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Catherine Gomez, Gauthier Hallot, Alexandra Pastor, Sophie Laurent, Emilie Brun, et al.. Metallic bismuth nanoparticles: Towards a robust, productive and ultrasound assisted synthesis from batch to flow-continuous chemistry. Ultrasonics Sonochemistry, 2019, 56, pp.167-173. 10.1016/j.ultsonch.2019.04.012 . hal-02310980

HAL Id: hal-02310980
https://cnam.hal.science/hal-02310980

Submitted on 22 Oct 2021

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Version of Record: https://www.sciencedirect.com/science/article/pii/S1350417718314809
Manuscript_c4bd9aa1d2064631502f2967cba6876a

Metallic bismuth nanoparticles: towards a robust, productive and ultrasound assisted synthesis from batch to flow-continuous chemistry

Catherine Gomez,*[1] Gauthier Hallot,[1] Alexandra Pastor,[1] Sophie Laurent,[2] Emilie Brun,[3] Cécile Sicard-Roselli[3] and Marc Port*[1]

[1]Laboratoire de Génomique, Bioinformatique et Chimie Moléculaire (EA 7528), Equipe Chimie Moléculaire, Conservatoire National des Arts et Métiers (Cnam), HESAM Université, 2 rue Conté, 75003 Paris, France.

[2]Laboratoire de RMN et d'Imagerie Moléculaire, Université de Mons, 19 avenue Maistriau, B-7000 Mons, Belgique.

[3]Laboratoire de Chimie Physique, CNRS UMR 8000, Université Paris-Saclay, 91405 Orsay Cedex, France.

E-mail corresponding author: catherine.gomez@lecnam.net

Abstract

Bismuth is a highly biocompatible and inexpensive metal with a high atomic number, which confers an important X-rays opacity. While bismuth oxide or bismuth sulphide have been extensively studied in imaging, little is known about metallic bismuth nanoparticles. The latter are more attractive for X-rays imaging because they contain neither oxygen nor sulfur, so that a high amount of metal atoms is contained within the nanoparticles. We report here a robust, efficient and green ultrasound assisted synthesis to obtain metallic bismuth NPs. The procedure, which has been optimized to get a reproducible synthesis, will also tend to minimize chemical hazards to health and environment. By applying the green chemistry principles, several experimental parameters have been studied such as reaction time, reactants stoichiometry, temperature, starting material quantities and purification steps number. Two energy delivery system (classical heating and sonication) were compared. ***The production of small metallic bismuth NPs on a large scale by flow chemistry coupled to sonication was showed for the first time***. These optimizations of the process were completed by a comparison of two purification methods (centrifugation and ultrafiltration) to isolate purified thin black powders of D-glucose-coated bismuth NPs. Several analytical

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techniques were used to characterize products (structures, sizes and morphology) such as Fourier Transform InfraRed (FT-IR) spectroscopy, Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM), Energy-dispersive X-ray spectrometry (EDX) and X-Ray Diffraction (XRD). All these analyses corroborated well with the structure of metallic bismuth NPs coated with a D-glucose shell.

Keywords : Nanoparticles, Green Chemistry, Bismuth, Robust process, D-glucose, Ultrasound assisted synthesis, Flow chemistry, Productivity.

1. Introduction

Bismuth, which is a diamagnetic semimetal, shows several properties such as high magnetoresistance, thermal conductivity and high anisotropic electronic behavior. This element has a high atomic number (Z = 83) which confers an important X-rays opacity (high absorption) [1] and shows a good biological tolerance *in vitro* evaluated primarily by cell viability experiments [2].

Bismuth nanoparticles (NPs) have gathered increased interest for X-rays imaging over the past few years. While bismuth oxide (Bi_2O_3) [3] or bismuth sulphide (Bi_2S_3) [4] were studied extensively as X-rays contrast agents (XCA), little is known about metallic bismuth NPs. To obtain optimal XCA, a high quantity of metal atoms must be contained inside the NPs. Yet the drawback of Bi_2O_3 or Bi_2S_3 is the lower concentration of bismuth atoms per particle which limits X-rays imaging sensitivity. Moreover, hydrolysis of Bi_2S_3 could be problematic because hydrogen sulphide (H_2S), a toxic gas, can be generated *in vivo* under endogenous acidic conditions [5]. To counteract these drawbacks, the use of metallic bismuth NPs should be preferred.

