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Intelligent recognitive systems in nanomedicine

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Abstract

There is a bright future in the development and utilization of nanoscale systems based on intelligent materials that can respond to external input providing a beneficial function. Specific functional groups can be incorporated into polymers to make them responsive to environmental stimuli such as pH, temperature, or varying concentrations of biomolecules. The fusion of such "intelligent" biomaterials with nanotechnology has led to the development of powerful therapeutic and diagnostic platforms. For example, targeted release of proteins and chemotherapeutic drugs has been achieved using pH-responsive nanocarriers while biosensors with ultra-trace detection limits are being made using nanoscale, molecularly imprinted polymers. The efficacy of therapeutics and the sensitivity of diagnostic platforms will continue to progress as unique combinations of responsive polymers and nanomaterials emerge.

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Introduction

Inspiration for the development of intelligent polymers is often drawn from nature. Almost all biological processes are triggered by local variations in pH, temperature, or analyte concentration. Biomolecules are able to respond to their environment because they have functional groups that participate in combinations of non-covalent interactions. Through rational chemical synthesis, scientists can capture the responsive essence of biomolecules in synthetic materials. The ability to fabricate these materials at the nanoscale allows further manipulation of their properties and brings them to a size that is more clinically relevant than bulk materials [1–3]. The responsive character of these nanomaterials can be exploited for a number of applications, including controlled delivery of therapeutics or molecular recognition for sensing applications (Figure 1) [4–5].

Along with the ability to respond to external stimuli, the small size itself imparts unique characteristics to nanomaterials, and thus it is our belief that such nanomaterials will be used in a large number of chemical and biomedical engineering applications. They are ideal transducing elements for translation of a chemical, physical or mechanical input to a beneficial output. In the simplest possible system, the relationship between input and output is a linear function. Yet, this linearity is almost never achieved for polymers due to the viscoelastic nature of macromolecular systems, which calls for a nonlinear response. However, as the dimension of the material approaches the nanoscale, the response approaches linearity. Additionally, materials have unique physical properties at the nanoscale because of quantum confinement and surface effects, offering improvements in detection applications [6].

There are also distinct biological responses to materials that have been fabricated at the nanoscale. For example, several transport processes in the body are size dependent, with many that are exclusive to materials lower than100 nm in diameter [7,8]. Furthermore, nano-patterning on substrates can control protein adhesion and cell spreading behavior because nanoscale features emulate those present in a cell’s native extracellular matrix [9]. The marriage of stimuli-responsive and nanosized materials has resulted in brilliant materials with tremendous potential in medical applications. Here we underline some impressive research from recent years and offer our scientific opinion on the promising future of intelligent biomaterials in nanomedicine.

Stimuli-responsive materials

The capability of systems to selectively target diseased tissues and intelligently respond to physiological changes helps provide rapid treatment without systemic side effects [10]. There are a large number of explored stimuli-responsive systems that include pH, temperature, light, magnetic fields, and molecule specific interactions. The most widely studied include pH and temperature and are the main focus of present developments and new systems. Gradients of pH exist between organs, cancerous tissue, and intracellular compartments, allowing pH responsive systems to target areas based on intrinsic properties rather than external triggering. The relevant nanomaterials, triggered by a pH change,

undergo swelling, dissociation, or changes in surface charge to elicit a desired action whether for drug delivery, sensing, or other applications.

