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Controlling the Burst Effect of a Drug by Introducing Starch in the Structure of Magnetic Polyurethane Microspheres Containing Superparamagnetic Iron Oxide Nanoparticles

M. Mahmoudi[1,*] **and S. Laurent**[2]

Abstract. *The aim of this research is to prepare superparamagnetic polyurethane microspheres using SPIONs. Theophylline was used as a drug and the various stoichiometric ratios of isocyanate/polyol were studied to assess their application as a targeting delivery system. Magnetic polyurethane microspheres containing superparamagnetic iron oxide nanoparticles loaded with theophylline were prepared by the water in oil in water emulsion technique. The ratio of hexamethylenediisocyanate and polyol (ε-polycaprolactone and starch) was modified and the release of theophylline was determined for a period of 20 days. These microspheres were characterized by TEM, SEM, FTIR and magnetometry. The microscopy images show the morphological shape of the superparamagnetic microspheres with an average size of 5 μm. The FTIR and the magnetometry confirmed the presence of superparamagnetic nanoparticles in the microspheres. The release of theophylline was studied and dosed by UV spectrophotometer. With the use of PCL with a low molecular weight or in the presence of starch in the structure of polyurethane, the burst effect of drug is decreased. Finally, a SEM study showed an important degradation of the microspheres after the release process. The use of starch as a polyol caused significant improvement in burst effect of the superparamagnetic polyurethane microspheres.*

Keywords: *Superparamagnetic iron oxide nanoparticles; Polyurethane; Magnetic microspheres; Theophylline.*

INTRODUCTION

Polyurethane, which is a biodegradable polymer, has been employed extensively in various biomedical applications, such as tissue engineering (e.g. skin, cardiovascular and bone), ureteral stents, meniscal reconstruction and drug delivery [1-9]. A distinguishing feature of polyurethane is its great biocompatibility without causing tissue damage or inducing a considerable inflammatory response [10,11]. Furthermore, the decomposition products of polyurethane, which are obtained due to its biodegradability, have been well recognized to be not only non-cytotoxic, but also a supporter for cell growth [12,13]. Biodegradable microparticles have been intensively investigated as controlled release systems for drugs and biomolecules [14]. A major advantage of microparticles and microspheres is the possibility of controlled drug release rate, which is obtained by their degradation rate, as well as the fact that the bioactive molecules are protected from an unfavorable environment [15,16]. In this regard, the drugs/biomolecules should be enclosed within a polyurethane shell via a facile microencapsulation method.

Several groups have investigated polyurethane microspheres containing various drugs [17,18] (e.g. theophylline [19] which is used for the treatment of asthma and chronic bronchitis [20]). Rafienia et al. [6] probed the preparation and characterization of polyurethane microspheres containing theophylline.

Nowadays, multi-functional microspheres with both biocompatible and superparamagnetic properties

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1. *National Cell Bank, Pasteur Institute of Iran, Tehran, P.O. Box 11365-8639, Iran.*
2. *Department of General, Organic, and Biomedical Chemistry, NMR and Molecular Imaging Laboratory, University of Mons, B-7000 Mons, Belgium.*
*. *Corresponding author. E-mail: mahmoudi@biospion.com*

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have received tremendous attention, due to their excellent ability for targeting delivery [21]. The most general method for induction of magnetic properties to the polymeric microspheres is trapping the magnetic nanoparticles in the polymer structure through a polymerization route [22]. Due to their superparamagnetic properties, excellent biocompatibility, controllable shape and size, the most promising candidates are superparamagnetic iron oxide nanoparticles (SPIONs) [23-33].

To our knowledge, magnetic nanoparticles have not been used yet in polyurethane microspheres to increase their ability for targeting purposes; therefore, the purpose of this research is to prepare superparamagnetic polyurethane microspheres using SPIONs. Theophylline was used as a drug and the various stoichiometric ratios of isocyanate/polyol were studied to assess their application as a targeting delivery system. Additionally, the effect of starch (a polysaccharide with alpha-D-glucopyranose links) as a polyol was probed to explore any improvement in burst effect of superparamagnetic polyurethane microspheres.

MATERIALS

Chemicals for SPIONs

Polyvinyl alcohol ($M_W = 30,000 - 40,000$ g/mol) was purchased from Fluka (USA). Iron chloride and sodium hydroxide (NaOH) of analytical grades were supplied by Merck Inc. (Germany) and used without further purification.

Chemicals for Microspheres

Polycaprolactone (PCL; molecular weights of 530 and 2000 g/mol) and polyvinyl pyrrolidone (PVP; molecular weight of 24 000 g/mol) which were used as a polyester polyol and suspension stabilizer, respectively, were obtained from Aldrich (Germany). The isocyanate (Hexamethylenediisocyanate (HMDI)), the chain extending agent (Butanediol (BD)), the polyurethane solvent (acetone) and further polyol (starch) were all acquired from Merck (Germany). Theophylline was obtained from Pharma Chemie Company (Iran).

