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journal homepage: www.elsevier.com/locate/jmmmAn integrated device for magnetically-driven drug release and *in situ* quantitative measurements: Design, fabrication and testingI.J. Bruvera^a, R. Hernández^b, C. Mijangos^b, G.F. Goya^{a,c,*}^a Aragon Institute of Nanoscience (INA), University of Zaragoza, 50018, Spain^b Instituto de Ciencia y Tecnología de Polímeros, CSIC, Juan Cierva 3, E-28006 Madrid, Spain^c Condensed Matter Physics Department, Science Faculty, University of Zaragoza, 50009, Spain

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ABSTRACT

We have developed a device capable of remote triggering and *in situ* quantification of therapeutic drugs, based on magnetically-responsive hydrogels of poly (*N*-isopropylacrylamide) and alginate (PNiPAAm). The heating efficiency of these hydrogels measured by their specific power absorption (SPA) values showed that the values between 100 and 300 W/g of the material were high enough to reach the lower critical solution temperature (LCST) of the polymeric matrix within few minutes. The drug release through application of AC magnetic fields could be controlled by time-modulated field pulses in order to deliver the desired amount of drug. Using B12 vitamin as a concept drug, the device was calibrated to measure amounts of drug released as small as $25(2) \times 10^{-9}$ g, demonstrating the potential of this device for very precise quantitative control of drug release.

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1. Introduction

Magnetic controlled drug delivery is based on the employment of a magnetic field to trigger on-demand drug release employing magnetic nanoparticles (MNPs) as heating agents [1]. The ability of generating heat on the MNPs is measured by the specific power absorption (SPA), which is the power absorbed per unit mass of magnetic nanoparticles [2,3]. The physical mechanisms of heat generation of the single-domain MNPs under an AC field were first studied by Hergt et al. [4] Some years later, a simple model was developed by Rosensweig [5] based on the magnetic and rotational relaxation for the specific case of single domain magnetic particles dispersed in a liquid matrix. This and other subsequent theoretical models have successfully explained the physical mechanisms by which the energy of the alternating magnetic field is absorbed by an assembly of single-domain MNPs [5–8]. At the frequencies involved in our experiments the power absorption can be described through the relaxation of the magnetic moment induced by thermal fluctuations, known as the Neel–Brown relaxation process. The SPA values expected for single domain MNPs of a given material (*i.e.*, a specific magnetic anisotropy) is known to depend strongly on the average particle size as well as the size distribution [9]. In the specific case of Fe₃O₄ magnetic cores, the

maximum SPA have been reported to be around particle sizes of ≈ 30 nm [10].

To date, a number of magnetic controlled released materials for drug delivery have been reported, many of which are based on the incorporation of magnetic iron oxide nanoparticles on thermo-sensitive polymer hydrogels to give rise to polymer ferrogels. As depicted in Fig. 1, an alternating current (AC) magnetic field can be used to trigger localized heating of a MNP-loaded hydrogel, inducing a volume change in the host polymer matrix and allows diffusion and release of drugs [11–14].

Among thermo-sensitive hydrogels, hydrogels based on poly (*N*-isopropyl acrylamide) (PNiPAAm) and related copolymers are one of the most studied for biomedical applications. PNiPAAm contains hydrophobic groups that provide a lower critical solution temperature (LCST) of ~ 32 °C in water. At room temperature PNiPAAm is relatively hydrophilic and can be highly swollen. When heated above a critical temperature, the PNiPAAm becomes relatively hydrophobic, so the hydrogel collapse [15,16]. In magnetically-loaded PNiPAAm, the temperature rise is obtained, by power absorption of the embedded MNPs, from an externally applied AC field [17].

One of the drawbacks in the employment of PNiPAAm gels for controlled drug release is the slow response to temperature changes which restricts wider applications, such as on–off valves, artificial muscles or drug delivery applications [18]. One strategy to overcome this drawback is the combination of crosslinked PNiPAAm with a natural polymer such as alginate in the form of a semi-interpenetrating polymer network. The resulting material

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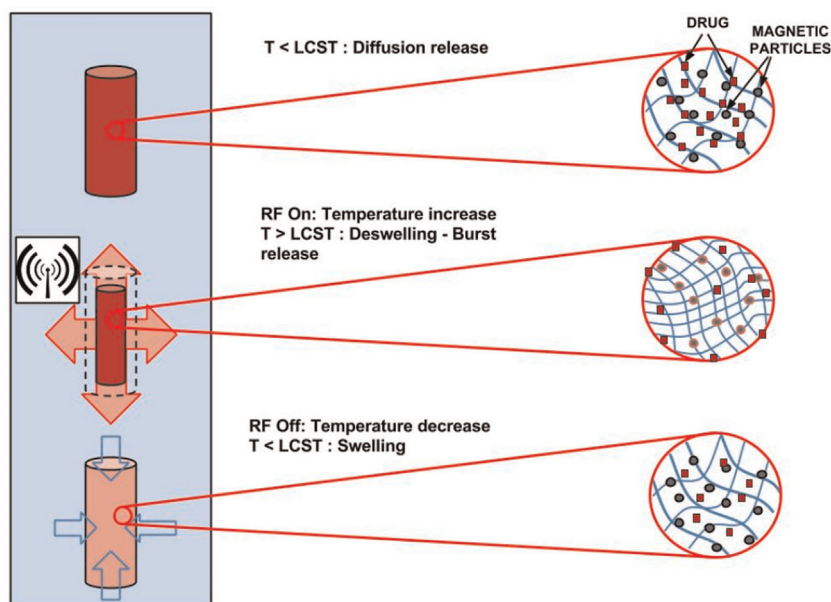


