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Grafting of allylimidazole and *n*-vinylcaprolactam as a thermosensitive polymer onto magnetic nano-particles for the extraction and determination of celecoxib in biological samples

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ABSTRACT

In this research, a novel method is reported for the surface grafting of *n*-vinylcaprolactam as a thermosensitive agent and allylimidazole with affinity toward celecoxib onto magnetic nano-particles. The grafted nano-particles were characterized by Fourier transform infrared spectroscopy, elemental analysis, and thermogravimetric analysis. The surface morphology was studied using Scanning Electron Microscopy. The resulting grafted nano-particles were used for the determination of trace celecoxib in biological human fluids and pharmaceutical samples. The profile of celecoxib uptake by the modified magnetic nano-particles indicated good accessibility of the active sites in the grafted copolymer. It was found that the adsorption behavior could be fitted by the Langmuir adsorption isotherm model. Solid phase extraction for biological fluids such as urine and serum were investigated. In this study, urine extraction recovery of more than 95% was obtained.

1. Introduction

Celecoxib4-[5-(4methylphenyl)-3(trifluromethyl) Pyrazol-1yl] benzene sulfonamide (as shown in Fig. 1) is a selective cyclooxygenase-2(cox-2) inhibitor approved for the relief of inflammation associated with osteoarthritis (Sherry Chow et al., 2004). Celecoxib is used for rheumatoid arthritis and pain, with conventional non-steroidal anti-inflammatory drugs (Lane, 1997). Non-steroidal anti-inflammatory drugs are used to reduce the effects of pain. The enzyme cyclooxygenase, converts arachidonic acid to prostaglandins. Among the two types of cyclooxygenase enzymes in the body (cox-1 and cox-2), cox-2 is specifically inhibited by celecoxib (Tran-Thanh et al., 2010). Several analytical methods, such as high performance liquid chromatography-ultraviolet detection (HPLC-UV), have been used to determine the concentration of celecoxib in human plasma (Linnoila et al., 1983; Lieb et al., 1983; Calabrese et al., 1986; Ohishi et al., 1988; Seji et al., 1989; Musselman et al., 2001; Capuron and Gumnick, 2002). Celecoxib is marketed under the brand name celecoxib to minimize the adverse effect associated with classical nonspecific drug (Sherry Chow et al., 2004). It is also used to reduce inflammation after surgery.

Polymer-grafting have been applied for effective targeted drug delivery. The magnetic nano-particles used in an external magnetic field to guide and target specific points in the body are of priority (Gupta et al., 2007). The magnetic nano-particles in catalytic fields (Orita et al., 2013; Tsang et al., 2004), magnetic fluid (Chikazumi et al., 1987), and biotechnology (Gupta and Gupta, 2005), for drug release (Mahmoudi et al., 2009), targeted drug delivery (Laurent et al., 2011), and elimination of environmental pollution, have been taken into consideration. Magnetic nano-particles (MNP) are prepared using co-precipitation micro emulsion and hydrothermal methods. Smart polymers are macromolecules whose performance change as a result of a change in environmental conditions such as pH, temperature, electric field, ionic factors and magnetic field. These materials are also used in the biomedical field. Smart polymers have very promising application in the biomedical field as drug delivery systems. They are sensitive to temperature and therefore, an increase in temperature may result in drug release due to the shrinking of polymer chains. In the present study, magnetic nanoparticles were synthesized using co-precipitation method, and the graft co-polymerization of *n*-vinylcaprolactam and allylimidazole a functional monomer was done on the magnetic nano-particles surface. The grafted magnetic nano-particle was used as a nano-sorbent for the extraction of celecoxib from human biological fluids (Zhang et al., 2010; Pavaloiu et al., 2014; Li et al., 2012; Nampi et al., 2012).

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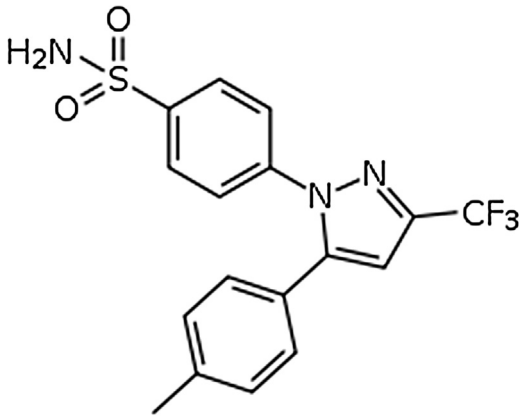

Fig. 1. Chemical structure of celecoxib.

2. Experimental

2.1. Chemicals and materials

All chemicals are of analytical standard and were used directly without further purification; including 3-mercaptopropyltrimethoxysilane, tetraethylortosilica (TEOS), trifluoroacetic acid (TFA), *n*-vinylcaprolactam (NVC), allylimidazole (AI), methanol (HPLC gradient grade), acetic acid, ethanol, 2,2-azobisisobutyronitrile (AIBN), and other materials and salts were purchased from Merck (Darmstadt, Germany). The active ingredient of the drug celecoxib was prepared from Razi Pharmaceutical Company. Stock standard solution of each celecoxib with concentration of 100 mg L^{-1} was prepared separately in methanol and stored at 4 °C.