METHODS

Synthesis of Monodisperse SPIONs

The SPIONs were prepared according to the optimal co-precipitation parameters as reported elsewhere [28]. Typically, solutions were prepared using deionized (DI) water after 30 minutes bubbling with neutral gas (i.e. argon) for de-oxygenation. The iron salts were dissolved in DI water containing 0.5 M HCl where the mole fraction of Fe^{2+} to Fe^{3+} was adjusted to 1:2. The black color magnetite nanoparticles were achieved by dropwise addition of an iron salt solution to a 1.6 M NaOH aqueous solution under an inert atmosphere and vigorous stirring rate for homogenization (with stirring rate of 9000 rpm). The reactions for the formation of magnetite nanoparticles are [28]:

$$\mathrm{Fe^{3+} + 3OH^- \rightarrow Fe(OH)_3}, \tag{1}$$

$$\mathrm{Fe(OH)_3 \rightarrow FeOOH + H_2O}, \tag{2}$$

$$\mathrm{Fe^{2+} + 2OH^- \rightarrow Fe(OH)_2}, \tag{3}$$

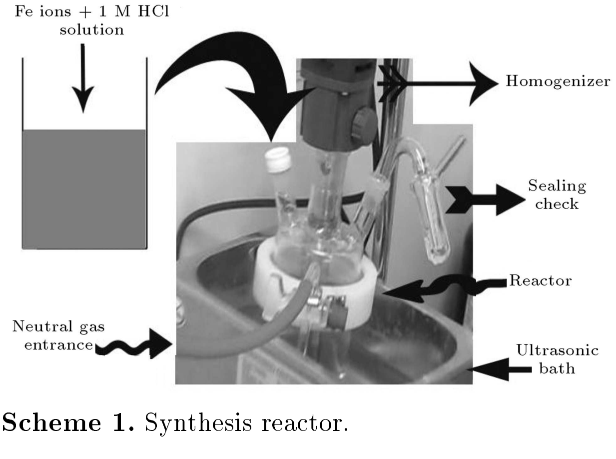
$$\mathrm{2FeOOH + Fe(OH)_2 \rightarrow Fe_3O_4 + 2H_2O}. \tag{4}$$

In order to control mass transfer which may allow particles to combine and build larger polycrystalline particles turbulent flow was created by placing the reaction flask in an ultrasonic bath (the reactor is illustrated in Scheme 1) [28]. After 30 min, the obtained SPIONs were collected via a strong magnet, and washed with DI water several times. Consequently, a PVA solution with a suitable polymer concentration (polymer/iron mass ratio of 2) [32] was added by syringe as a stabilizer, and the reaction mixture was stirred at a constant temperature of 35°C for an additional 30 min. The nanoparticles were collected by magnetic field and washed several times with DI water; the obtained ferrofluid was kept at 4°C for future use.

Preparation of Magnetic Microspheres

Microspheres were achieved via the well-known water in oil in water emulsion technique. Various molar stoichiometries of HMDI, PCL (molecular weight of 530 g/mol), starch and BD were employed, as shown in Table 1.

As seen in Table 1, group A contains PCL only as polyol and group B contains the same amount of



Scheme 1. Synthesis reactor.

Table 1. Molar equivalents of BD and PCL (M_W = 530 g/mol or M_W = 2000 g/mol) for samples A or C and that of BD, starch and PCL (M_W = 530 g/mol or M_W = 2000 g/mol) for samples B or D.

Sample	**A_1** **C_1**	**A_2** **C_2**	**A_3** **C_3**	**A_4** **C_4**	**A_5** **C_5**	**A_6** **C_6**	**A_7** **C_7**	**A_8** **C_8**
PCL	0.5	0.75	1	1.25	1.5	1.75	2	2.5
BD	2.5	2.25	2	1.75	1.5	1.25	1	0.5
Sample	**B_1** **D_1**	**B_2** **D_2**	**B_3** **D_3**	**B_4** **D_4**	**B_5** **D_5**	**B_6** **D_6**	**B_7** **D_7**	**B_8** **D_8**
PCL	0.25	0.375	0.5	0.625	0.75	0.875	1	1.25
Starch	0.25	0.375	0.5	0.625	0.75	0.875	1	1.25
BD	2.5	2.25	2	1.75	1.5	1.25	1	0.5