Fig. 1. Schematic drawing of the ON–OFF cycles and their effect on the thermoresponsive nanocomposites of PNiPAAm. The ac magnetic field triggers the heating and drug burst release by the contraction of the ferrogel network when crossing the LCST (lower critical solution temperature).

presents an increased dwelling rate with respect to raw poly(NiPAAm), due to an increased porosity promoted during the reaction of crosslinking of the N-isopropylacrylamide monomer in the presence of alginate [19]. The presence of alginate allows for the *in situ* synthesis of iron oxide MNPs due to the fact that the carboxylic groups in alginate can bind to iron cations [20].

In this work, a proof-of-concept device was designed and constructed in order to test the validity of magnetically loaded semi-interpenetrating polymer networks of alginate and PNiPAAm as materials for magnetically controlled drug release. The device was capable to control the amount of a model drug released (vitamin B12) through a time-controlled magnetic pulse and, after proper calibration, to quantify released vitamin B12 amounts as small as 25(2) ng.

2. Materials and methods

2.1. Materials

The N-Isopropylacrylamide (N-AAm) (Panreac), the initiator potassium persulfate (Fluka), the crosslinker *N,N*-Methylenebisacrylamide (Bis) (Aldrich), and the accelerator *N,N,N',N'*-Tetramethylethylenediamine (TEMED) (Bio-Rad) were used as received. Alginic acid sodium salt from brown algae with a 65–70% guluronic acid and $M_w=100$ –200 kDa according to the manufacturer was purchased from Aldrich and used as received. Alginate stock solutions were prepared by dissolving alginate powder in distilled water to yield 1 g/100 mL solutions. Ferrous chloride ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$), ferric chloride ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) and vitamin B12 were purchased from Aldrich and used as received.

2.2. Preparation and chemical characterization of ferrogels

Semi-interpenetrating (semi-IPN) polymer networks constituted by alginate and PNiPAAm (Alg-PNiPAAm) were obtained by polymerizing 3 g of N-AAm and 0.15 g of Bis in 40 mL of an 1 wt% alginate aqueous solution. Solutions were poured out into Teflon molds having 8 mm diameter and 40 mm length and allowed to react at room temperature for 24 h. Samples obtained

were dialyzed against fresh water during 2 days to remove all the unreacted monomer.

For the *in situ* synthesis of iron oxide MNPs, Alg-PNiPAAm samples were immersed in 200 mL aqueous solution containing 2.1 g $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and 5.8 g $\text{FeCl}_3 \cdot \text{H}_2\text{O}$ under constant N_2 bubbling during 4 h. After that period of time, yellowish gels were obtained that were immersed in a 0.5 M NH_3 (30 wt%) under constant N_2 bubbling during 30 min. The resulting black Alg-PNiPAAm ferrogels were washed with distilled water for 24 h. The procedure of oxidation was repeated three times. Thermogravimetric measurements were performed on dried gels on a Q500 TA Instruments TGA, using a nitrogen stream as the purge gas, at a heating rate of 10 °C/min over the range 40–900 °C. The residual weight obtained at 900 °C obtained for Alg-PNiPAAm ferrogels can be taken as an indication of the iron oxide content in the samples. The total water content, W_t , was calculated from the mass of the hydrated (m_s) and dried (m_{dry}) gels through

$$W_t = \frac{m_s - m_{dry}}{m_{dry}}$$

The iron oxide content determined through TGA measurements was 22 wt% and the water content was found to be 90 wt%. The particle $\langle d \rangle$ size of the iron oxide MNPs was found to be $\langle d \rangle = 20$ nm as determined through transmission electron microscopy combined with small angle-X-ray measurements [21].

2.3. Magnetic characterization of the ferrogels

Magnetization vs. field curves $M(H)$ were performed on a previously dried fraction of the ferrogel having mass 6.5(1) mg, and a control sample (*i.e.* without MNPs) of dry mass 14.2(1) mg. The control sample measurement was used to identify the diamagnetic contribution of the hydrogel matrix. Measurements were performed on a Vibrating Sample Magnetometer (LakeShore 7304) in fields up to $H=1.5$ MA/m at room temperature. Specific power absorption (SPA) measurements were done using a commercial induction heating station (EasyHeat, Ambrell) working at $f=360$ kHz and field amplitudes up to $H=45$ kA/m. The working space was conditioned with an adiabatic sample holder for a measuring volume up to 500 μl . The temperature was measured

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