Recently, we have reviewed the different published syntheses of metallic bismuth NPs [6]. Most syntheses of metallic bismuth use a bottom-up approach. In this kind of synthesis, bismuth (0) is obtained by a reduction from bismuth (III) or more rarely bismuth (V) in presence of a capping agent. Several reductive conditions are described with a wide variety of reductant (sodium borohydride [7], hydrazine hydrate [8], sodium hypophosphite [9], sodium hydride or ascorbic acid) associated to different kind of solvent (water or organic solvents such as THF [10], DMF [11], ethylene glycol or DMSO). A great variety of capping agents such as D-glucose polymer dextran [7a], starch [7b] or sodium oleate [8a-9] were also used to control the

growth of bismuth nuclei and to stabilize these metallic bismuth NPs after the reduction step. These syntheses used quite different temperature conditions (from ambient temperature up to 350°C). This review of the literature shows that most of the reaction conditions used to obtain metallic bismuth NPs are poorly compatible with green chemistry criteria applied to nanoparticles [6].

The synthesis conditions probably the most compatible with the principles of green chemistry applied to NPs have been proposed by Brown et al. who produced metallic bismuth NPs coated by hydrophilic moieties [2]. Their strategy uses environmental benign materials from renewable feedstock such as biocompatible solvent 1,2-propanediol (PPD) [12] and D-glucose as capping agent. Moreover, they demonstrated *in vitro* biocompatibility of their metallic bismuth NPs.

To minimize chemical hazards to health and environment [13], the complete reduction of bismuth salt has been ***optimized by sonochemistry coupled to continuous flow to produce metallic bismuth NPs. The development of a new greener fully optimized protocol has allowed to*** :

1) decrease the quantities of D-glucose and therefore reduce waste
2) optimize the energy delivery system by using sonochemistry
3) completely reduce the bismuth salt
4) optimize the purification step and minimize time consuming process
5) improve the productivity. Indeed, this sonochemical protocol was extended in a large scale by transposing optimized conditions obtained in batch to continuous flow.

This new continuous process coupled to sonication applied to metallic bismuth NPs synthesis is simple reliable, productive and allows the control of their size, shape and distribution. To our knowledge, very little research have described production of metallic or semi-conductor NPs using sonication coupled to continuous flow process [14] and no synthesis of metallic bismuth NPs has described the use of this technology [6].

The main parameter used to follow our optimization process was to measure the NPs size by dynamic light scattering (DLS) in water. We choose to express hydrodynamic diameters in number. Then, the metallic bismuth NPs obtained in optimized

conditions were further characterized by additional techniques such as TEM, FT-IR, XRD and EDX.

2. Experimental Section

2.1. Reagents.

Bismuth nitrate pentahydrate (Acros, 98%), borane morpholine complex (Acros, 97%), D-glucose (Sigma, 99,5%), 1,2-propanediol (Acros, 99%). All solutions were prepared using fresh, distillated H_2O.

2.2. Synthesis of metallic bismuth NPs.

In a 25 mL two necks round bottom flask with a thermometer, D-glucose (10 eq, 2.1 mmol) dissolved in 1,2-propanediol (PPD) (2 mL) was introduced under argon. To this mixture, was added bismuth nitrate pentahydrate $Bi(NO_3)_3$ (100 mg, 0.21 mmol) dissolved in PPD (1 mL) then a solution of borane morpholine (3 eq, 0.62 mmol) in PPD (2 mL). The reaction was quickly stirred by magnetic stirring for 1 or 10 min and heated in oil bath at 80°C. NPs were formed after a few minutes and the mixture became black. The crude was then poured into water (5 mL) and purification by centrifugation (Heraeus Primo centrifuges RCF) was performed. After three centrifugations at 4000 rpm (2.585g) for 90 min, purified NPs dispersed in water by sonication (5 min, Sonoclean bath 3L, 35 kHz, 80-160W) were lyophilized and characterized by DLS.

2.3. Synthesis of bismuth NPs under sonication (Table 1, entry 7, 8 and 9).

In a 25 mL two necks round bottom flask with a thermometer, D-glucose (10 eq, 2.1 mmol) dissolved in 1,2-propanediol (PPD) (2 mL) was introduced under argon. To this mixture, was added bismuth nitrate pentahydrate $Bi(NO_3)_3$ (100 mg, 0.21 mmol) dissolved in PPD (1 mL) then a solution of borane morpholine (3 eq, 0.62 mmol) in PPD (2 mL). The reaction was quickly stirred by sonication (Sonopuls HD2070, Bandelin, the highest ultrasound frequency 20 kHz, power 40%, 70W, Ø 3 mm, 9 cycles (pulsed mode 0.9s on/0.1s off)). NPs were formed after a few minutes and the mixture became black. The crude was then poured into water (5 mL) and purification by ultrafiltration (filtration membrane of 5000 MWCO) was performed. After three

water washings (3 x 40 mL), purified NPs dispersed in water by sonication were lyophilized and characterized by DLS.

