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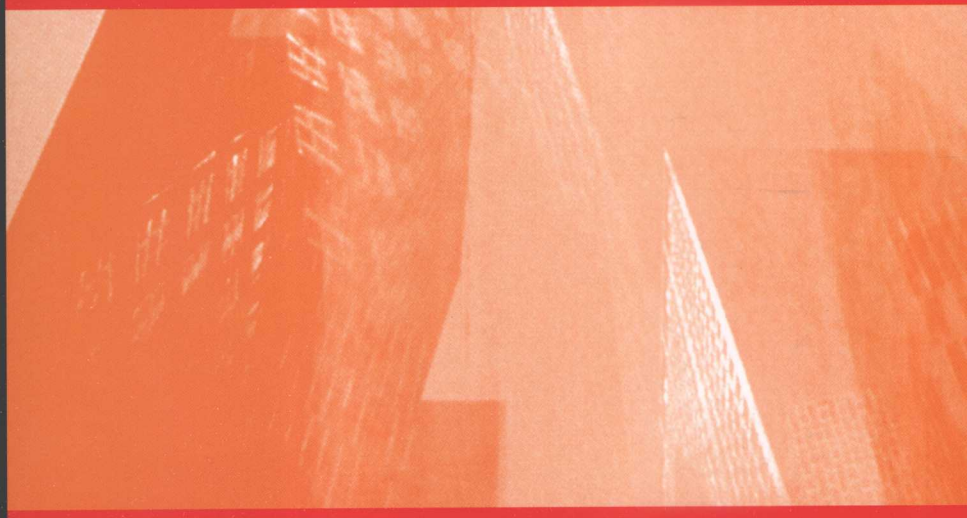
Nanostructured Biomaterials



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Preface

Nanostructured materials with designed biofunctions have been bringing rapid and significant changes in materials sciences. Nanostructured Biomaterials provides up-to-date reviews of different routes for the syntheses of new types of such materials and discusses their cutting-edge technological applications. The chemical synthesis and physicochemical preparation of nanosized materials are summarized with particular attention on the self-assembly of specific molecular and nanosized building blocks into functional nanostructures. The reviews mainly focus on potential applications of nanostructured materials in biology and medical sciences. The book is of general interest to a wide community of graduate students and researchers active in chemistry, materials science, engineering, biology, and physics.

Within the last decades, rapid advances in nanotechnology spurred great interest in nanostructured materials. In particular nanostructures with biofunctional properties are most promising, challenging traditional materials in many ways. Meanwhile a large variety of nanostructured artificial biomaterials with tailored morphologies and functionalities have been designed and fabricated.

In this book, we present recent achievements in the synthesis and application of nanostructured biomaterials. We will show our readers the exciting challenges in this unique research area and we hope to convince them of the many new research opportunities.

Silica-based mesoporous nanomaterials show remarkable potential as drug-delivery systems and biosensors. They are reviewed by Yang Yang and Junbai Li in Chapter 1. Natural substances possess sophisticated hierarchal structures. Yuanqing Gu and Jianguo Huang summarize in Chapter 2 how they are utilized as templates and/or scaffolds for the fabrication of nanostructured materials. In Chapter 3, Peiqin Tang and Jingcheng Hao introduce polyoxometalate-based hybrid nanomaterials, which are used especially for thin films formed by different deposition techniques. Nanometer-precise coatings of metal oxides on morphologically complex surfaces of natural cellulose substances are addressed in Chapter 4. It is shown how metal oxide, polymer, and protein-immobilized nanomaterials are produced by using "old-fashioned" biocellulose. In the last chapter, Yue Cui, Qiang He and Junbai Li describe functional nanomaterials that are synthesized by employing porous membranes as templates.

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Silica-based Nanostructured Porous Biomaterials

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1.1 Introduction

Recently, the application of nanomaterials in medical and biological fields has become more important. Nanoparticles (NPs) have been used as sensors, fluorescent markers, clinical diagnoses, drug delivery and MRI contrast agents (Lin et al., 2005). Inorganic, porous, ceramic nanoparticles have several advantages in biological applications. They are readily engineered with the desired size, shape, and porosity, and are often inert. The ceramic materials have surfaces with hydroxyl groups, and thus they are always hydrophilic (Paul, Sharma, 2001; Roy et al., 2003; Gemeinhart et al., 2005). Such natural hydrophilicity can decrease oxide particle clearance by the immune system, and thus increases their circulation time in blood (Barbe et al., 2004). Growing interest has recently emerged in utilizing porous ceramic nanomaterials as carriers in biological systems, exploring typical biocompatible ceramic nanoparticles, such as silica, alumina, and titania (Yih, Al-Fandi, 2006).

