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Scale-up synthesis of iron oxide nanoparticles by microwave-assisted thermal decomposition

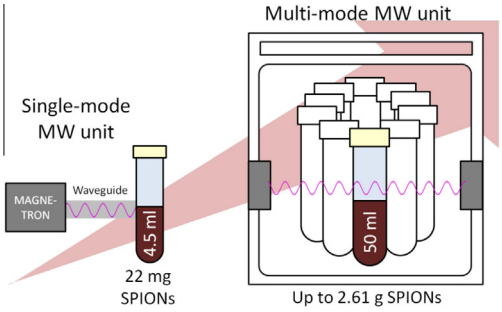
Laura Gonzalez-Moragas [1], Si-Ming Yu [1], Nerea Murillo-Cremaes, Anna Laromaine, Anna Roig *

Institut de Ciència de Materials de Barcelona (ICMAB-CSIC), Campus de la UAB, Bellaterra, Catalonia E-08193, Spain

HIGHLIGHTS

- Scale-up of SPIONs to 3 g/batch with a multi-mode microwave unit is demonstrated.
- SPIONs are dispersible in water, monodisperse with high saturation magnetization.
- Energy and cost-efficient scaled-up microwave-assisted SPIONs synthesis is validated.

GRAPHICAL ABSTRACT



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ABSTRACT

We report the multi-gram production of water-dispersible superparamagnetic iron oxide nanoparticles (SPIONs) by microwave-assisted reaction. A laboratory-scale reaction performed in a single-mode microwave unit (4.5 mL, producing 22 mg of Fe_2O_3) was scaled-up in a multi-mode equipment (up to 500 mL, corresponding to 2.61 g Fe_2O_3). The quality of the final material in terms of size, colloidal stability and magnetic properties, and the yield of the reaction (~80%) were not compromised in the large-scale setup. Hence, these results reinforce the potential of microwave irradiation in industrial laboratories to synthesize high quality nanoparticles readily dispersible in water and in a short time.

1. Introduction

Superparamagnetic iron oxide nanoparticles (SPIONs), due to their ultra small size, excellent magnetic properties, biocompatibility and low toxicity, [1,2] have been extensively studied and used for magnetic resonance imaging (MRI), hyperthermia therapy and drug delivery [3–5]. To date, many methods have been established for the synthesis of SPIONs, including co-precipitation, microemulsion, hydrothermal synthesis, thermal decomposition, and microwave-assisted synthesis [6]. Each of those methods displays advantages as well as some drawbacks, which are detailed in Table 1. In the last few years, microwave-assisted synthesis of SPIONs has attracted considerable interest since it is a facile and fast synthetic route to produce monodisperse nanoparticles with good magnetic properties under moderate temperature, as we recently reported [7,8]. Moreover, considering 1 g of SPIONs, we showed that microwave synthesis

Abbreviations: SPIONs, superparamagnetic iron oxide nanoparticles; NPs, nanoparticles; $Fe(acac)_3$, iron (III) acetylacetonate; Na_3Cit, trisodium citrate dihydrate; MQ, MilliQ water; MW, microwave; RT, room temperature; LS, laboratory-scale; SU, scale-up.

* Corresponding author at: Institut de Ciència de Materials de Barcelona (ICMAB-CSIC), Campus de la UAB, Bellaterra, Catalonia E-08193, Spain. Tel.: +34 935801853x325; fax: +34 935805729.
E-mail address: roig@icmab.es (A. Roig).
URL: http://www.icmab.es/nn (A. Roig).

[1] Equal contribution.

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Table 1
Advantages and drawbacks of the main synthetic routes for SPIONs [6].

Method	Advantages	Drawbacks
Co-precipitation	• Simple • Aqueous media • Large amounts of NPs can be synthesized (grams) • Size and morphology control • Generally performed at RT • Easy surface functionalization	• Broad size distribution • Poor crystallinity • Basic pH is required • Long reaction times (hours)
Microemulsion	• Narrow size range • High crystallinity • Uniform physical properties • Size and morphology control	• Low yield ($\leqslant$3% per mass of microemulsion) • Requires large amounts of organic solvents
Hydrothermal synthesis	• Aqueous media • Size control	• High temperature ($\geqslant$200 °C) • High pressure ($\geqslant$2000 psi) • Special reactors or autoclaves are required
Thermal decomposition	• Narrow size distribution (high monodispersity) • High crystallinity • High yield (~80%) • Size and morphology control	• High temperature (~300 °C) • Long reaction times (hours) • Requires organic solvents • Hydrophobic particles; ligand-exchange is required to transform them into hydrophilic but aggregation may occur. • Safety issues
Microwave-assisted synthesis	• Narrow size distribution (high monodispersity) • High crystallinity • High yield (~80%) • Water dispersible • Short reaction times (minutes) • Moderate temperature (160 ~ 210 °C) • Efficient heating, resulting in low energy consumption • Easy surface functionalization after synthesis	• Requires organic solvents • Limited penetration depth of the microwave