2.4. Synthesis of bismuth NPs by flow chemistry under sonication (Table 2, entry 2)

In a 100 mL round bottom flask, D-glucose (10 eq, 21 mmol) dissolved in 1,2-propanediol (PPD) (20 mL) was introduced under argon. To this mixture, was added bismuth nitrate pentahydrate $Bi(NO_3)_3$ (1 g, 2.1 mmol) dissolved in PPD (10 mL) then a solution of borane morpholine (3 eq, 6.2 mmol) in PPD (20 mL). The solution was pumped through the reactor via a HPLC pump (Waters, 600 controller). The flow reactor, made of Teflon tubing with an outer diameter of 0.32 cm (1/8), an inner diameter of 2.4 mm and furnished with a flow regulator (1.5 mL/min), was immersed in a sonication bath (Bandelin electronic, the highest ultrasound frequency 35 kHz, 240W) at 60°C. Residence time of about 5 min corresponds to flow rates of 1,5 mL/min. The hot fluid was cooled in the tubing and collected in a flask. The crude was then purified by ultrafiltration (filtration membrane of 5000 MWCO). After three water washings (3 x 40 mL), purified NPs dispersed in water by sonication were characterized by DLS.

2.5. Characterisation of bismuth nanomaterials.

NPs were analyzed by Fourier Transform InfraRed (FT-IR) spectroscopy and compared to starting material on a Perkin Elmer Spectrum II equipped with a diffuse reflectance accessory. 2mg of nanoparticles were mixed with 300 mg of KBr. The spectra were recorded with a resolution of 4 cm^{-1} and with 64 scans. Dynamic Light Scattering (DLS) measurements were performed on a Malvern ZetaSizer ZEN3600 instrument equipped with a 633 nm laser (scattering angle 175°) at 25°C on a bismuth NPs solution (1 mM) diluted in water (RI 1.33, viscosity 0.8872) and sonicated before analysis. Three replicate measurements were performed by analysis in a cuvette ZEN0118 (200 µl). An instrumental algorithm was used to supply the hydrodynamic diameters as number distributions (bismuth RI 2.145, absorption 2.988). The measurements were presented with the average size of NPs ± standard deviation. Images were taken by Transmission Electron Microscopy (TEM) on Philips CM120

transmission electron microscope operating at 80 kV. Microscopy analyses were performed as follows: 2 µL droplets of the colloidal dispersion were cast onto formvar/carbon-coated copper grids (400 mesh) for a few minutes. From the TEM images, the bismuth NPs diameter distribution was determined from recorded images with ImageJ software version 1.48 (at least 300 counted particles). The measurements were presented with the average size of NPs ± standard deviation. The absorption spectra of irradiated solutions were measured by an UV-Vis spectrophotometer (Genesys 10 UV-Vis scanning). The concentration of bismuth (III) nitrate pentahydrate was determined by complexation method using the dithizone [15]. The absorption peak of [Bi(dithizone)$_3$] was observed at 468 nm. The rhombohedral crystallinity was determined by using the X-ray Diffractometer (XRD: D5000 Siemens diffractometer) equipped with Cu K_α as X-ray radiation ($\lambda = 0.15406$ nm). Diffractograms were interpreted using the Debye-Sherrer formula (D5000 Siemens Data Viewer software) to estimate the rhombohedral structure of bismuth NPs. The scattering intensities were measured over an angular range of $20° < 2\Theta < 80°$ for all samples. One measurement was recorded every 0.05° during 25 seconds. The measurements were recorded at room temperature. The elementary analyses were performed on transmission electron microscope (120 kV) equipped with an energy-dispersive X-ray (EDX) detector (SamX).

3. Results and discussion

As mentioned before, we decided to follow the known procedure described initially by Brown et al., using borane morpholine as reducing agent and D-glucose as capping agent and PPD as solvent.