The International Union of Pure and Applied Chemistry (IUPAC) categorizes porous materials into three classes: microporous (<2 nm), mesoporous (2~50 nm), and macroporous (>50 nm). According to their pore sizes, terms such as porous nanomaterials, nanoporous materials, and nanostructured porous materials have been widely used to cover a variety of porous materials studied under bionanotechnology

(Sing et al., 1985). We will focus on the silica-based nanostructured porous materials with pore sizes ranging from a few nanometers to several tens of nanometers.

1.2 Silica Porous Materials in Drug Release Systems

Controlled drug-delivery systems (DDSs) have been facing a big challenge since the last decades. These silica-based nanostructured materials contain pores to provide spaces in loading drugs. By controlling morphological size and the shape of the material, one can design the required systems for the control of drug delivery.

1.2.1 Conventional Delivery Systems

An important prerequisite for designing an efficient delivery system is the capability to transport the desired guest molecules to the targets and release them in a controlled manner (Jin, Ye, 2007). Some toxic anti-tumor drugs are not expected to release before reaching the targeted cells or tissues. Biodegradable polymer-based drug-delivery systems highly rely on the hydrolysis-induced erosion of the carrier structure (Couvreur et al., 1995). The release of encapsulated compounds usually takes place too quickly as they are dispersed in water. In the process of drug loading, the polymer systems typically require the use of organic solvents, which might lead to the change of the undesirable structure and/or function of the encapsulated molecules. The *in vivo* degradation of synthetic polymers poses toxicity problems (Couvreur et al., 1995). The naturally selected polymers have problems with the monomer purity. Liposomes or micelles suffer from poor chemical stability. Thus the newly designed materials need to overcome the above shortcomings.

1.2.2 Silica Porous Materials for Release Systems

Since MCM-41 was synthesized in the 1990s as a member of the M41S family of molecular sieves (Kresge et al., 1992), the mesoporous silica material had been proposed as a DDS to solve the above mentioned problems. In general, mesoporous materials are derived from molecular assemblies of surfactants as templates during synthesis (Kresge et al., 1992; Huo et al., 1994; Zhao et al., 1998; Sakamoto et al., 2004). After the removal of the surfactants, the silica mesoporous materials are achieved. As drug carriers, they possess the following features:

(1) An ordered pore network and homogeneous size for the purpose of the drug loading;

(2) A high pore volume to host the required amount of drug molecules;

(3) A high surface area with a high potential for drug adsorption;

(4) A silanol-containing functionalized surface allows better control over drug loading and release;

(5) Micro- to mesoporous silicas can selectively host molecules (Vallet-Regí et al., 2007). These unique features make mesoporous materials good candidates for controlled drug-delivery systems, based on the many investigations which have been done in recent years.

1.2.3 Various Mesoporous Silica in Drug Delivery Systems

Various mesoporous silica such as M41S, FSM, TUD, and SBA have been designed into DDSs. MCM-41 is the most frequently used mesoporous silica material based drug carrier. They have the ordered hexagonal molecular sieve with large surface areas (>1000 m^2/g), high pore volumes (>0.7 cm^3/g), and a very uniform pore structure (pore diameter 2~3 nm) (Beck et al., 1992; Kresge et al., 1992). MCM-41 is applied with different pharmaceutical compounds such as ibuprofen (Vallet-Regí et al., 2001; Andersson et al., 2004; Charnay et al., 2004), vancomycin (Lai et al., 2003), model compound fluorescein (Karen, Fisher, 2003), diflunisal and naproxen (Cavallaro et al., 2004), hypocrellin A (Zhang et al., 2004), and aspirin (Zeng et al., 2005). And it is also used by including proteins such as cytochrome C and myoglobin for therapy (Deere et al., 2003). MCM-48, the cubic ordered silica material, has also been utilized for the immobilization of protein (Washmon-Kriel et al., 2000) as well as for the encapsulation of small molecule drugs (Izquierdo-Barba et al., 2005). Kuroda et al. reported that Taxol, an anticancer substance, was adsorbed into FSM-type mesoporous silicas with the pore sizes larger than 1.8 nm, while it was not adsorbed into the channels with the pore sizes less than 1.6 nm, indicating that mesoporous silicas have a molecular sieving property for relatively large molecules. The results obtained indicate the potential application of mesoporous silica as a new synthetic vessel (Hata et al., 1999). Moreover, the siliceous mesoporous material, Technische Universiteit Delft (TUD-1), was also studied as a drug delivery vehicle (Jansen et al., 2001). TUD-1 is one of the new mesoporous materials. TUD-1 is synthesized as siliceous, containing only biocompatible amorphous mesostructured silica. It has a foam-like mesoporous structure, where the mesopores are randomly connected in three dimensions. Heikkila's study proved that the highly accessible mesopore network allowed ibuprofen to be adsorbed into TUD-1 with a very high efficiency and the amount of loaded drug exceeded the reported values for other biocompatible mesoporous silicas such as MCM-41 and MCM-48. The drug dissolution profile of TUD-1 material was found to be much faster and to have more diffusion when compared to the mesoporous MCM-41 material (Heikkila et al., 2007). Another mesostructured silica with 2D hexagonal structures, SBA, was also often used as DDSs. Qu et al. employed MCM-41 and SBA materials with variable pore sizes and morphologies as controlled delivery systems for the water soluble drug captopril. Captopril could be successfully loaded

