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Magnetic silica hybrids modified with guanidine containing co-polymers for drug delivery applications

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ABSTRACT

Guanidine containing co-polymers grafted onto silica nanoparticles to form core-shell structure were prepared by sol-gel method in the presence of γ-Fe_2O_3 nanoparticles. The morphological features for uncoated and coated silica particles have been characterized with scanning electron microscopy. The results show that the polymer coated silicas exhibit spherical morphology with rough polymeric surface covered by γ-Fe_2O_3 nanoparticles. The grafting amount of guanidine containing co-polymers evaluated by thermogravimetric analysis was in the range from 17 to 30%. Then, the drug loading properties and cumulative release of silica hybrids modified with guanidine containing co-polymers were evaluated using molsidomine as a model drug. It was shown that after polymer grafting the loading content of molsidomine could reach up to 3.42 ± 0.21 and 2.34 ± 0.14 mg/g respectively. The maximum drug release of molsidomine is achieved at pH 1.6 (approximately 71–75% release at 37 °C), whereas at pH 7.4 drug release is lower (50.4–59.6% release at 37 °C). These results have an important implication that our magneto-controlled silica hybrids modified with guanidine containing co-polymers are promising as drug carriers with controlled behaviour under influence of magnetic field.

1. Introduction

Inorganic nanoparticles are frequently engineered with organic components containing different functional groups in order to improve their physicochemical properties [1–3]. The numerous works have been published concerning modification of surface of nanoparticles by functional groups or polymers [4–6]. Such polymer coated nanoparticles have found a great interest in many branches of science and industrial areas as well. By varying the type of polymer the interaction of polymer coated nanoparticles with biological objects or biomolecules can be controlled [7]. Such valuable property has been successfully used for addressing some of the most significant biomolecules such as drugs at diseased tissues and cells.

It is well known that the surfaces of nanosized materials have a high free energy providing a high reactivity. Therefore, the surfaces of nanoparticles will adsorb biomolecules when it comes into contact with biological fluids leading to dysfunction of metabolism of cells [8–10]. Several methods have been suggested for reducing toxicity of nanoparticles. One of this is to manufacture protein corona nanoparticles based on surface modification of nanoparticles by proteins [11]. Although, such topic is new and relevant, several papers about protein corona have already been published [12,13]. All authors in these papers announced about the problem of protein modification: structure of protein is very sensitive and gentle which may lead to protein denaturation and loss of its biological activity [13]. Another approach is based on polymer coating in order to form «core-shell» structure consisting of inorganic core (gold, silica, titania and zinc oxide etc.) and polymeric shell (Fig. 1a). The aim of polymeric shell is to protect from hazardous and toxic effect of nanoparticle. However, essential requirements have been involved for choosing polymers to modify surface of nanoparticles. They should be biocompatible, non-toxic, have its biological activity and high binding ability [14,15].

Compared with widely reported nanoparticles functionalized with organic compounds or biological species, silica coated with responsive polymers are of special interests due to the diversity, multifunctional capability [16]. Various polymers have been already synthesized and applied for surface modification of silica. The most commonly studies include application of poly(acrylamide) [17], polyethylene glycol [18], polyacrylic acid [19]. However, in an effort to further improve the physicochemical properties of polymer coated silica nanoparticles, new types of polymer hybrids should be considered. According to our recent studies concerning polymer coated silica, it has been suggested to consider guanidine containing polymers as the most promising candidates for surface modification due to their non-toxicity, biological activity and high binding ability [20,21]. It was demonstrated that polymethacryloyl

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guanidine hydrochloride (PMCGH) and polyacrylate guanidine (PAG) are pH-responsive. The drug loading and release behaviour of silica hybrids modified with PMCGH and PAG were carefully investigated by our research group. The obtained results emphasized that PMCGH and PAG are excellent candidates for surface functionalization and formation of pH sensitive nanoparticles which can be further recommended as drug carriers and effective hemoadsorbents for bilirubin removal [21, 22]. Here, we have continued our research focusing on application of new type of guanidine containing co-polymers: methacrylate guanidine with dialdehyde cellulose (MAG + DAC); diallyl dimethyl ammonium chloride with diallyl guanidine acetate (DDAC + DGA, 75:25) (Fig. 1b). Despite the fact that many researches deal with polymer coated silica using pH-responsive polymers, the application of guanidine containing co-polymers such as MAG + DAC and DDAC + DGA has not been reported so far to the best of our knowledge.

In recent years, application of magneto-controlled nanoparticles has become leading area in nanomedicine [23]. The high mobility of magnetic nanoparticles in solution under magnetic field allows using of nanoscale magnetic nanoparticles for highly selective and rapid separation of bacteria or delivery of anticancer drugs in blood plasma using a magnetic microfluidic device [24]. Many scientists have concentrated on synthesis and application of iron oxide nanocrystals in individual form (Fe_3O_4 and γ-Fe_2O_3) [25,26]. However, investigations in the field of multifunctional nanoparticles containing iron oxide nanocrystals as additional component are still relevant. In this contribution, we report sol-gel synthesis of polymer coated silica particles modified with guanidine containing co-polymers and γ-Fe_2O_3 nanoparticles. There are three types of immobilization of γ-Fe_2O_3 nanoparticles (Fig. 1c). Here, γ-Fe_2O_3 nanoparticles were immobilized onto surface of silica particles with core-shell structure. Basically, it was developed new type of polymer coated γ-Fe_2O_3/silica hybrids that allows the loading and transportation of drugs. To achieve that, the guanidine containing co-polymers were used. According to the works of E. V. Parfenyuk and A.V. Agafonov [27,28] molsidomine was chosen (Fig. 1d) as the most promising candidate for the study of drug loading and cumulative release. There are only several papers are about molsidomine loading and study of its release. As it was reported in [27] that molsidomine is an active substance of a series of cardiovascular drugs which are widely used clinically. In accordance with work of A.V. Agafonov [27], the isoelectric point of molsidomine equals 4.4. It means the net charge on molsidomine can become positive or negative by changing the value of pH. Therefore, after preparation of our polymer coated silica particles, the drug loading and drug release of molsidomine were carefully investigated. The drug release of molsidomine was performed at pH 1.6 (stomach) and 7.4 (blood) with respect to suggestion to apply a novel form of molsidomine for oral and intravenous administration. The influence of guanidine containing co-polymers on drug loading and its release behaviour is discussed and recommendations concerning application of our prepared materials are suggested.

