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 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, wherein said aqueous solution is substantially free of an alcohol.

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

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; 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, wherein said aqueous solution is substantially free of an alcohol.

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.

3. The method as claimed in claim ~~2~~1, 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, 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 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 said encapsulating step is undertaken for a period of time from 4 hours to 45 hours.

8. The method as claimed in claim 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.

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

~~10.~~9. The method as claimed in claim 1, wherein said coating precursor is selected from a silane compound.

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

~~12.~~11. The method as claimed in claim 1, wherein said increasing step is undertaken for a period of time from at least 2 hours.

~~13.~~12. The method as claimed in any one of the preceding claims, wherein said metallic core comprises a transition metal selected from the group consisting of silver, gold, platinum and copper.

~~14.~~13. 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.

~~15.~~14. 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.

~~16.~~15. The method as claimed in claim 1, wherein the thickness of said silica shell before said increasing step is selected from 2 nm to 10 nm.

~~17.~~16. The method as claimed in claim 1, wherein the thickness of said silica layer after said increasing step is selected from 10 nm to 1100 nm.

~~18.~~17. A particle prepared from the method of any one of claims 1 to ~~17~~ 16 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.

~~19.~~18. The particle as claimed in claim ~~18~~17, wherein said biocompatiable protective shell comprises silica.

~~20.~~19. The particle as claimed in claim ~~19~~18, wherein said silica shell has a thickness selected from 2 nm to 1100 nm.

~~21.~~20. The particle as claimed in claim ~~18~~19 ~~or19~~, wherein said metallic core comprises a transition metal selected from the group consisting of silver, gold, platinum and copper.

~~22.~~21. The particle as claimed in any one of claims ~~18~~ 17 to ~~21~~20, wherein said metallic core has a cross-sectional diameter selected from 60 to 1000 nm.

~~23.~~22. The particle as claimed in any one of claims ~~18~~ 17 to ~~22~~21, 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,