into the channel of mesoporous silica materials. The drug loading and release kinetics was correlated to morphologies and pore sizes of mesoporous silica (Qu et al., 2006). Adsorption experiments carried out with alendronate (Vallet-Regí et al., 2007) (small molecule) and albumin (Manzano et al., 2006) (macromolecule) on SBA-15 indicate that the very high or very low drug molecule/pore size ratios are, in both cases, inadequate for incorporating large amounts of drugs.

1.2.4 Stimuli-responsive Mesoporous Silica for Delivery Systems

It is highly desirable to design delivery systems that can respond to external stimuli and release the guest molecules at specific sites. To achieve this goal, several groups developed a series of stimuli-responsive mesoporous silica delivery systems, including photo-responsive, pH-responsive, thermo-responsive, and enzyme-responsive delivery systems.

1.2.4.1 Photo-responsive System

Fujiwara et al. have developed a photo-responsive release system for direct-drug release applications based on pore-entrance modification with coumarin groups. These groups undergo reversible dimerization upon irradiation with UV light at wavelengths longer than 310 nm, and return to the monomer form by subsequent irradiation at shorter wavelengths. The dimer form of the coumarin, when grafted on the surface of mesoporous silica systems, reduces the effective pore size of the matrix, and subsequently hinders the adsorption of molecules into the pore voids as well as their release from them. Adequate irradiation of the material opens the entrance to the pores and the adsorbed drugs can be released (Mal et al., 2003a; 2003b). Another photo controlled DDS based mesoporous silica is a kind of molecular machine called a "nanoimpeller" developed by Zink group (Angelos et al., 2007a; Lu et al., 2008). It was made by immobilizing an active molecule having photo responsive behaviors such as azobenzene derivatives to the mesostructured silica framework. It is reported that azobenzenes in nanostructured silica will go through *cis*-trans isomerization after continuous illumination at 413 nm (Liu et al., 2003a; Sierocki et al., 2006). The bifunctional strategy was used to attach a small azobenzene to the interiors of the pores templated by the surfactant. This method involved the coupling reaction of the azobenzene with a silane linker followed by co-condensation with the TEOS silica precursor (Liu et al., 2003b). After removing the surfactant, particles contained azobenzenes with one side bonded to the inner pore walls and the other free to undergo reversible isomerization which creates a large amplitude wagging motion capable of functioning as nanoimpellers to release pore contents from the particles (Fig.1.1).