2. Experimental section

2.1. Chemicals

TEOS ($Si(OC_2H_5)_4$, M_w = 208.3 g/mol, 99%) and ammonia solution (4 wt%) were purchased from commercial chemical company "Ecos-1" (Russian Federation). NaOH, $FeCl_3$ (M_w = 162.2 g/mol, 99%) and molsidomine ($C_9H_{14}N_4O_4$, M_w = 243.23 g/mol) were purchased from Sigma-Aldrich (USA). The guanidine containing co-polymers: co-polymer of methacrylate guanidine and dialdehyde cellulose (MAG + DAC); copolymer of diallyl dimethyl ammonium chloride with diallyl guanidine acetate (DDAC + DGA, 75:25) were provided by the department of macromolecular compounds of the Kabardino-Balkar State University and by the department of Chemistry of polyelectrolytes and biomedical polymers of A.V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Science. The full description of these guanidine containing co-polymers can be found in [29,30].

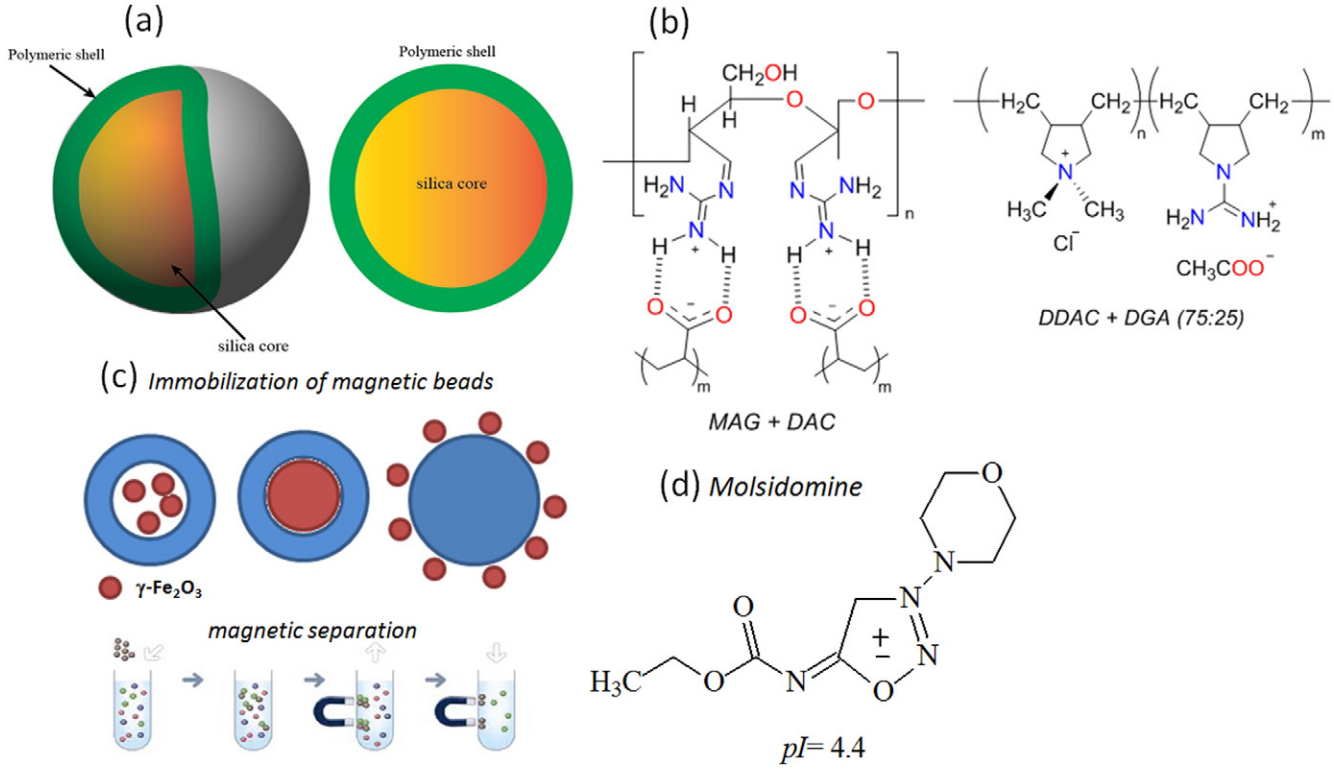

Fig. 1. (a) Schematic illustration of silica particle with «core-shell» structure; (b) structures of MAG + DAC and DDAC + DGA (75:25); (c) immobilization of magnetic beads and its use for magnetic separation; (d) molecular structure of molsidomine.