both polyols (PCL and starch). By repeating the same molar amount of PCL as in groups A and B, but with molecular weight of 2000 g/mol, groups C and D were achieved, respectively. PCL was dried under vacuum at 60°C for 9 hours, dissolved in acetone and mixed with theophylline in a 1 litre glass reactor. HMDI was dissolved in acetone and added dropwise to the reactor. After 1 hour, the SPIONs (iron concentration of 15 mg/ml) were added to the reactor. It is worth noting that the volume of the ferrofluid was 10 times lower than the mixture quantity. Consequently, the chain extender was added to the reactor contents and the reaction mixture was continued for an additional three hours. The total amount of incorporated theophylline in each sample was 5% (w/w) of the glass reactor contents. The mixture was homogenized at 1200 rpm under neutral atmosphere (argon gas) in oil bath and the temperature was fixed at 60°C. In order to prepare the water phase, 2 g of the surfactant (PVP) was dissolved in 200 ml of DI water and transferred to a new reactor with vigorous homogenization rate (10 800 rpm). The obtained pre-polymer (30 cm^3) was added dropwise to the 1% (w/v) solution of PVP in DI water to obtain microspheres. The superparamagnetic microspheres were trapped from the solution using magnetic columns (MACS; A Mini MACS® Separation Unit, Miltenyi Biotec Inc, Germany) and washed several times with DI water in order to remove the solvent residuals, which have toxic effects, together with the suspension stabilizer and the free theophylline. Upon removing the magnetic column from the strong magnetic fields, the microspheres were collected and freeze-dried for two days at −60°C and kept in a desiccator with silica gel.

Characterizations

The morphologies of the nano- and micro-particles were characterized by Transmission Electron Microscopy (TEM;ZEISS, EM-10C, Germany) and Scanning Electron Microscopy (SEM;Philips, XL30), operating at 100 kV and 20 kV, respectively. Polyurethane formations were confirmed by Fourier-transform infrared spectra (FTIR) of the samples with KBr pellets using an ABB Bomem MB-100 FTIR spectrophotometer. Phase characterization was accomplished using the X-ray diffraction (XRD;Siemens, D5000, Germany) technique with Cu Kα radiation. The magnetization of the samples in a variable magnetic field was measured using a vibrating sample magnetometer (VSM) with a sensitivity of 10^{-3} emu and a maximum magnetic field of 8 kOe. A UV spectrophotometer (Milton Roy Spectronic 601) was used for defining the drug concentration in solution.

In Vitro Drug Loading and Release

The loading of theophylline was measured by UV spectrophotometer (Milton Roy Spectronic 601) after solubilisation of the magnetic microsphere particles in acetonitrile. The insoluble SPIONs from the theophylline-containing solutions were removed by centrifugation at 14000 rpm. The quantity of drug in the supernatant was analyzed using a UV spectrophotometer at wavelength of 274 nm. Typically, one gram of superparamagnetic microspheres was dissolved in 10 ml buffer solution and the release of drug was tracked using the UV spectrophotometer. In this regard, the calibration curve was determined at different theophylline concentrations (0.1-1 mg/ml) in phosphate buffer saline (PBS; a buffer solution which is commonly used in biological research) at pH=7.4. Finally, in vitro theophylline release was studied for all groups for a period of 20 days.

RESULTS AND DISCUSSION

Transmission electron microscopy (TEM) of the prepared superparamagnetic iron oxide nanoparticles revealed the formation of spherically-shaped SPIONs

