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Thermo-responsive molecularly imprinted polymer containing magnetic nanoparticles: Synthesis, characterization and adsorption properties for curcumin

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ABSTRACT

A novel intelligent thermoresponsive-magnetic molecularly imprinted polymer (TMMIP) nanocomposite based on N-isopropylacrylamide (NIPAM) & Fe_3O_4 was designed for the controlled & sustained release of Curcumin (CUR) with the ability to response external stimulus. The TMMIP nanocomposite was prepared using acryl functionalized β-cyclodextrin (β-CD) and NIPAM as functional monomers and CUR as target molecule. The recognition cavities which caused by host-guest interactions had direct influence to enhanced drug loading and sustained release of CUR. According to *in-vitro* release experiment in two different temperatures (below & above LCST of NIPAM) the prolonged & controlled release of CUR were observed. The release rate could be controlled by changing the temperature because of the phase transition behavior of NIPAM monomer. Also, the proposed biosensor displayed effective role in separation science, reasonable adsorption capacity (77 mg g^{-1}), fast recognition (10 min equilibration), selective extraction toward CUR in the presence of structural analogues and easily separation using external magnetic field. Moreover, the synthesized TMMIP was confirmed by various characterization

1. Introduction

Curcumin (CUR) is a natural and low molecular weight phenolic compound that isolated from the plant *Curcuma longa.* The CUR has a wide range of pharmacological actions and biological activities, including anti-tumor, anti-microbial, anti-inflammatory, anti-amyloid, anti-HIV and anti-parasitic with low or no intrinsic toxicity with promising clinical applications [1,2]. Despite of its wide pharmacological properties due to some disadvantageous properties, successful clinical applications of this compound is hampered. Low aqueous solubility (11 ng mL^{-1}) and rapid metabolism and elimination of CUR lead to poor bioavailability after oral or topical administration especially [3–5]. Therefore, improvement of the solubility, stability and also bioactivity of CUR is necessary. Numerous approaches to increase bioavailability of CUR are under research, such as encapsulation, liposomes [2], PLGA [6] and other polymeric nanoparticles using specialized polymers [7]. On the other hand, due to its wide application and anticancer potential some drug delivery systems with molecular recognition properties, could facilate prolonged and sustained delivery. Molecular imprinted polymers (MIPs) is one of the most promising drug delivery vehicles have been recently used [8–14]. These synthetic polymers have molecular recognition cavities for specific target molecule to bind and release. The formation of recognition sites in MIP was achieved by polymerization of matrix and monomers in the presence of target molecule with the aid of a crosslinker and followed by extraction of target molecules[15,16]. The recognition sites are complementary in size, shape and functional groups with target molecules, thus the restricted mass transfer would decrease and the target could be easily attached to the binding sites in this way[17]. MIPs have some advantages such as easily preparation, selectivity and high mechanical and chemical stability [18–23]. MIPs have been used in wide variety of fields such as chemosensors [24,25], solid phase extraction [26] and drug delivery systems [8–14]. One of the most promising fields in drug delivery systems is the possibility of modulate drug release in the response to a specific external stimulus. Smart polymers can be respond to changes in external stimuli such as pH, temperature, ultrasonic frequency and light. Polymers that experience these stimulus undergoes physio-chemical changes and can be applied for remote controlled

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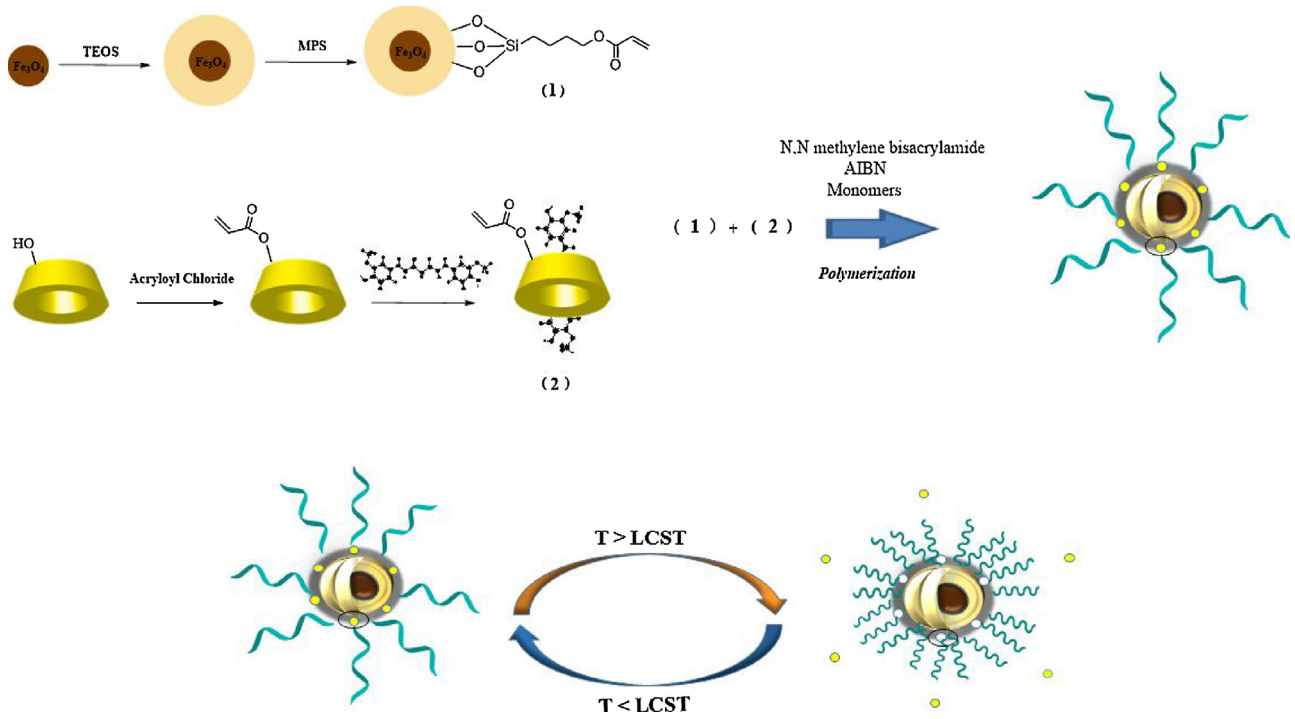