pH-Responsive systems for transmucosal drug delivery

pH-Responsive systems are major components of new devices for detection of external changes in pH, leading to associated thermodynamic, mechanical or morphological changes. The ensuing dimensional changes are often associated with increased hydraulic or osmotic pressure leading to the intelligent response. Of particular interest and promise for additional future uses we find pH-responsive polymers, and especially hydrogels, applicable to drug, peptide, or protein release in the nasal, buccal, sublingual, gastrointestinal, or vaginal areas. The pH transitions in these areas have often been utilized for drug delivery to protect them from damaging conditions and release molecules in the right location as seen in Figure 2 for both oral and intratumoral delivery. These systems often involve hydrophilic polymer networks that remain complexed at low pH but swell at the neutral pH of the intestine. The mechanism by which nanoparticle hydrogels undergo swelling is well understood and is dependent on the type of pendant groups present on the polymer backbone. A thorough review of hydrogels, swelling behavior, and their applications in medicine is beyond the scope of this article, but we note here such reviews that describe their fundamental behavior [11,12]. Briefly, ionization of weakly acidic (e.g., carboxylic acids) or basic (e.g., amines) pendant groups changes with pH, producing an osmotic gradient between the interior and exterior of the gel causing water to be imbibed or expelled. Networks containing acidic groups swell with increasing pH, as they are deprotonated, while basic groups swell with decreasing pH as depicted by the solid and dashed lines in Figure 2A, respectively [13,14].

While oral delivery is acceptable for certain compounds, other degradable therapeutics, in particular proteins such as insulin and calcitonin, must be protected from the low pH and digestive enzymes of the stomach before being released in the more neutral pH of the intestine. In the past 20 years, numerous technologies have been proposed and used in such applications. These systems include swollen crosslinked polymeric networks (hydrogels) containing acrylic acid, methacrylic acid, 2-(diethyl amino)ethyl methacrylate, and related anionic and cationic polymers.

We find hydrogel micro- and nanoparticles of poly(methacrylic acid)-grafted-poly(ethylene glycol) and poly(methacrylic acid-co-N-vinylpyrrolidone) as promising carriers that have demonstrated an intestinally relevant pH swelling response for proteins by forming a complex at low pH and swelling at higher pH [15]. With rational selection of the monomer units, molar feed ratios, and crosslinking density, both low and high molecular weight proteins like insulin, calcitonin, and growth hormone were delivered and the kinetics modified [16,17]. Schoener et al. investigated two systems that improved the loading and release of hydrophobic drugs like chemotherapeutics by including an interpenetrating network of hydrophobic poly(n-butyl acrylate) [18]. Alternatively, they also encapsulated hydrophobic poly(methyl methacrylate) nanoparticles into the pH-responsive hydrophilic networks [19].

pH-Responsive materials in cancer therapy

Another developing area of interest for pH-responsive nanoparticles lies in the detection and treatment of cancer. Tumors have an acidic extracellular environment due to their high metabolic rates and hypoxic environment that result in ATP hydrolysis and lactic acid production [20]. pH-responsive systems can increase drug concentration at the tumor while limiting exposure to healthy tissues. Again, for a more extensive review of cancer biology and applications of nanoparticles for treatment consult [21–23].

One approach is to load drug into the hydrophobic core of block copolymer micelles with that segment containing the pH-sensitive copolymer poly(β-amino esters) [24]. Due to protonation at low pH, this segment has higher hydrophilicity resulting in an increased release rate of hydrophobic doxorubicin. Another chemotherapeutic, paclitaxel, was loaded into acetylated cyclodextrin nanoparticles that undergo hydrolysis at a slightly acidic pH of 5, but not at 7.4, and consequently showed improved cytotoxicity to tumors in a mouse model over solubilized paclitaxel [25]. In this instance, the pH-sensitivity works in the researchers' favor for both release at the tumor tissue and for those particles endocytosed by tumor cells. The drug loaded nanoparticles showed improved cytotoxity to multidrug resistant cancer cell lines likely due to the nanoparticles release of paclitaxel within the low pH of the endosome and thus overcoming the P-glycoprotein efflux pump.

A novel approach for the delivery of proteins into cells for cancer therapy and other applications involved the synthesis of a thin, pH-sensitive polymeric coating around single proteins. First, vinyl groups were covalently attached to the protein and then polymerized with monomers 2-diethylaminoethyl methacrylate and acrylamide and degradable crosslinker glycerol dimethacrylate. Nanoparticle size and surface charge could be modified by varying monomer ratios. The resulting thin polymer shell protected proteins from proteolysis and increased uptake compared to cell penetrating peptide conjugated proteins. The shell degraded within the endosome to release a functional protein [26].