To produce bismuth NPs according to Brown's protocol, a solution of bismuth (III) nitrate pentahydrate in PPD was mixed with D-glucose partially dissolved in PPD. Bismuth (III) was reduced in bismuth (0) by using borane morpholine, a mild reducing agent, dissolved in PPD and the reaction was heated at 80°C during 60 s. Several successive steps of purification were then performed: centrifugation, sonication, dialysis and filtration.

In all our study, we use the minimum stoichiometric quantity of borane morpholine (3 equivalents relative to bismuth). Borane morpholine is essential to reduce the bismuth salt otherwise no nanoparticles were synthesized which means that in these conditions D-glucose is not an efficient reducer [16].

Like the initial conditions of Brown's experiment, 300 equivalents (relative to bismuth) of D-glucose and a magnetic stirring were tested. In these conditions, reaction mixture was heterogeneous (incomplete solubility of D-glucose in PPD at C=3.5M). Reaction time was enough difficult to control (60 s before quenching by pouring the mixture on ice water) that could explain the high hydrodynamic diameter obtained in our hands around 300 nm.

In order to better identify the key parameters of this reaction, several experiments were conducted (Table 1). To avoid this insolubility constraint (which is a main drawback to consider a synthesis using continuous flow) and to minimize the quantities of reactant in a green chemistry approach, D-glucose stoichiometry was reduced to 100 and 10 equivalents (Table 1, entry 1 and 2). Interestingly, when 10 equivalents of D-glucose (totally soluble in PPD at C=1.0M) were introduced, the hydrodynamic size of bismuth NPs decreased to 141 ± 91 nm in number. The reduction of D-glucose amount is essential to develop a process in a large scale according to green chemistry.

Table 1. Optimization of D-glucose quantities and reaction time by using magnetic stirring and sonication

Entry	D-Glucose (eq)	Activation	Purification	Time (min)	Hydrodynamic diameter nm (DLS) (Number)
1	100	heating	centrifugation	1	322 ± 18
2	10	heating	centrifugation	1	141 ± 91
3	10[a]	heating	centrifugation	1	227 ± 155
4	10[b] (**Sorbitol**)	heating	centrifugation	1	256 ± 61
5	10	heating	centrifugation	10	75 ± 32
6 (reproductibility)	10	heating	centrifugation	10	72 ± 30

7	10	sonication[c]	ultrafiltration	10	77 ± 34
8 (reproductibility)	10	sonication	ultrafiltration	10	80 ± 37
9 (reproductibility)	10	sonication	ultrafiltration	10	70 ± 49

[a] Modification of the order for reactants introduction.
[b] Sorbitol in place of D-glucose.
[c] Sonication conditions (0.9s on/0.1s off : 9 cycles)

Then we modified the order of introduction of reactants. Bismuth nitrate pentahydrate solution followed by borane morpholine solution and D-glucose (10 eq.) were successively added. The size measurement of NPs was quite similar (227 ± 155 nm in number) whatever the addition order (Table 1, entry 3). Therefore, no change was effected for reactants introduction in the following experiments. As borane morpholine could also reduce D-glucose into sorbitol, the same procedure was used with sorbitol (10 eq.) in place of D-glucose. We obtained bismuth NPs with a hydrodynamic diameter of 256 ± 61 nm in number (Table 1, entry 4) whereas Brown et al. did not observed formation of bismuth NPs at all with sorbitol. This result confirms that D-glucose was not implicated in the reduction step of Bi (III) to Bi (0).

After having studied the influence of D-glucose stoichiometry, we investigated reaction times from 1 to 10 minutes in order to provide more easily reproducible protocols (Table 1, entry 2 and 5). After a few minutes, the mixture became black corresponding to bismuth NPs formation. Interestingly, bismuth NPs size decreased when reaction time increased to 10 minutes, (Table 1, entry 5) allowing to obtain a hydrodynamic diameter enough similar to the one described by Brown et al. (86 ± 35 nm in number). This result was reproduced a second time and a similar size of bismuth NPs was observed (Table 1, entry 6).

We then compared two energy delivery systems: a classical heating system at 80°C and sonication providing a maximum temperature of 40°C in batch (due to our instrumentation). With a reaction time of 10 minutes, the sizes of bismuth NPs were similar by using classical heating or sonication (Table 1, entry 5, 6, 7). Moreover a complete reduction of bismuth (III) nitrate pentahydrate was observed in these sonication conditions (0.9s on/0.1s off : 9 cycles) as shown below in figure 1. Interestingly, sonication at 40 °C allowed the smooth formation of bismuth NPs with an efficient stirring and less thermic energy as we observed a size of bismuth NPs around 77 nm in DLS (Table 1, entry 7). Ultrasound assisted synthesis allowed an

efficient stirring *via* physical effects such as microjets and shockwaves in the solution [17] and has been described as a favorable approach to control the NPs size [18] and their monodispersity.