reduced 10 times the energy consumption, and decreased 40% the overall fabrication cost compared to the high temperature thermal decomposition approach [7].

As the number of applications of SPIONs for nanomedicine increases, larger amounts of material at reasonable cost will be in high demand. Microwave-assisted synthesis results in top quality SPIONs, however, the typical reaction vessel volume ranges from 1 to 5 mL leading to yields of less than 20 mg of SPIONs [7]. As an example, the FDA-approved MRI contrast agent Gastromark® requires 52.5 mg Fe per a single adult dose. Therefore, efforts to turn a laboratory milligram-scale synthesis into a gram-scale production are of great value.

Attempts to demonstrate large-scale synthesis of SPIONs have already been published. Co-precipitation was used by Kolen'ko et al. to scale-up the synthesis of SPIONs using $FeCl_3{\cdot}4H_2O$ and $FeCl_3{\cdot}6H_2O$ as iron precursors [9]. However, the yield was relatively low (68%) and the resulting nanoparticles had poor monodispersity (polydispersity was 46%). Ibarra-Sánchez et al. evaluated the high temperature decomposition of $Fe(acac)_3$ in a large scale and found the reaction was sensitive to several conditions; the stirring rate, the stirring periods and the reaction temperature [10]. Unfortunately, SPIONs obtained by thermal decomposition are hydrophobic, and require of a ligand exchange before can be used *in vivo*. Based on the potential applications of SPIONs, the synthetic methods to scale-up should not only be simple, safe, and energy and cost efficient, but also yield water dispersible, biocompatible and high saturation magnetization NPs. All these requirements could be achieved by scaling up a microwave-assisted reaction.

To the best of our knowledge, no previous attempts have been performed on the scale-up of microwave synthesis of SPIONs. Many factors as increased heat loss, changes in absorption, limited penetration depth of the radiation into the reaction medium and the additional reflection of the microwaves, make the scaling-up not straightforward [11]. Based on the scale-up of microwave-assisted organic reactions, two main approaches could be used to scale-up SPIONs production: a flow approach and a batch-type approach [11]. In the flow method, the reaction mixture is pumped in and out of the reaction vessel using a peristaltic pump. Although it avoids the limitations of small vessel volumes and offers complete automatisation, this approach is unsuitable for handling heterogeneous mixtures, viscous liquids and particulate materials. The batch-type approach consists of a MW equipment with a larger cavity than the one used in the previous method where reactions can be performed either in one open large vessel or in multiple sealed vessels. In the open-vessel configuration, standard glassware can be employed (i.e. round-bottom flask) and it is usually attached to a condenser to control any vapours produced [12]. Using this strategy, considerable scale-up can be achieved, but penetration depth of the irradiation and power density can become important issues as the vessel size increases. By contrast, the use of sealed vessels allows carrying out reactions in heterogeneous conditions, in the presence of solvents and under pressure. The limiting factor here, for safety concerns, is the vapour pressure generated by a superheated solvent [11]. Characteristic features of the microwave scale-up approaches are summarised in Table 2. In the last couple of years, a new generation of microwave devices that offer scale-up capabilities in a single large vessel ($\leqslant$1 L) under pressure have been also developed and are commercially available (i.e. Masterwave BTR from Anton-Paar or SYTHwave from Milestone). Despite their great potential in increasing the productivity with minimal reaction optimization requirements, they are not widely implemented in synthetic laboratories compared to routinely used single-mode units or multi-mode systems.

This work aims to demonstrate SPIONs scale-up production in a multi-mode unit for multigram quantity, which is a challenge objective. For this purpose, we evaluate the impact of different microwave-specific factors (equipment, reaction time,