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Thermosensitive magnetic polymer particles as contactless controllable drug carriers

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Abstract

Spherically shaped thermosensitive micro and nanoparticles based on *N*-isopropylacrylamide were synthesized using a novel inverse suspension polymerization technique which enables a bead formation within minutes. In addition to the rapidity, the suspension procedure provides an effective platform for the encapsulation of magnetic colloids and simultaneous drug analogous substances. The presence of the magnetic colloids allows an inductive heating of the particles using an alternating magnetic field above the polymer transition temperature (>35 °C). This results in a pronounced de-swelling accompanied by a release of the encapsulated substances. The potential of this technology for a new contactless controllable drug releasing approach is exemplarily demonstrated using rhodamine B and methylene blue as drug analogous substances.

Keywords: Magnetic particles; Thermosensitive particles; Nanoparticles; *N*-isopropyl-acrylamide; Drug release; Alternating magnetic field

1. Introduction

Thermosensitive polymers have long been established in polymer sciences. The mostly used polymers are, e.g. *N*-isopropylacrylamide, hydroxypropylcellulose or poly(ethylene glycol) [1–4] and their special feature is that at a critical phase transition temperature, a phase separation occurs resulting from a positive value of the free energy of mixing which is accompanied by a distinct de-swelling process. At this "lower critical solution temperature" which lies within a range of 30–45 °C among the above-stated polymers [1–5], the gels release a substantial portion of their water content so that a pronounced shrinking can simultaneously be observed. This special parallel behaviour of shrinking and water release has been exploited in the past for the design of stimuli–responsive bulk polymers and polymer carriers [1–8]. Apart from basic investigations concerning physical–chemical properties such as swelling kinetic, change of the transition temperature as function of the polymerisation conditions, copolymerization, type of polymer and polymer composition [6,9,10], this thermosensitive principle has been investigated for its potential use as nano-valves [11], light-modulation materials [12], separation processes [2,13], protein immobilization [14] sensors [15] and catalyst [16]. The application of thermosensitive polymer carriers in combination with the encapsulation of magnetic colloids for enzyme immobilization, cell separation and antibody purification [2,3,13,17,18] has also been described. The use of this thermosensitive stimulus–response principle for drug release purposes was the subject of intensive research in the past in the search for more effective drug delivery systems [4,19,20]. These carriers, however, cannot be used for remote-triggered in vivo drug release applications nor are the described carriers spherical nano- or microparticles, a prerequisite for drug release purposes. A recent approach described by Hirsch et al. [21] using near infrared light to heat up gold-nano-shells encapsulated into a *N*-isopropylacrylamide matrices cannot be applied for an overall in vivo remote controlled drug release because

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of the restricted penetration depth of the used infrared light.

The present work describes spherically shaped *N*-isopropylacrylamide micro- and nanocarriers in which drug model substances are simultaneously encapsulated together with magnetic colloids using a newly developed inverse suspension polymerisation technique, which for the first time provides a basis for an in vivo contactless controlled drug release.

2. Methods and materials

2.1. Preparation of magnetic colloids

All chemicals supplied by Sigma, Aldrich and Fluka Germany, were of analytical grade and used without further purification. The preparation of the magnetic colloids was performed according to the methods described by Shinkai et al. [22]. Deviating from the published method, the basic magnetite particles were subjected to a three-second lasting treatment using an ultrasonic finger (Bandelin, Sonopuls, Germany, power output 60 W) after every precipitation step. The particle sizes are in the range of 10–20 nm, determined by electron microscopy (for details see legend Fig. 3).

2.2. Preparation of N-isopropylacrylamide beads

The *N*-isopropylacrylamide polymer beads were synthesized using a water-in-oil suspension polymerisation technique according to the method described elsewhere [23]. In brief, 21.5 vol% ferrofluid (magnetite content 15%) and 2.15 vol% ammonium persulfate solution (4%) were added to a monomer phase consisting of 43 vol% *N*-isopropylacrylamide (10% solution), 10.75 vol% Igepal CO-520 and 10.75 vol% of an acrylamide *N,N′*-methylene bisacrylamide solution (37.5:1). The mixture was treated for 30 s. in a conventional ultrasonic bath. Optionally, 5–10.75 vol% of a 3.5% methylene blue or rhodamine B solution is added and the mixture suspended under stirring in an cottonseed oil phase (volume ratio monomer phase to oil phase 1:15, viscosity of the oil: 40–80 mPas). The oil phase contains 0.7% Span 60, 0.15% Brij 72 and 0.1% Prisorine. 1 vol% *N,N,N′,N′*-tetramethylethylene-diamine (TEMED) was added during stirring which is then continued for 2 min. The mixture was left for a further 20 min without stirring. Several washing steps with acetone, methanol and water followed. A conventional stirrer with 800–2000 rpm can be used for the preparation of beads with a size $>20\,\mu m$, whereas for the synthesis of beads of $<10\,\mu m$, a high-speed dispersion tool (Ultra-Turrax T25, IKA Werke, Germany) enabling a stirring speed >5000 rpm is required. For the immobilization of bioligands for a specific cell targeting, carboxyl groups can be introduced into the polymer matrix by adding the sodium salt of acrylic acid to the standard monomer preparation. The concentration can be varied optionally between 0.5% and 2.5%, a concentration which does not impair the bead formation. These carboxyl groups can be activated for ligand coupling via the well-known *N*-hydroxysuccinimide method [24].

The same monomer/comonomer compositions and stirring modes was used for the synthesis of nanobeads. The oil phases for a typical nanobead preparation contain the following surfactants: Pluronic F 127 (0.3%) or Prisorine 3700 (0.5%) and Aerosol AOT (8.3%).

2.3. Ferromagnetic inductive heating

Inductive heating was performed using a generator–oscillator-combination (TIG 5/300, Hüttinger, Freiburg, Germany) with a maximum power dissipation of 5 kW.The coil-shaped and water-cooled antenna was made of 8 copper windings with an inner diameter of 20 mm and connected to a water-cooled resonance circuit which produced the electromagnetic field. The system created a maximum field strength up to 90 kA/m in the centre of the coil.

The inductive heating tests were conducted using a field amplitude of 20 kA/m in combination with a frequency of 360 kHz.These field parameters deposit sufficient energy into the sample thereby reaching the required transition temperatures ($>35\,^{\circ}C$) which result in a measurable dyestuff release within minutes. Inductive heating was performed in standard Eppendorf tubes (1 ml aqueous suspension volume) placed in the centre of the coil. The temperature of the suspension was measured by inserting an optical fibre probe into the centre of the sample.

2.4. Release measurements

The release experiments were carried out by measuring the extinction of the released dyestuffs in the supernatant using a LKB, Ultrospec 2000 II at 670 (methylene blue) and 565 nm (rhodamine B).

2.5. De-swelling measurements

The de-swelling kinetics was determined by measuring the volume of the gel particles before and after heating at two different temperatures (38 and $50\,^{\circ}C$). The swelling tests were carried out in standard NMR tubes. The degree of shrinking was evaluated from the swelling height before and after heating, whereby the volumes were determined after equilibrium settling enforced by a neodymium–boron–iron hand magnet. The degree of shrinking is defined as the difference of the swelling height before (i.e. 100%) and after heating (Fig. 1).

3. Results and discussion

In view of the fact that established techniques for the preparation of spherically shaped polymer beads require between 3 and 24 h synthesis [2,3,8,10,13,25–27], a novel