The reproducibility was tested on three runs to ensure robustness of our protocol, which is a major issue in nanoparticles synthesis [19]. Two further experiments, under sonication in 10 min, provided similar DLS size distributions in number (Table 1, entry 7, 8 and 9). Only the Bi NPs obtained in our best experimental conditions (entry 9, table 1) were measured by TEM (figure 4). The hydrodynamic size measured by DLS (70 ± 49 nm) is greater than the size measured in TEM (5.2 ± 0.5 nm) which indicates an aggregation of Bi NPs in solution.

From a mechanistic point of view, we have verified that the sonication does not induce the phenomenon of reduction of the Bi (III) salt. Indeed no nanoparticles were observed without the introduction of borane morpholine as reducing agent under sonication.

The influence of irradiation cycles on the reduction rate of bismuth (III) nitrate pentahydrate reduction has been also studied by analogy with the work performed on gold NPs [20].

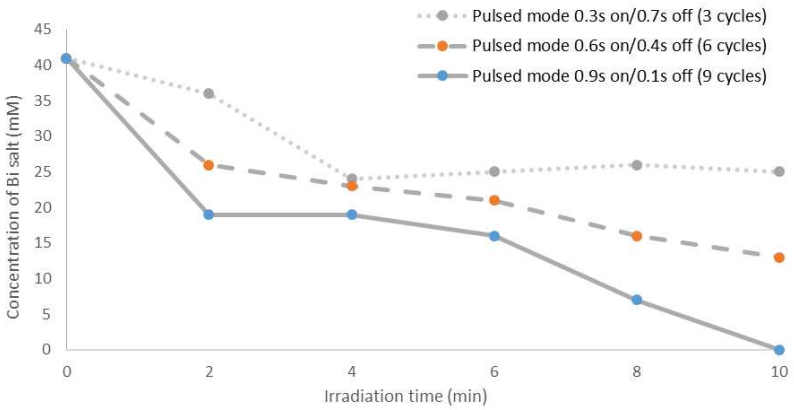


Figure 1. Concentration of Bi (III) according to irradiation time for different pulsed modes

At the beginning (t = 0, Figure 1), the measured Bi (III) concentration (41 mM) was identical to the initial Bi (III) concentration. The rate of bismuth (III) nitrate pentahydrate reduction increased with the number of irradiation cycles (3 cycles < 6 cycles < 9 cycles). So only 16 mM of bismuth (III) nitrate pentahydrate were reduced

with a pulsed mode of 0.3s on/0.6s off (3 cycles) whereas a complete reduction was obtained in 10 min with a pulsed mode of 0.9s on/0.1s off (9 cycles) (Figure 1).

These interesting results reported above in batch were then adapted to continuous flow conditions in order to improve the productivity of metallic bismuth NPs synthesis. The literature shows that continuous flow systems allow in particular to improve the mass and heat transfer as well as reduce the synthesis reaction times [21], which is a major advantage especially in term of reproducibility and scaling-up of metallic NPs synthesis [22].

For that purpose, we designed a millifluidic set up consisting of a HLPC pump with a flow rate of 1.5 mL/min to inject the reactional mixture in Teflon tubing heated by sonication (Figure 2). The reactor of the continuous flow system is inspired from the literature [23] and is made of a Teflon cylinder that holds the Teflon tubing. The synthesized metallic bismuth NPs were cooled at the exit of the cylinder at room temperature and then collected.

Figure 2. a. A photograph of millifluidic system b. A photograph of the reactor with Teflon tubing.



The ultrasound assisted synthesis conditions developed in batch (stoichiometry, concentration) have been preserved to adapt bismuth NPs synthesis to the continuous flow. To compare batch process to continuous flow, hydrodynamic diameters were measured by DLS (Table 2).

