~~18, wherein said biocompatiable protective shell comprises silica.

~~23.~~20. The particle as claimed in claim ~~22~~19, wherein said silica shell has a thickness selected from 2 nm to 1100 nm.

~~24.~~21. The particle as claimed in claim ~~21~~18 or ~~23~~19, wherein said metallic core comprises a transition metal.

~~25.~~22. The particle as claimed in any one of claims ~~21~~18 to ~~24~~ 21, wherein said metallic core has a cross-sectional diameter selected from 60 to 1000 nm.

~~26.~~23. The particle as claimed in any one of claims ~~21~~18 to ~~25~~22, wherein said Raman molecule is selected from the group consisting of a NIR-SERS active organic dye which belongs to the tricarbocyanine library (CyNAMLA), 4-(4-Aminophenylazo)phenylarsonic acid monosodium salt,