Recently there has been increased interest in using recombinant synthesis to construct delivery vehicles from proteins or DNA. Recombinant synthesis allows very specific structure, functionality, and nearly identical size distribution of particles, in addition to natural degradation byproducts. For example, the dihydrolipolyl acyltransferase subunit (E2) of pyruvate dehydrogenase forms a hollow 25 nm dodecahedral protein cage. The protein complex has been modified to allow conjugation of molecules both within the interior for delivery and externally for targeting. Researchers added pH-sensitivity to the subunit-subunit interactions by adding histidine at an interface. At low pH the histidines are protonated and charge repulsion reduces the stability of the cage [27]. When the interior of the cage was modified with cysteines for doxorubicin conjugation, researchers observed accumulation in the endosomes as required for pH-responsive release and subsequent cytotoxicity of MDA-MB-231 human breast cancer cells [28].

We believe that efforts in this field will increase in the years to come with design of advanced nanoparticulate systems that will be targeted to specific sites and uptaken by cells to provide therapeutic conditions [29,30]. Of course, other authors have pointed out some of the shortcomings of nanoscale systems for treatment of certain types of cancers [31,32].

pH-Responsive materials for imaging and sensing

Responsive systems have found new applications in theranostics, an emerging field that combines intelligent behavior, recognitive characteristics, imaging capabilities, and therapeutic advantages [33]. Theranostic carriers have key components such as targeting moieties, therapeutic agents, noninvasive imaging components, and polymer carriers including conjugates that provide desirable drug delivery windows [34].

The identification of diseased tissues has benefited from pH-responsive nanosystems as well. Researchers developed a diblock copolymer micelle with the pH-responsive element, poly(β-amino ester), at the core containing hydrophobic Fe_3O_4 nanoparticles. The tertiary amine groups switch the element from hydrophobic to hydrophilic by protonation in an acidic environment releasing the magnetic nanoparticles at both tumor and ischemic tissue [35]. The researchers then modified the system to include amido amines to increase resistance to hydrolysis and further investigated its use for imaging cerebral ischemia in a diseased rat model. They observed changes in MRI images indicating gradual accumulation of Fe_3O_4 particles in the damaged area [36]. Wu et al. synthesized a pH-sensitive poly(ethylene glycol-co-methacrylic acid) hydrogel synthesized around an Ag coated Ni magnetic core nanoparticle. They utilized the pH response of poly(ethylene glycol-co-methacrylic acid) to increase both accumulation and photoluminescence at low pH [37]. The particles swell at higher pH, inhibiting diffusion and thus slowing accumulation rate as compared to low pH. Other exciting systems combine functionalities. Guo et al. coated superparamagnetic Fe_3O_4 cores with a pH-responsive polymer shell to use as an MRI contrast agent for live particle tracking and diagnostics. When protonated at low pH, this system releases hydrophobic adriamycin. Additionally, by adding folate to the nanoparticle they are able to preferentially target tumor cells. By combining functionalities this system can image tumor tissue, deliver drug, and allow evaluation of the nanoparticles' targeting efficacy [38].

Nanoscale sensors can respond rapidly to changes in their environment and be utilized in new ways due to their small size. Lee et al. synthesized nanorods and nanospheres capable of ratiometric sensing over a physiologically relevant range using a chromophoric crosslinker in shell-crosslinked knedel-like nanoparticles [39]. Another ratiometric polyurethane nanogel system utilized fluorescence resonance energy transfer (FRET) of the encapsulated fluorophores coumarin 6 (C6) and Nile Red in the presence of bromothymol blue (BTB). BTB undergoes an absorption spectra shift that overlaps with C6 and Nile Red emission at low and high pH, respectively [40]. Another sensor involves pH-responsive hydrogels polymerized on top of silicon microcantilevers. As the hydrogel swelled with increasing pH it caused a deflection of the beam that was measured optically with high sensitivity [41].