Table 2. Comparison of reaction conditions between sonication in batch or continuous flow

Entry	D-Glucose (eq)	Activation	Temperature	Flow rates	Hydrodynamic diameter nm (DLS) (Number)
1	10	batch sonication	40°C	-	70 ± 49
2	10	batch sonication	60°C	-	70 ± 16
3	10	continuous flow / sonication	60°C	1,5 ml/min	45 ± 14

In batch conditions, the increase of temperature from 40°C to 60°C has no significant influence on Bi NPs sizes (Table 2, entry 1 and 2) as similar hydrodynamic diameters were obtained (70 ± 16 nm against 70 ± 49 nm).
In flow conditions coupled to sonication, a minimum temperature of 60 ° C is necessary (at lower temperature, no nanoparticles were observed). Smaller sizes were measured by DLS when using continuous flow coupled to sonication (Table 2, entry 3) in comparison to batch conditions (Table 2, entry 1 and 2). The better control of hydrodynamic particle size and monodispersity is frequently observed in flow system. These results were confirmed by TEM analyses and compared below (Figure 3, A, B). ***As regards of productivity, our millifluidic set up has allowed to produce 1.5g of bismuth NPs per hour against 400mg under sonication in batch.***

After optimization of the different parameters (D-glucose quantities (10 equiv.), time (10 min), heating mode (classical or sonication) and scale up of bismuth NPs synthesis using continuous flow coupled to sonication), we compared two techniques to purify metallic bismuth NPs : centrifugation and ultrafiltration.

First, by reducing the amount of D-glucose used in the reaction, purification steps were simplified. Consequently, less water washings were required to remove excess of reactants or byproducts. Centrifugation is among the most established techniques for isolating NPs from the bulk reaction mixture and for all described synthesis of metallic bismuth NPs, this mode of purification was used [6]. Centrifugation was used for optimization of the reaction (Table 1, entry 1 to 6). However, centrifugation is time and solvent consuming. To eliminate byproducts and excess reagents, we opted for ultrafiltration, which is faster, reliable and safer in comparison to centrifugation [13]. Further, the conductivity of the filtrate was controlled during the ultrafiltration to minimize the water volume and to purify bismuth NPs from any residual salts.

Purification by ultrafiltration gave results in terms of hydrodynamic size comparable to those obtained by centrifugation (Table 1, entry 5 and 7). These results showed an easy, fast and efficient (decrease of reagents quantities, less wastes) purification procedure to isolate bismuth NPs. Therefore ultrafiltration has been chosen to purify bismuth NPs obtained by flow chemistry coupled to sonication.

Further characterizations of bismuth NPs obtained by sonication in batch (Table 1, entry 7) and flow chemistry (Table 2, entry 2) were performed.

Isolated NPs were characterized by Fourier Transform InfraRed (FT-IR) spectroscopy and compared to starting material (Figure 3). Differences between D-glucose alone and bismuth NPs are numerous. A large band centered at 3375 cm^{-1} for OH function on bismuth NPs showed the presence of D-glucose as an essential component of NPs coating. A significant shift from 3250 to 3375 cm^{-1}suggested a high association between D-glucose and surface of bismuth NPs. Others major peaks such as C-C bands (1384 cm^{-1}, 1347 cm^{-1}) and C-O band (1075 cm^{-1}) demonstrated the presence of D-glucose. Nevertheless, bands arising from PPD cannot be totally excluded. Another band at 528 cm^{-1} is also observed related to Bi-O bonds [24] between the bismuth and the D-glucose coating.