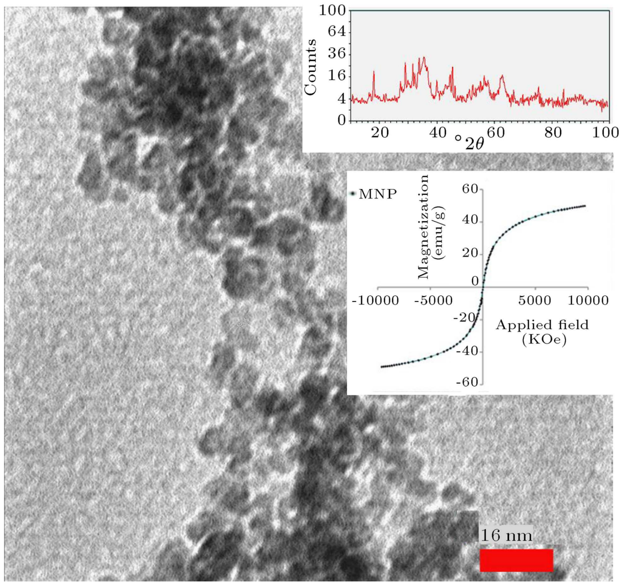
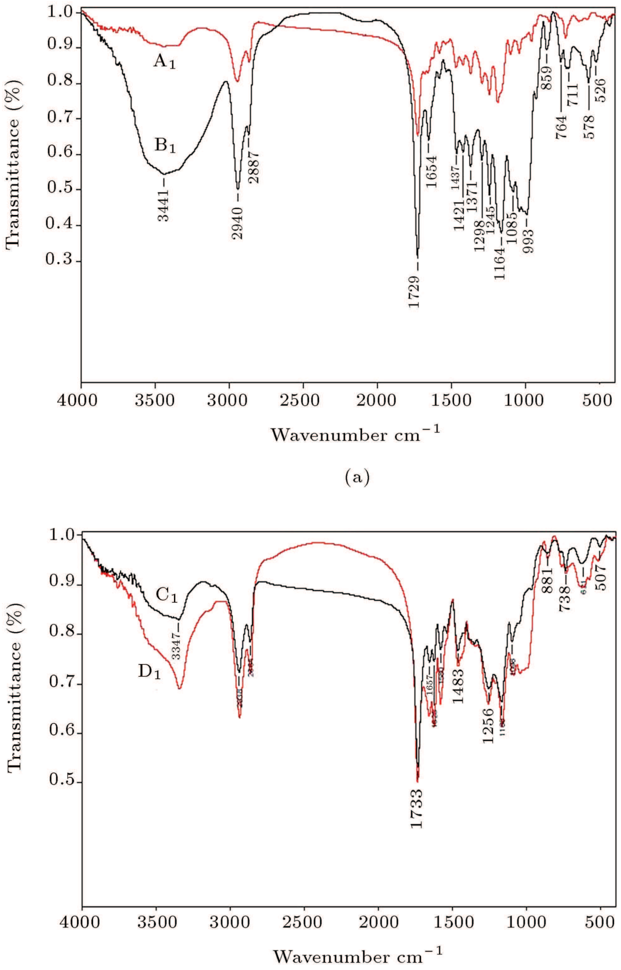


Figure 1. TEM image, XRD pattern and VSM curve of synthesized SPIONs.

with an average size of 4 nm and a narrow size distribution (Figure 1). Furthermore, the XRD spectra match well with magnetite (Fe_3O_4, reference JCPDS No. 82-1533), indicating that the samples have a cubic crystal system [33]. In addition, the sample was analyzed by VSM and showed negligible remanence and coercivity in the hysteresis loops, which confirmed the superparamagnetic behavior, with a magnetic saturation of 50 emu/g (Figure 1).

Figure 2 shows the FTIR spectrum of each group candidate (i.e. A_1, B_1, C_1 and D_1) confirming the formation of a polyurethane structure given the presence of carbonyl (C=O) and (N-H) peaks at about 1733 and 3340 cm^{-1}, respectively, and the absence of an isocyanate (NCO) peak at around 2270 cm^{-1}. Thus, there is almost no residue of the monomer remaining in the polymer and pure and compatible polyurethanes are formed in the reactions. Furthermore, the FTIR spectra confirm the existence of SPIONs that exhibit a band in the low-frequency region (1000-500 cm^{-1}) due to the iron oxide skeleton [28]; more specifically, the characteristic band of Fe-O at 572 cm^{-1} shows that the microspheres consist of Fe_3O_4.

The results of the Scanning Electron Microscopy (SEM) are presented in Figure 3. The SEM images show the morphology of synthesized superparamagnetic microspheres containing theophylline as a round spherical shape (average size of 5 μm) and that there is little difference between samples with various PCL molecular weights. More specifically, the average size distribution of those superparamagnetic microspheres which were synthesized by PCL with lower molecular weight is smaller. The reason is that the lower molecular weight could decline the viscosity which may increase the stirring speed and consequently results in smaller microspheres [34]. Moreover, groups B and D, which contain both starch and PCL, have lower average particle sizes than groups A and C due to the attribution of the starch effect in declining the viscosity of the solution during the formation of microspheres [34]. However, addition of starch to the samples caused surface roughness due to the granular shape of starch particles which were trapped in the polymeric network [35].