Temperature responsive materials

As mentioned previously, pH-responsive materials have gained the most attention but other systems use temperature change as a stimulus, usually for drug delivery. Gold nanoparticles coated with a thermally responsive interpenetrating network of polyacrylamide and poly(acrylic acid) showed a strong swelling response to temperature. These could be useful

for drug delivery through external triggering by local temperature increases from laser heating [42]. Introducing local hyperthermia to trigger a targeted response has repeatedly shown promise, including in vivo. Temperature sensitive liposomes (TSLs) have received particular interest due to a melting temperature of 39–42°C that can be achieved with mild hyperthermia [43]. TSLs can dose heated tumor tissue with 7.6 fold greater concentrations of doxorubicin than freely administered drug while also administering it more evenly through the tumor tissue including the core [44]. Other researchers used TSLs to encapsulate the MRI contrast agent [Gd(HPDO3A)(H_2O)] with doxorubicin to enable imaging and quantitative analysis of the drug released [43].

Temperature responsive poly(N-isopropylacrylamide) (PNIPAAm) polymers have been used as micromolds for several applications. In one application, the molds allow cell aggregates to be retrieved with higher efficiency than PEG molds by decreasing the temperature from 37°C to 24°C with the resulting swelling effectively pushing the aggregates out of the well [45]. The molds' shape change at two temperatures also permits a sequential molding step allowing new spatial orientations like cylinders and cubes that contain two compartments. These compartments can encapsulate different compounds or cells within each layer making it a useful tool for drug delivery or tissue engineering. Additionally the molds enable the use of a wider range of polymers than photolithography which requires photoreactive crosslinkers [46].

Materials capable of molecular recognition

Synthetic materials with recognition characteristics are another popular subset of intelligent biomaterials. Molecularly imprinted polymers (MIPs) are polymers capable of selective recognition of a target molecule. The recognition properties of MIPs are achieved by selecting monomers with functional groups complementary to those on the surface of a target molecule. Polymerization is carried out in the presence of the target molecule (i.e., template), which is subsequently washed out, leaving cavities that are complementary to the template in both shape and functionality. In recent years, there has been a remarkable increase in the number of studies that employ MIPs [47]. Advances in the development of nanoscale MIPs are reviewed in great detail elsewhere [48–50].

Many areas of medical research, including pharmaceutical development, diagnostics, and therapeutics rely on sensitive recognition elements, which are most often biomolecules such as antibodies, enzymes, or nucleic acids. The ease of production, chemical tunability, and relatively low cost of MIPs has promoted their use in place of natural biomolecules for such applications. This section will highlight a small selection of exciting, recent studies investigating the use of imprinted nanomaterials for medical applications.

Pharmaceutical Development

The biological activity of molecules is highly dependent on their size, orientation, and functionality. Even enantiomers can have significantly different biological activities and thus it is often necessary to quantify and separate enantiomers during pharmaceutical development. For example, malic acid (MA) is a chiral molecule, where only the L-form is pharmaceutically useful. Prasad and Pandey developed ultra-thin (i.e., 4.1nm),

enantioselective MIP films for MA on the gold surface of a quartz-crystal microbalance (QCM). Even in complex media such as serum, the MIP-modified QCM sensors could selectively recognize their target enantiomer, demonstrating the ability of MIPs to imitate the recognition sites of the natural MA receptor [51]. Another way to exploit this receptor-mimicking characteristic of MIPs is in ligand-based screening, where a known ligand is used for imprinting and the resultant MIP is used to probe binding affinity of other potential ligands. Lakka, et al. demonstrated this by imprinting polymers with a known Hypoxia-Inducible Factor-1 (HIF-1) inhibitor, quercetin. HIF-1 is a protein whose transcriptional activity is increased in the hypoxic environment of tumors. By incubating the MIPs with frankincense, a natural anticancer remedy, they identified and isolated other bioactive compounds that work as HIF-1 inhibitors [52].