2.2. Instrumentals

The ultra violet-visible (UV/vis) spectra were recorded using Perkin Elmer/Lambda 25 UV–vis spectrophotometer (USA). The pH measurement was done with a Metrohm 632-Switzerland. Chromatography separation was recorded using Agilent Technologist 1200 series/diode array detector/column C_{18}, 15 cm, 4.6 mm, 5 μm size particles (USA). The SEM micrographs (model SEM-PHILIPS XL30) was used for morphology measurement. Thermogravimetric analysis (TGA) was performed using TG/Sample+ correction TGA/DTA in Al_2O_3 crucibles at a heating rate of 10 °C/min from 820 to 200 mg under nitrogen purging.

2.3. Synthesis of functional polymer-grafted magnetic nano particles

Nano- particles can be synthesized using several chemical methods with their elemental composition or physical properties (Mahmoudi et al., 2009). The methodology used to synthesize, modify and polymerize is summarized in Fig. 2.

2.3.1. Synthesis of magnetic nano-particles

Here, co-precipitation method was used (Li et al., 2012). Briefly, a certain amount of $FeCl_3$·6H2O and $FeCl_2$·$4H_2O$ was prepared in 100 mL water. Thereafter, diluted ammonia solution was added to the contents under continuous nitrogen atmosphere for 2.5 h at 80 °C, until the color of the reactant turned black. Then, 40 mL of TEOS was added to the solution and mechanical stirred under ambient condition for 2 days. Finally, the nano-particles in the solution were separated by a strong magnet bar, then washed with ethanol and water, and dried in a desiccating vacuum.

2.3.2. Modification of iron nanoparticles by 3-mercaptoprpyltreemethoxysilane

In this step, a solution of 3-mercaptopropyltrimethoxysilane (5%) in toluene was prepared. Then 2 g of iron oxide nano-particle in 50 mL of above solution was refluxed for 48 h at 90 °C. The modified nano-particles were separated using a strong magnet, and washed twice with 20 mL of toluene and then dried in a vacuum oven at 40 °C.

2.3.3. Polymer grafting of NVC and AI onto MNP (NVC/AI-MNP)

Several methods have been used for grafting polymers onto magnetic nanoparticles. The functional monomer (AI) and thermosensitive polymer (NVC) were grafted onto the modified iron oxide nano-particles from the previous step. A mixture containing 3 g of thermosensitive monomer (NVC), 3 mL of AI, and modified iron oxide nano-particles from the previous step in 50 mL ethanol were prepared. Thereafter 0.1 g AIBN was added to the mixture and then refluxed under nitrogen atmosphere for 7 h at 65 °C. The grafted nano-particles were separated by strong magnet and washed with ethanol and then dried at room temperature.

2.4. Isotherm studies

In this study, isotherm adsorption studies were conducted with the addition of a certain value of NVC/AI-MNP to micro tubes with an equilibrium concentration of celecoxib at pH 5. Then the micro tubes were shaken at 25 °C for 30 min and centrifuged for 10 min. The adsorption equilibrium isotherms were fitted by Freundlich, Langmuir, Temkin and Redlich-Peterson isotherms. The values of celecoxib at equilibrium q_e (mg g^{-1}) on NVC/AI-MNP was measured using the following formula:

$$Q_e = V(C_0 - C_e)/W \quad (1)$$

In this equation, C_0 (mg L^{-1}) represents the initial concentration, C_e (mg L^{-1}) is the equilibrium concentration, V is the volume of the solution in liters, and W (g) is the mass of the NVC/AI-MNP.

2.5. HPLC system

The degassed mixture of 1 mL phosphoric acid 98% and 1 mL triethylamine in 600 mL water and 400 mL acetonitrile, at a flow rate of 1 mL min^{-1}, was used as a mobile phase in isocratic elution mode. The injection volume was 10 μL for all samples, and the detection was performed at a wavelength of 268 nm.

2.6. Batch method of celecoxib adsorption/desorption

A set of solutions (1.5 mL) containing 1 μg mL^{-1} of celecoxib were made, transferred to micro-tubes and the pH levels were adjusted to 5. NVC/AI-MNP (0.02 g) was added to each solution, and the mixture was vortexed for 10 min. The NVC/AI-MNP was separated from mixture magnetically and the adsorbed celecoxib was eluted using a methanol/acetic acid (3%) solution with ultrasonic assistant. The concentration of celecoxib in the methanol/acetic acid (3%) was determined by HPLC.

2.7. In vitro drug release

The release profiles of celecoxib from NVC/AI-MNP were determined in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.4). The celecoxib-loaded NVC/AI-MNP was put into beakers with shaking (30 rpm) at 37 °C. At scheduled time intervals, samples were taken, and the celecoxib content of each sample was determined by HPLC.