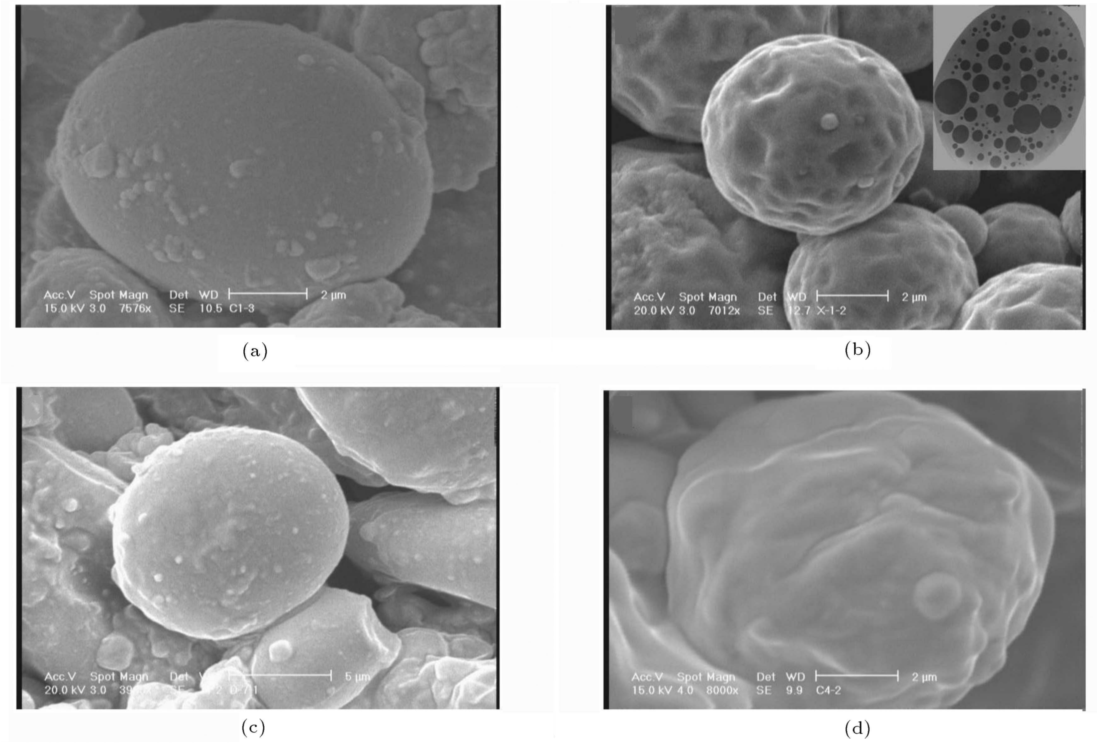


(a)

(b)

Figure 2. FTIR spectra of (a) A_1 (PCL (M_W = 530 g/mol)) and B_1 (PCL (M_W = 530 g/mol) and starch), and (b) C_1 (PCL (M_W = 2000 g/mol)) and D_1 (PCL (M_W = 2000 g/mol) and starch).

The VSM curves of the superparamagnetic microspheres are presented in Figure 4. Figure 5 shows the result of calibration curve which has been determined at different theophylline concentrations. Figure 6 shows the release graphs of all samples. According to these graphs, all groups have a burst effect of between 15-65 percent during their first 4 hours of the release process. As can be seen, by decreasing the molecular weight of PCL, the burst effect is decreased for groups



(a) (b)

(c) (d)

Figure 3. SEM micrographs of superparamagnetic polyurethane microspheres for (a) A_1 (PCL ($M_W = 530$ g/mol)), (b) B_2 (PCL ($M_W = 530$ g/mol) and starch), (c) C_3 (PCL ($M_W = 2000$ g/mol)) and (d) D_4 (PCL ($M_W = 2000$ g/mol) and starch). Inset at the top right is the TEM image of a microsphere.

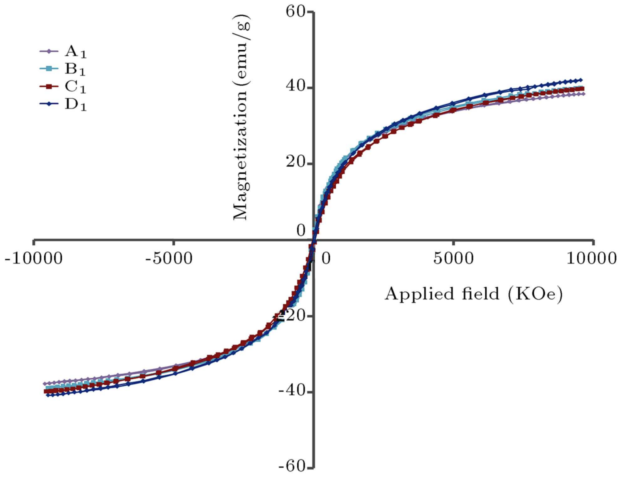


Figure 4. Magnetization curves for samples (a) A_1 (PCL ($M_W = 530$ g/mol)), (b) B_1 (PCL ($M_W = 530$ g/mol) and starch), (c) C_1 (PCL ($M_W = 2000$ g/mol)) and (d) D_1 (PCL ($M_W = 2000$ g/mol) and starch).