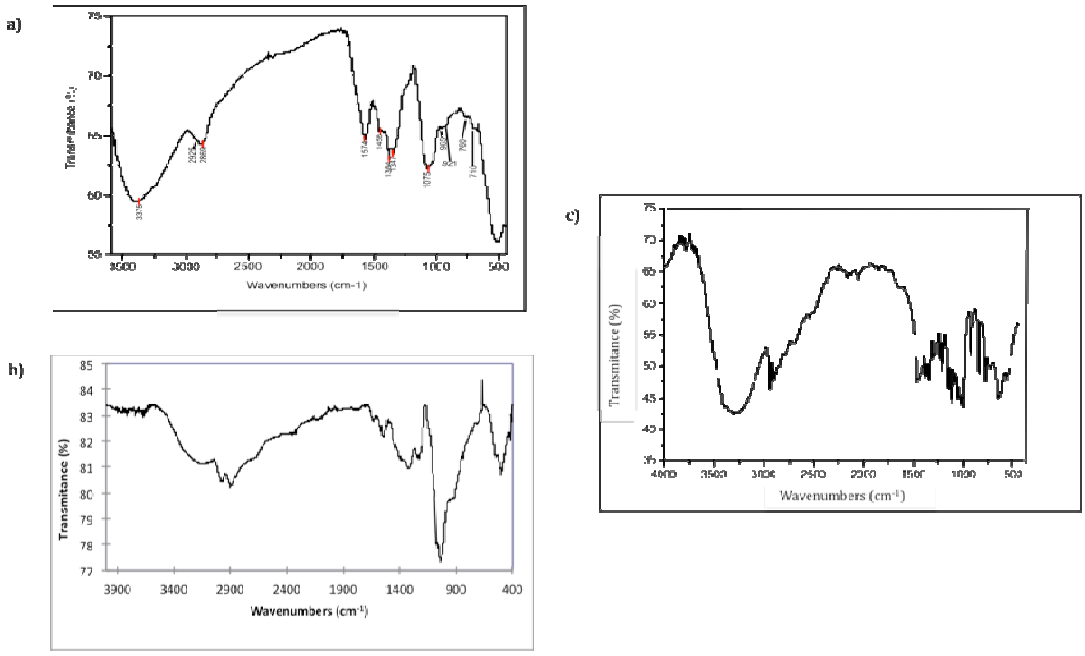


Figure 3. FT-IR spectra of bismuth NPs obtained under sonication in batch (a), bismuth NPs under continuous flow coupled to sonication (b) and D-glucose (c).

Complementary analyses were done by TEM to characterize size and morphology of bismuth NPs (Figure 4). This size distribution was manually measured for 300 NPs per TEM grid. A mean diameter in TEM of 5.2 ± 0.5 nm (Figure 4, A) was measured for bismuth NPs obtained under sonication in batch (Table 1, entries 7-9) and a relatively similar particle size distribution was observed for homogenous bismuth NPs obtained by flow chemistry coupled to sonication (5.8 ± 0.5 nm) (Figure 4, B).

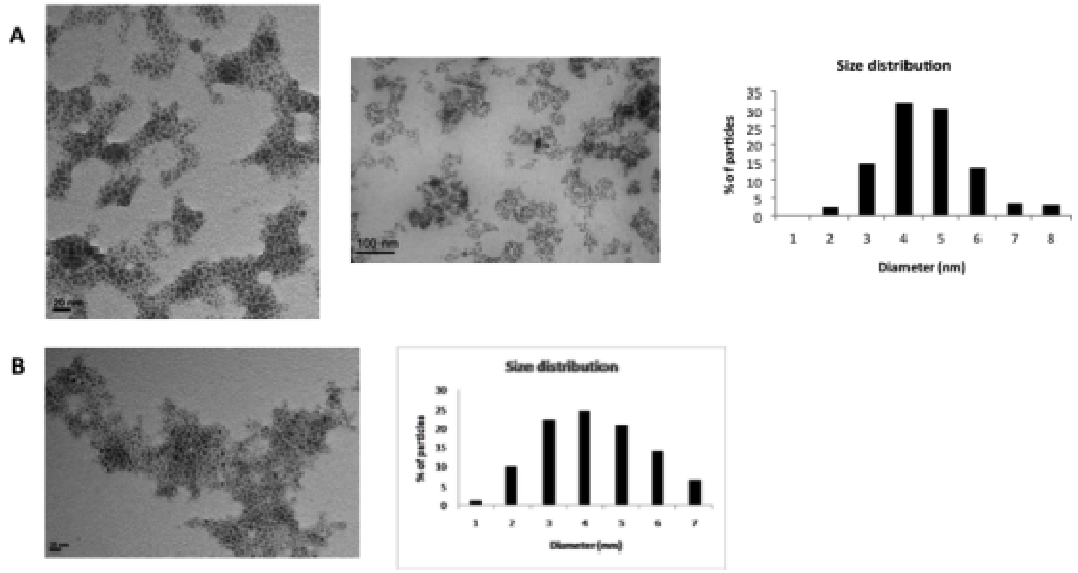


Figure 4. (A) Transmission Electron Microscopy images of synthesized bismuth NPs under sonication in batch and size distribution. (B) Transmission Electron Microscopy images of spherical synthesized bismuth NPs by flow chemistry coupled to sonication and size distribution.

Faceted nanoparticles and few spherical nanoparticles were observed in the samples in batch and continuous flow. The sizes obtained by TEM are much smaller than the hydrodynamic diameters measured by DLS, which shows that the hydrodynamic sizes represent aggregates of bismuth NPs and that the continuous flow process coupled to sonication decreases the size of the aggregates (table 2).