Furthermore, coupling MIPs with carbon nanotubes is extremely powerful for ultrasensitive electrochemical detection of clinically relevant molecules, such as drugs. Accurate and sensitive determination of drug levels in biological and pharmaceutical samples is crucial for assigning dosages that will maximize efficacy and minimize side effects. Afkhami, et al. developed a novel electrochemical sensor capable of detecting sub-micromolar levels of tramadol, a centrally acting analgesic that can be fatal if overdosed, in urine and in pharmaceutical tablets for sample analysis purposes. A MIP for tramadol was synthesized on the surface of silica-coated magnetite nanoparticles. Then, carbon paste electrodes (CPE) were modified with these MIP-nanoparticles and multi-walled carbon nanotubes (MWCNTs). Compared to both a CPE modified with NIP-MWCNT and an unmodified CPE, the MIP-MWCNT CPE had the highest sensitivity [53].

Diagnostics

Sensors that combine nanomaterials and MIPs can also be used for diagnostic applications. These sensors are promising alternatives to current diagnostic tests that often have low specificity, insufficient detection limits, or employ expensive, unstable biomolecules as the recognition element. In a very recent study, Cai, et al. synthesized non-conductive, protein-imprinted polymers on the tips of carbon nanotubes for electrochemical sensors. The modified sensors discriminated between structurally similar proteins, as well as between different conformations of the same protein. The detection level was around 10 pg/L, a value comparable to the sensitivity seen with biomolecule-based nanosensors [54].

Microfluidic paper-based analytical devices are leading candidates for inexpensive, portable sensors for point-of-care diagnostics. In particular, origami paper analytical devices are gaining significant attention because of their low cost and simplicity [55]. However, like most diagnostic tests, they rely on natural biomolecules for recognition and/or signal transduction. Maintaining the stability and activity of these molecules during fabrication and transportation is challenging if not impossible. As an alternative, lab-on-paper devices that utilize MIPs as the recognition element have recently been explored for the first time. Researchers fabricated a microfluidic electro-analytical origami device capable of enantioselective, nanomolar-level detection of D-glutamic acid, an excitatory neurotransmitter [56]. Brain damage can occur if extracellular levels are elevated due to a central nervous system disorder. These researchers also demonstrated the use of a similar

device for detection of heptachlor [57], rendering MIP-based origami paper analytical devices potentially useful for point-of-care diagnosis.

The application and success of MIPs in optical-based nanosensors has also been shown. Quantum dots (QDs) have unique optical properties that make them useful for diagnostics and thus are a popular substrate choice for surface imprinting. For example, in response to protein binding, MIP-coated, Mn-doped ZnS QDs showed a concentration dependent decrease in phosphorescence activity [58]. Lee, et al. also used MIP-QDs, but their sensor took advantage of the fluorescent property of QDs to replace fluorescently tagged antibodies in an ELISA-type assay for detection of three target proteins [59]. Other popular nano-substrates for imprinting are noble metal nanomaterials. Abbas et al. exploited the localized surface plasmon resonance (LSPR) of gold nanorods to sensitively detect protein biomarkers. By synthesizing thin, biomarker-imprinted polymers on the nanorod ends, concentration dependent shifts in the LSPR wavelength were observed with a sensitivity of 0.25 nm/nM. LSPR wavelength shifts due to non-specific adsorption of competitor proteins were minimal (< 1nm) [60]. These studies have shown that inclusion of nanomaterials with unique properties can lead to MIP-based biosensors with remarkably low detection limits, as summarized in Table 1.