Scheme 1. Schematic represents the preparation of TMMIP nanocomposite.

therapies [27–29]. Among smart polymers, thermoresponsive polymers specially poly(*N*-isopropylacrylamide) (PNIPAM) has been extensively investigated with potential applications. With utilization this type of materials the ability of the resulting MIP in capturing and releasing target molecules can be adjusted by external temperature. These polymers exhibit phase transition change from hydrophilic to hydrophobic upon change in temperature. The PNIPAM has lower critical solution temperature (LCST) at 32 °C. When the temperature is below LCST, PNIPAM exhibit hydrophilic state and the polymeric chains are expanded and flexible to load drug molecule but above LCST, it turned to hydrophobic state and PNIPAM formed globules, and interaction between drug and polymer disrupt. This phase change process from hydrophilic to hydrophobic is reversible, which can be used to load and deliver therapeutics [30–33]. The combination of thermoresponsive polymers with magnetic nanoparticles such as Fe_3O_4 with great superparamagnetic properties and also biocompatibility and low toxicity to form a magneto-thermo responsive MIP would have great advantages for targeted drug delivery [34,35]. Such nanocarrier could selectively target the affected tissues in the presence of an external magnetic field [36–43]. Another important features of MIPs is the interaction of the template with functional monomer which is accomplished by physical entrapment or chemical bonding method on the structures. In order to improve the molecular recognition properties and better interactions of template chemical bonding is suggested. In this regard, the modification of β-CD with acrylate functional group was carried out which leads to improve polymerization step and generates covalent bonds in polymeric matrix [44].

In this paper we reported on thermoresponsive magnetic molecularly imprinted polymer (TMMIP). TMMIP was synthesized through radical polymerization of PNIPAM and acryl functionalized β-cyclodextrin (β–CD) as monomers, CUR as target molecule, N,N′ methylenebis (acrylamide) and azobisisobutyronitrile as crosslinker and initiator, respectively. The results shown that the release of CUR with utilization of PNIPAM and β–CD was sustained and prolonged. Moreover, the inclusion complex of CUR with β–CD improves the bioavailability of CUR [43] (Scheme 1). The synthesized TMMIP was characterized using SEM, FT-IR, XRD and TGA. The batch adsorption and release profile of CUR were investigated in details.

2. Experimental

2.1. Reagents and materials

Iron (III) chloride hexahydrate ($FeCl_3.6H_2O$), Iron (II) chloride tetrahydrate ($FeCl_2.4H_2O$), tetraethyl orthosilicate (TEOS), isopropanol, acryloyl chloride, triethylamine, azobisisobutyronitrile (AIBN), N, N methylene bisacrylamide (MBAm), Potassium hydroxide, acetone, acetonitrile, ammonia solution (25%), (purchased from Merck company), 3-methacryloxypropyltrimethoxysilane (MPS), NIPAM, β-CD (purchased from Sigma-Aldrich company).

2.2. Preparation of Fe_3O_4 nanoparticles (NPs)

Fe_3O_4 NPs were obtained by the chemical co-precipitation of Fe(II) and Fe(III) chloride salts (molar ratio 1:2), in the presence of ammonia solution[45]. Briefly 5 mmol of $FeCl_2.4H_2O$ and 10 mmol of $FeCl_3.6H_2O$ were dissolved in 70 mL distilled water and the mixture reaction heated to 80 °C under N_2 atmosphere. Then 15 mL of ammonia (25%) solution was added dropwise to the solution. After 30 min, the obtained product was separated using an external magnet and washed several time with distilled water and ethanol until a neutral pH was achieved. The precipitate was dried under vacuum oven in the room temperature overnight.

2.3. Preparation of Fe_3O_4@SiO_2 NPs

Modification of Fe_3O_4 NPs with SiO_2 was performed for the further stability, prevention of aggregation and also enhancement magnetic property of NPs. Fe_3O_4@SiO_2 NPs were prepared according to the Stober's method. Typically, 1 g of obtained Fe_3O_4 NPs were dispersed in the mixture of 120 mL isopropanol and 6 mL of