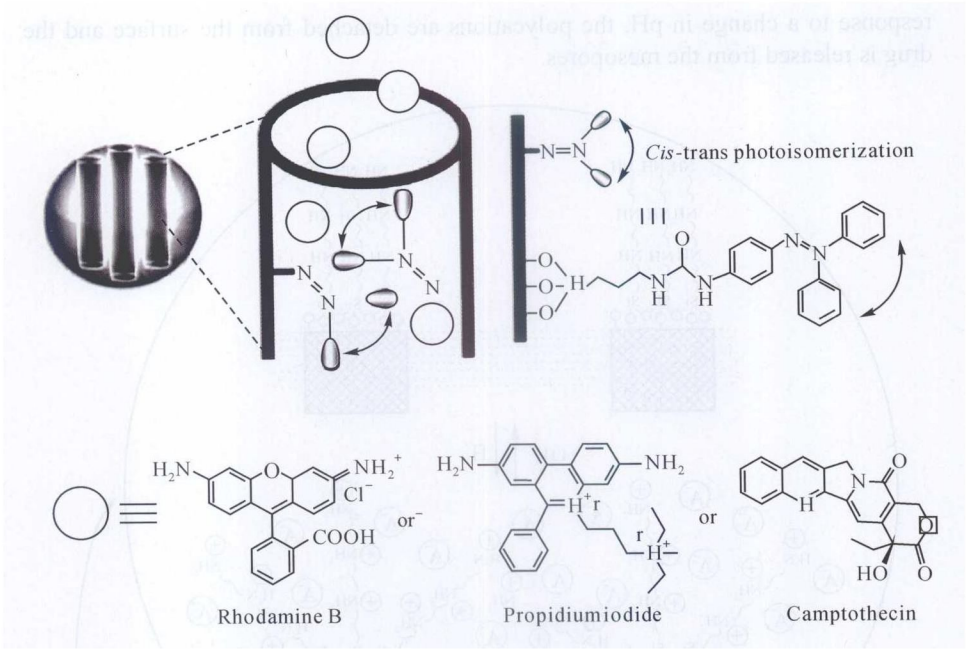

Fig.1.1. Designed pore interiors of the light-activated mesostructured silica (LAMS) nanoparticles functionalized with azobenzene derivatives. Continuous illumination at 413 nm causes a constant *cis*-rans photoisomerization about the N-N bond causing dynamic wagging motion of the azobenzene derivatives and results in the release of the molecules through and out of the mesopores. Copyright (2008), with permission from Wiley

1.2.4.2 pH-responsive System

Ionically controlled nanoscopic molecular gates were also designed by using functionalized mesoporous materials by Marinez-Manez et al. (Casasus et al., 2004). The molecular gate referred to a basic device that modulates the access to a certain site and whose state (opened or closed) can be controlled by certain external stimuli. In their study, the functionalized mesoporous silica materials were synthesized so that the polyamines groups were at the external surface while the mercaptothiol groups remained inside the mesopores (Fig.1.2). They introduced a pH-controlled gate mechanism which comes from hydrogen-bonding interactions between amines (open state) and coulombic repulsion between ammonium groups (closed state). They also verified pH-controlled and anion-controlled mechanisms by using a colorimetric reaction consisting of the selective bleaching of a blue squaraine dye by reaction with the mercaptopropyl groups. Xiao and co-workers also designed pH-responsive carriers in which polycations are grafted to anionic, carboxylic acid modified SBA-15 by ionic interactions (Yang et al., 2005). Drug molecules such as vancomycin can be stored and released from the pore voids of SBA-15 by changing pH at will. In this system, the polycations act as closed gates to store the drug within the mesopores (Fig.1.3). When the ionized carboxylic acid groups are protonated in

response to a change in pH, the polycations are detached from the surface and the drug is released from the mesopores.