Immunology and therapeutics

As discussed in the previous section, stimuli responsive nanomaterials are popular options for targeted delivery of therapeutics. To this aim, Puoci et al. included carbon nanotubes in microspheres that were imprinted with a model drug. Upon electrical stimulus, the MIP particles released the bound drug, a promising result for controlled release therapeutics [61]. A more obvious route for treating diseases with MIP-based nanomaterials is an immunological approach. Similar to how antibodies recognize toxins or viruses, imprinted polymers can be optimized to recognize these unwanted molecules. By imprinting on the surface of gold nanoparticles and using surface-enhanced Raman scattering, researchers were able to recognize bisphenol A (BPA), an endocrine disruptor often used in the manufacturing of plastic packaging. They described the recognition of BPA in the context of chemical contamination in liquids, but this idea could be extended to recognition of toxins in biological fluids as well [62].

In a noteworthy study by Hoshino et al., imprinted particles for melittin, the toxic peptide of bee venom, were synthesized and optimized for maximum affinity. When delivered in vivo, the nanoparticles were able to bind melittin before being recognized by macrophages as foreign objects. The nanoparticles localized in and were cleared by the liver, resulting in a 100% survival rate when the optimized MIP composition was used [63]. For the first time, researchers have also demonstrated the ability to imprint nanoparticle surfaces with whole viruses for use in treating infectious diseases. When infected by phage suspensions, bacterial cells had significantly improved growth if treated with the imprinted particles as compared to no treatment or treatment with non-imprinted particles [64].

Conclusions

In this short overview of recent developments we highlighted studies that are representative of current trends in intelligent nanomaterials and their applications in medicine. Advances in both chemical synthesis and nanofabrication techniques have fostered creative research in this area. Imparting responsiveness to nanomaterials helps achieve control over their behavior, which ultimately leads to more effective therapeutic, imaging, and sensing technologies. However, compared to the amount of research being done in the field, relatively few medical nanotechnologies have made it to the market. Clear demonstrations of biocompatibility and including biodegradable components will make these materials even more attractive for in vivo applications. Furthermore, development and implementation of scalable, cost-effective fabrication techniques will help promote clinical translation. Together, intelligent polymers and nanomaterials provide a versatile toolbox that we believe will revolutionize the future of modern medicine.

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***Highlights**

- Combining nanomaterials and responsive polymers is beneficial for medicine.
- Responsive materials are useful for controlled release, imaging, and sensing.
- Scalable, low-cost fabrication techniques will promote clinical translation.