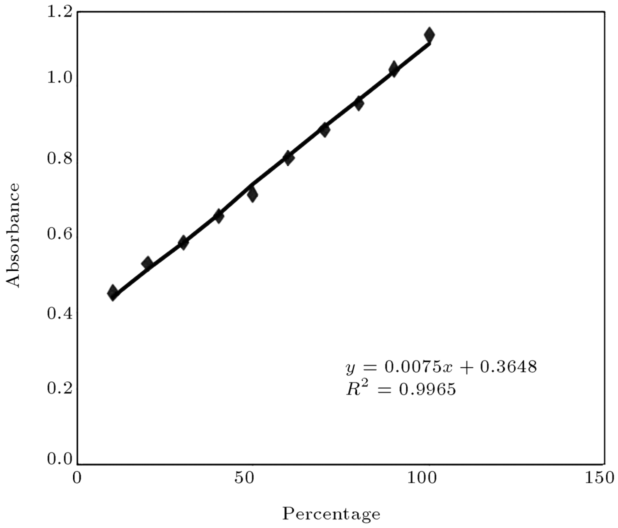
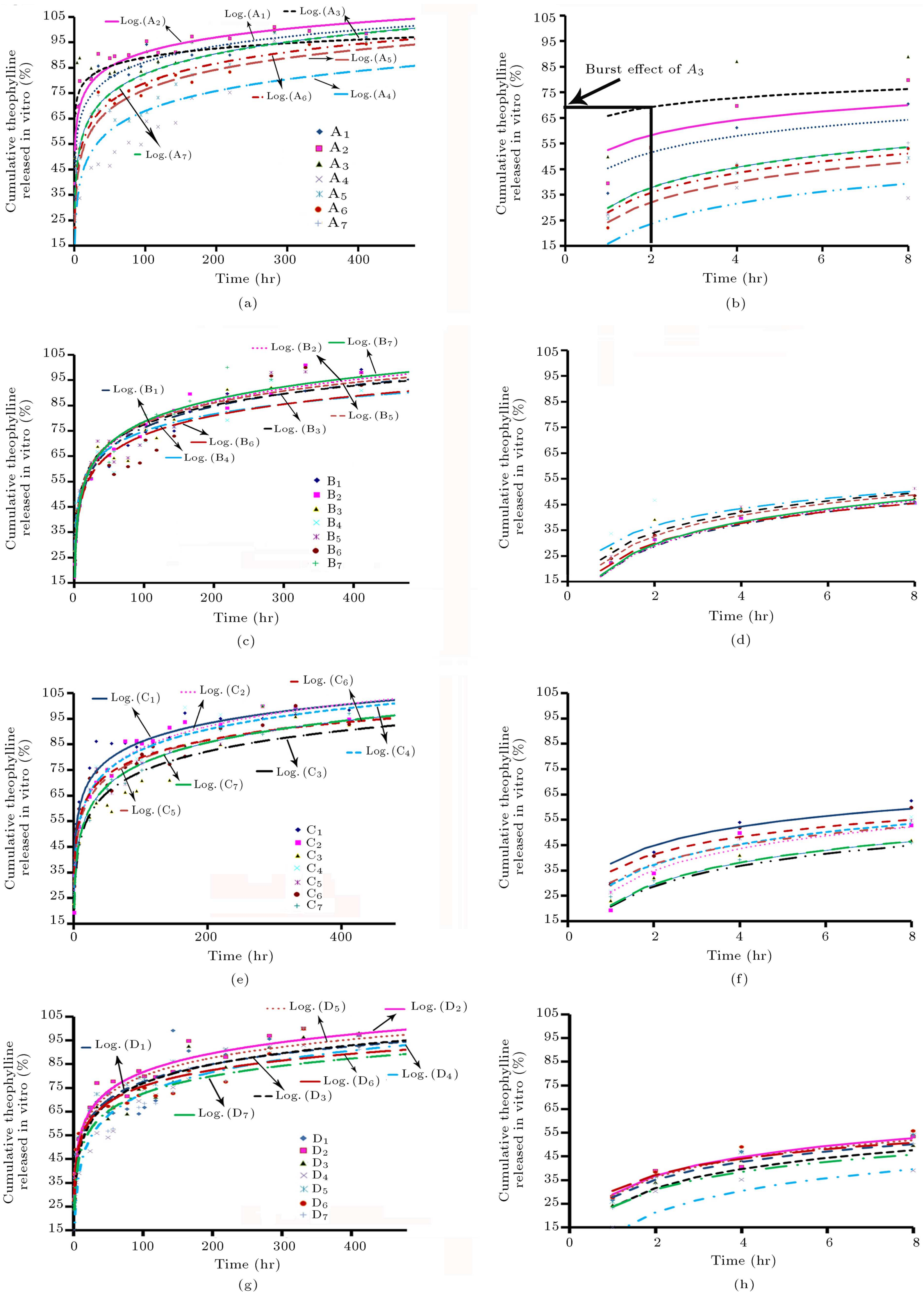


Figure 5. The calibration curve for theophylline concentrations determination according to its absorbance.