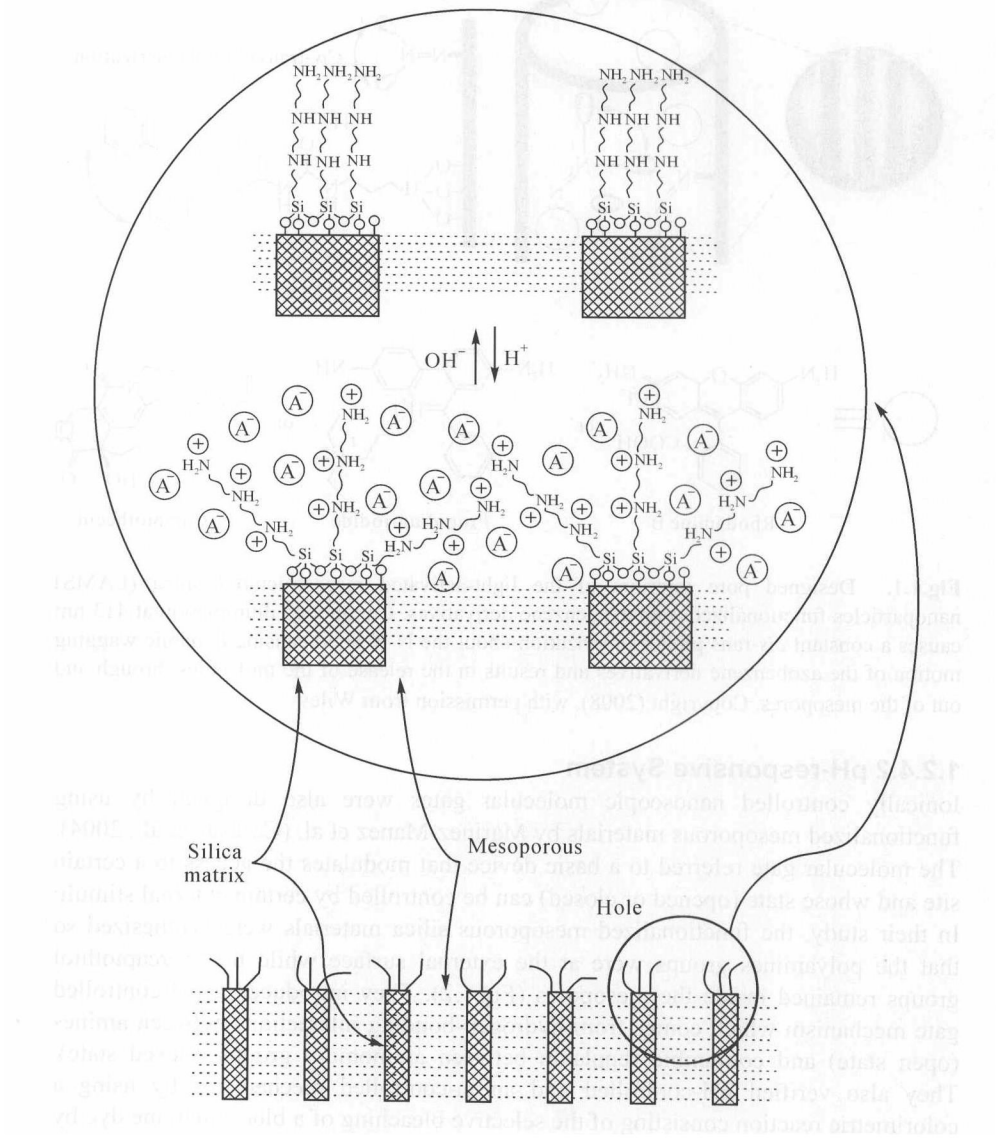

Fig.1.2. Representation of solid Si with a scheme of the ionically controlled nanoscopic "Molecular Gate" mechanism. Copyright (2004), with permission from the American Chemical Society

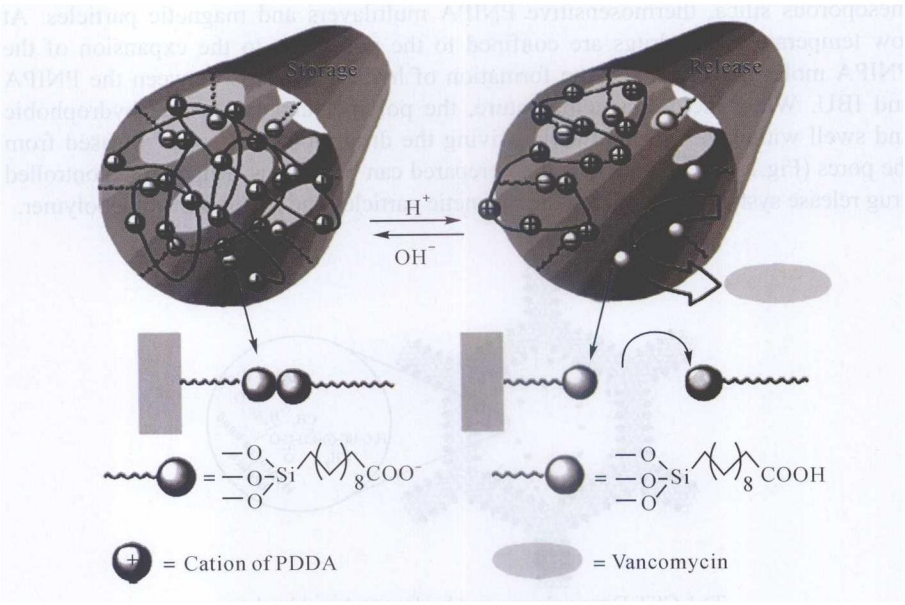

Fig.1.3. Schematic representation of pH-responsive storage-release drug delivery system. This pH-controlled system is based on the interaction between negative carboxylic acid modified SBA-15 silica rods with polycations. Copyright (2005), with permission from the American Chemical Society

