Highlights

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# The Quest of Smart Nanomaterials for Multiple Drug Delivery

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## Highlight

Recently, the research of smart nanomaterials embedded with molecular and nano-machines has gained much attention on accounting for their prolific applications in the fields of nanotechnology, in particular for controlled drug delivery and bio-mimetics. For biomolecules and various biological systems, the functions of the sensor, processor and effector are associated with the hierarchical structures based on covalent or noncovalent bonds. Combining these functions in synthetic nanomaterials could lead to a mimic of the natural feedback systems. The realization of the proposed research idea would hopefully shed light on mimicking functional enzyme systems [1-4].

For example, “smart” switchable interlocking molecules could be attached to the pore orifices of mesoporous silica nanoparticles. Subsequently, the macrocyclic component threaded on the interlocked molecule’s backbone by noncovalent interactions could serve as the gate that controls access of guest molecules into and out of the nanopores of the mesoporous silica nanoparticles, to act as nanovalves [5,6]. One of the attractive features of nanovalve systems is the ability to induce controlled release (a diffusion-controlled system) of guest molecules from the nanopores using various external stimuli such as pH change [7] addition of salts, [8] redox process, [9] and light [10]. Moreover, these ON/OFF switchable molecular nanovalves process superior properties of reversibility and reusability of the materials as well as the regional and temporal control of substrate release. To facilitate practical biomedical applications in vivo, the use of non-invasive low-intensity ultrasound [11] has been routinely employed for pregnancy diagnosis, as a stimulus to trigger drug release from the drug-encapsulated smart materials. On the other hand, the ability to carry hydrophobic and hydrophilic drugs to specific cancer site (targeting) is beneficial to cancer treatment with smart materials [12]. In particular, smart materials that are responsive to significant pH change between cancerous cells (pH~5) and normal cells (pH~7), are candidates for targeted therapy. Recently, relatively non-cytotoxic iron oxide magnetic nanocomposites with tunable particle and pore sizes and their hollow and core/shell derivatives were introduced to successfully demonstrate a better magnetic separation method for recycling the nanomaterials from the reaction mixture using a magnet [13-20]. Different magnetic hybrid nanostructures have been successfully fabricated in spheres, wires, etc, which would be capable to covalently attach or physically encapsulate supramolecules, organic molecules, and drugs [21-26]. For covalent attachment of molecules, the process can be performed by chemical coupling reactions between molecules with functional groups and nanoparticles with reactive surface at their periphery or at the mesopores. For physical encapsulation of molecules to the nanoparticles, porous nanoparticles with tunable pore size can be employed. Furthermore, several types of organic-inorganic hybrid magnetic nanoparticles based on superparamagnetic iron oxide (any size in the range of 10–250 nm) with tunable pore size (2, 5, 10 nm, etc.) could be successfully synthesized in high yields. These nanoparticles possess specific shapes hybrid coating (e.g., organic polymers), which require sophisticated, fine-tuned synthetic procedures. The as-synthesized iron oxide (Fe3O4)-based composite/hybrid nanoparticles can be superparamagnetic, which are crucial as contrast agents for magnetic resonance imaging (MRI).

Current attempts on loading two different drugs or both drug and gene together into porous nanoparticle systems have been demonstrated on successful drug and therapeutic gene codelivery [27-29]. Chen and Shi et al. surveyed a group of porous nanosystems (silica, iron oxide, gold, silver, quantum dot, carbon nanotube, graphene oxide, layered double hydroxide, etc.) for drug-gene codelivery at the same time [27]. Johnson et al. reported a poly(norbornene) nanoparticle system for triple drug (cisplatin, doxorubicin, and camptothecin) release with a controlled ratio [29].

In principle, smart multiple drug delivery to a particular targeted lesion site may produce miniaturized “cocktail therapy” and possibly overcome drug resistance. Different combinations of drugs can have synergistic pharmaceutical effects. The development of next-generation future multiple drug-loaded smart nanoparticle systems would have vast scope by multiple drug combinations for targeted diseases and cancers. The potential success in (1) combining different drug components (two or more) to be loaded into the nano-vehicle system with appropriate binding affinity or covalently attachment site; (2) tethering biotargeting vectors onto the surface of nanoparticles; (3) low cytotoxicity; (4) operating and monitoring of the multiple drug-loaded smart nanoparticle systems for stepwise and

controlled release of two or more different drugs by enzymatic cleavage, pH control, or ultrasound stimuli, etc; and (5) monitoring by imaging techniques such as MRI, fluorescent imaging, ultrasound imaging, etc, renders the feasibility of this work.

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