A and C, from 65 to 30%. It is worth noting that by decreasing the PCL molecular weight, the effect of polyol to the chain extender ration was minor and the scatter release profiles for samples in the same group were not observed (compare Figures 6a and 6c). On the other hand, by employing starch in the structure of the polyurethane texture, the burst effect showed a considerable decline from 65% (for groups A and C) to 20% (for groups B and D). In addition, the effect of polyol to the chain extender ration was negligible and did not change the release profile regardless of PCL's molecular weight.

High molecular weight starch chains together with their granular shape in lateral specimens may form entanglements with the polyurethane polymer, therefore causing the significant decline in the burst effect.



(a) (b) (c) (d) (e) (f) (g) (h)

Figure 6. In vitro drug release pattern of the samples in (a) group A (PCL (M_W = 530 g/mol)), (c) group B (PCL (M_W = 530 g/mol) and starch), (e) group C (PCL (M_W = 2000 g/mol)), and (g) group D (PCL (M_W = 2000 g/mol) and starch). (b), (d), (f) and (h) patterns are the release profile in the first 8 hours of (a), (c), (e) and (g), respectively. Plain lines represent the logarithmic fitting.

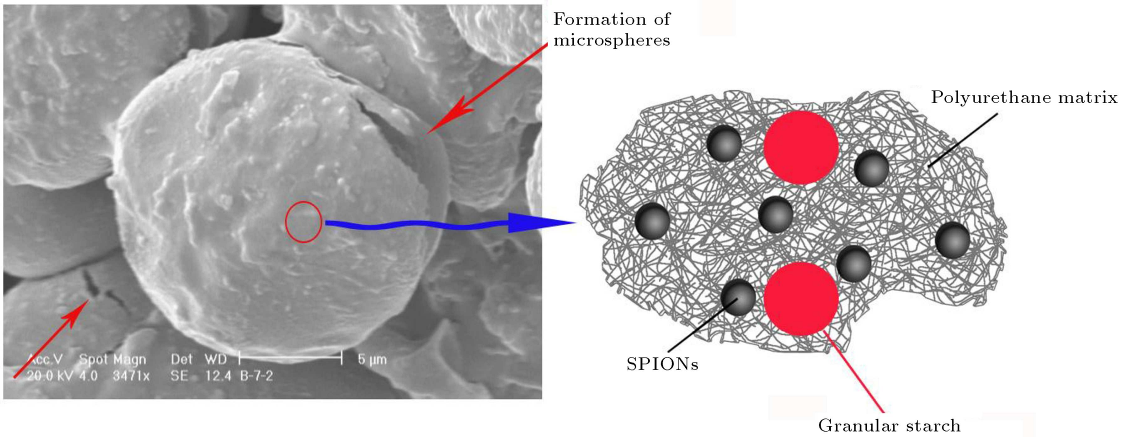
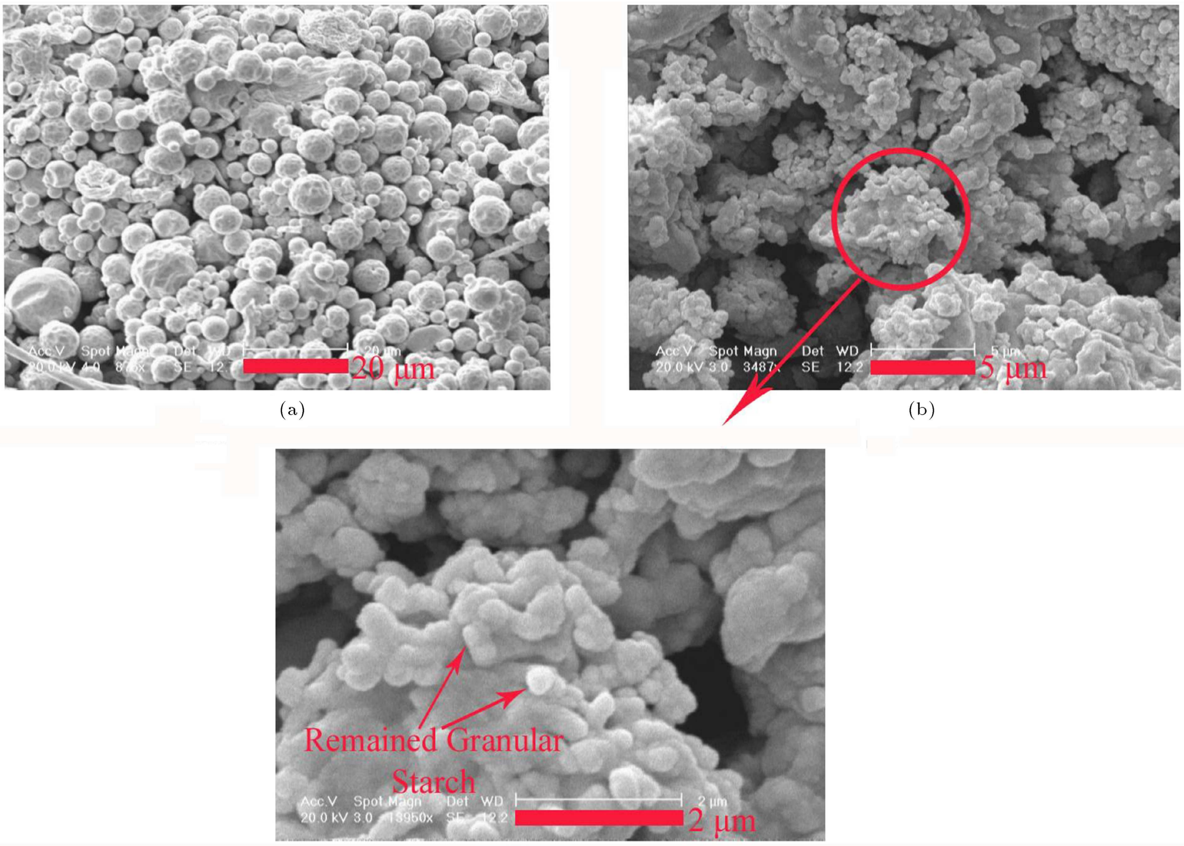