1.2.4.3 Thermo-responsive System

Thermosensitive polymer, such as poly (*N*-isopropylacrylamide) (PNIPA), has often been used as a drug delivery material because of its lower critical solution temperature (LCST) at about 32 °C which is close to physiological temperature (Pelton et al., 1989; Pelton, 2000; Li et al., 2007). PNIPA undergoes a thermo-induced conformational change from the swelled, hydrophilic state to the shrunken, hydrophobic state above LCST in water. López and co-workers prepared PNIPA-grafted MCM particles for controlling molecular transportation (Fu et al., 2003; 2007). In their work, the porous network of silica was modified by PNIPA by atom transfer radical polymerization (ATRP). At lower temperature, *e.g.* room temperature, the PNIPA is hydrated and extended, and inhibits transport of solutes; at higher temperature, *e.g.* 50 °C, it is hydrophobic and is collapsed within the pore network, thus allowing solute diffusion. Uptake and release of fluorescent dyes from the particles were verified by several characterization methods. Zhu et al. also fabricated a site-selective controlled delivery system for controlled ibuprofen (IBU) release through the *in situ* assembly of thermo-responsive ordered SBA-15 and magnetic particles (Zhu et al., 2007). The approach is based on the formation of ordered mesoporous silica with magnetic particles formed from $Fe(CO)_5$ via the surfactant-template sol–gel method and control of transport through polymerization

of *N*-isopropylacrylamide inside the pores. The system combines the advantages of mesoporous silica, thermosensitive PNIPA multilayers and magnetic particles. At low temperature, the drugs are confined to the pores due to the expansion of the PNIPA molecular chain and the formation of hydrogen bonds between the PNIPA and IBU. When increasing temperature, the polymer chains become hydrophobic and swell within the pore network, driving the drug molecules to be released from the pores (Fig.1.4). The materials they prepared can be used as temperature controlled drug release systems by inducing the magnetic particles and thermosensitive polymer.

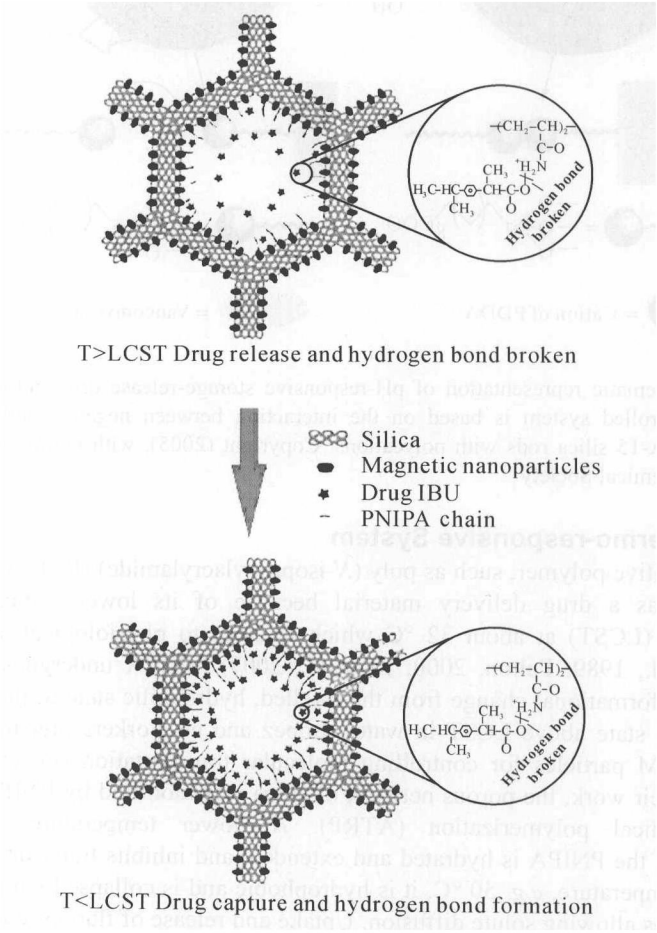

Fig.1.4. Schematic representation of the stimuli-responsive delivery system based on SBA-15 with magnetic particles formed as the target label (LCST: lower critical solution temperature). Copyright (2007), with permission from Wiley