The metallic character of bismuth NPs has been confirmed by XRD analysis and compared with known XRD data for bulk bismuth (JCPDS 85-1329) [25].

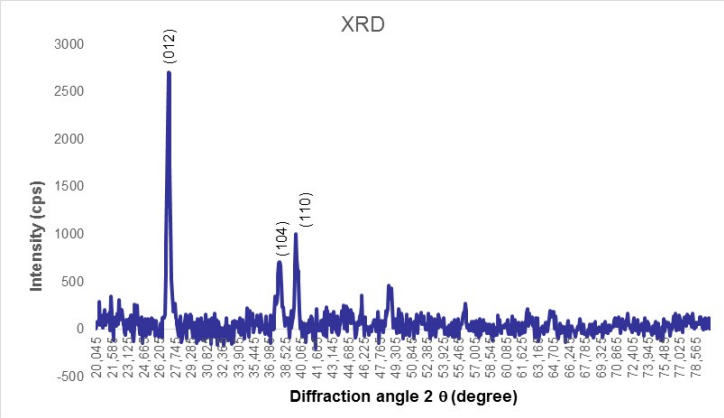


Figure 5. XRD pattern of the synthesized bismuth NPs under sonication.

The XRD peaks at 2θ of 27.12°, 37.97° and 39.58° can be respectively attributed to the (012), (104), (110) crystallographic planes of the bismuth crystal (Figure 5). The diffraction peaks could be indexed to the rhombohedral bismuth phase. The lattice constants were calculated with a = 4.54 Å and c = 11.85 Å, very close to the reported data a = 4.546 Å and c = 11.860 Å (JCPDS 05-0519).

The elementary composition analysis of bismuth NPs was performed by energy-dispersive X-ray analysis (Figure 6).

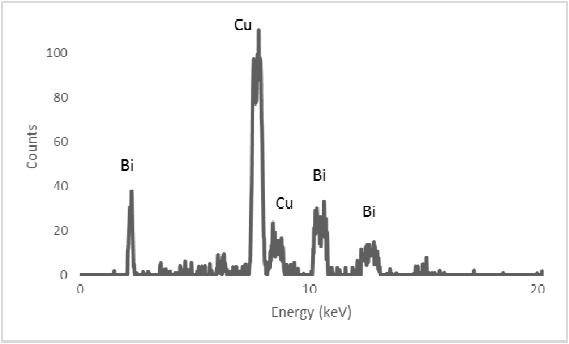


Figure 6. EDX pattern of the synthesized bismuth NPs under sonication.

This analysis demonstrates that bismuth NPs are composed only of bismuth as reported in the literature [9] (the copper peaks result from copper grids used for analysis).

All of the FT-IR, TEM, XRD and EDX analyses confirm the production of D-glucose coated metallic bismuth NPs.

4. Conclusion

To achieve a greener chemistry process to obtain metallic bismuth NPs, synthetic protocol and purification were optimized by minimizing reagents stoichiometry, energy cost, time of purification and reducing wastes. A robust, reproducible and productive process was proposed. Metallic bismuth NPs were synthesized by sonication in batch in 10 min and purified by ultrafiltration to get a reproductive DLS size distribution. For the first time, an experimental device of continuous flow coupled to sonochemistry has been developed to synthesize and produce, in a large scale, metallic bismuth NPs. In addition to improving productivity, this millifluidic system also allows to obtain bismuth NPs of smaller hydrodynamic size compared to the batch process.

Several parameters could be yet improved to provide optimal process in terms of green chemistry: especially replacing morpholine borane by a less harmful reducer and substituting PPD with a greener solvent.
Obtained by a promising synthesis in flow chemistry and a fast purification process, these nanomaterials are interesting for future medicinal applications as XCA.

Acknowledgements

The present work has benefited from the facilities and expertise of the Electron Microscopy facilities of Imagerie-Gif, (http://www.i2bc.paris-saclay.fr/spip.php?article282). This core facility is member of the Infrastructures en Biologie Santé et Agronomie (IBiSA), and is supported by the French national Research Agency under Investments for the Future programs “France-BioImaging”, and the Labex “Saclay Plant Science” (ANR-10-INSB-04-01 and ANR-11-IDEX-0003-02, respectively). We thank Isabelle Billault from the ICMMO Institute (Paris-Saclay University) for her assistance in the FTIR experiments. XRD analyses were performed in the laboratory of Chimie des Interactions Plasma-surface (ChIPS) (Mons University) by Adriano Panepinto.

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