Figure 7. SEM image of the microspheres objects and the possible schematic of their matrix, showing the linkage between various ingredients. Diagram is not to scale in representing the proportions of the different objects.



(a) (b)

(c)

Figure 8. SEM images of microspheres of sample B_1 for (a) before and (b) after the drug release process; (c) SEM image of (b) with higher magnification, showing the existence of granular starch after degradation of microspheres.

The predetermined starch barrier may also contribute to a lesser extent in the formation of polyurethane chains as a polyol. More specifically, PCL has a much lower molecular weight in comparison with starch, and therefore can offer a higher diffusion rate in comparison to starch for reaction with HMDI and BD. Figure 7 schematically illustrate the existence of starch in the polyurethane matrix; in this case, the diffusion rate of the drug from the polymeric matrix to the buffer solution would be decreased.

After the release study, the superparamagnetic microspheres were investigated by SEM (Figure 8). The results confirm that the most degradation of microspheres occurs after 20 days of interaction with a PBS environment. Probing SEM images of the degraded microspheres with higher magnifications (e.g. Figure 8c) proved the existence of the granular starch, confirming our claim in the dispersion of starch in the polymeric matrix.

CONCLUSION

Magnetic polyurethane microspheres loaded with theophylline were successfully prepared by the water in oil in water emulsion technique. Various molar stoichiometries of HMDI, PCL ($M_W = 530$ or 2000 g/mol), starch and BD were used. Polyurethane formation was confirmed by IR, and the morphology of the microparticles was characterized by TEM and SEM. The release of theophylline was studied during a period of 20 days and dosed by UV. With the use of PCL with a low molecular weight or in the presence of starch in the structure of polyurethane, the burst effect of the drug is decreased. A SEM study showed an important degradation of the microspheres after the release process. Thus, this kind of new superparamagnetic microspheres is very promising, since it offers the opportunity to control the drug release and also the biodegradable character of the particles.

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BIOGRAPHIES

Morteza Mahmoudi obtained his PhD in 2009 from Sharif University of Technology with specialization on the cytotoxicity of superparamagnetic iron oxide nanoparticles (SPION). He has received many awards such as the 2010 Dr. Mojtahedi Innovation Award for Distinguished Innovation in Research and Education at Sharif University of Technology and 2009 Kharazmi Young Festival Award. His current research involves the magic SPION for simultaneous diagnosis and therapeutic applications (http://www.biospion.com).

Sophie Laurent was born in 1967. Her studies were performed at the University of Mons-Hainaut (Belgium) where she received her Ph.D. in Chemistry in 1993. She joined then Prof R.N. Muller's team and was involved in the development (synthesis and physicochemical characterization) of paramagnetic Gd complexes and super paramagnetic iron oxide nanoparticles as contrast agents for MRI. She is currently working on the vectorization of contrast agents for molecular imaging. She is lecturer and co-author around 90 publications and more than 180 communications in international meetings.