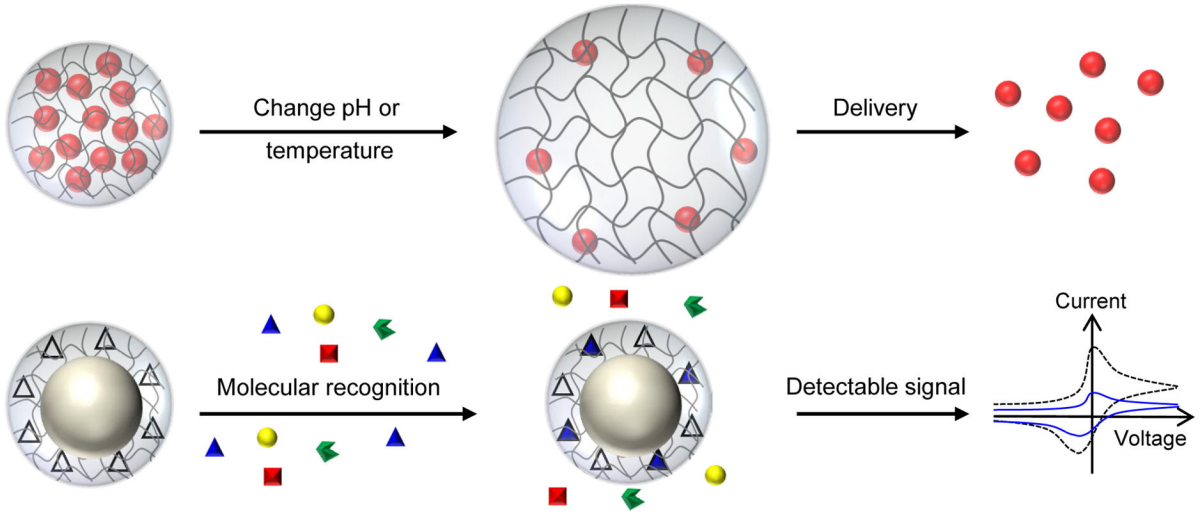

Figure 1.

Schematic depiction of input-driven responses of intelligent nanomaterials. (Top) Intelligent polymeric nanoparticles swell in response to changes in temperature or pH, resulting in the release of therapeutic agents. (Bottom) Nanoparticles with a molecularly imprinted shell recognize target molecules, producing a detectable signal for sensing applications.

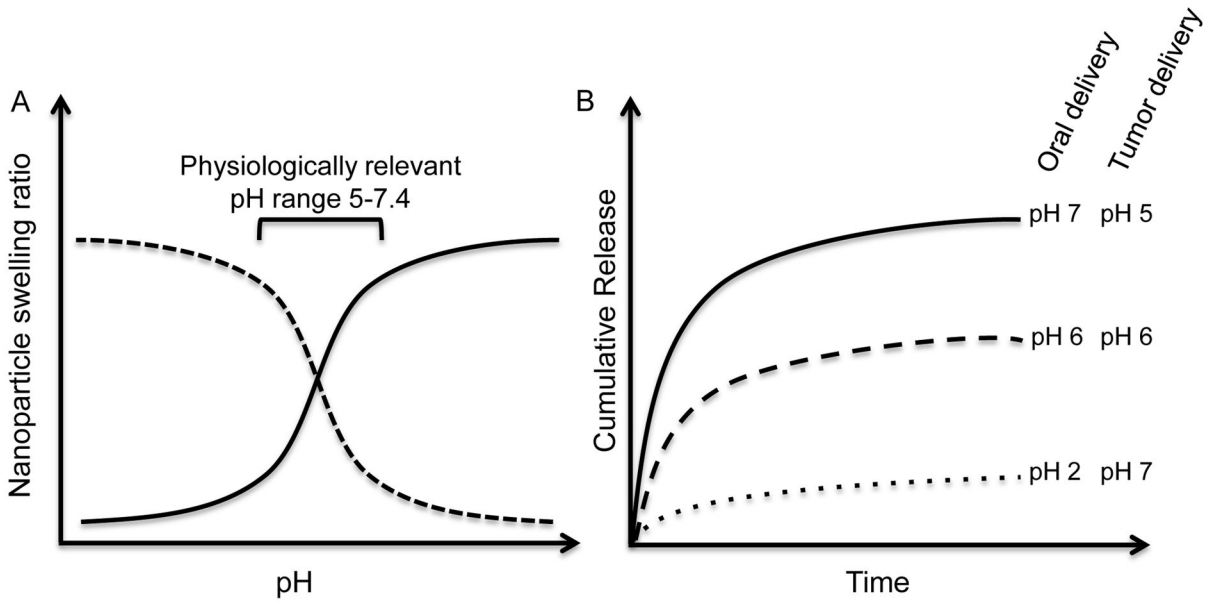

Figure 2.

Typical nanoparticle pH size response and drug release for delivery applications. (A) A typical pH response curve for nanoparticle size or swelling ratio for both oral drug delivery (solid line) and tumor targeting (dashed line). These systems undergo significant change in physiological ranges near neutral pH. (B) Time release profiles for a typical oral drug delivery system in different pH solutions.

Table 1

Reported detection limits of nanomaterial-based molecularly imprinted sensors

Sensor class	Target molecule	Detection limit (M)	Ref.
Gravimetric			
Quartz crystal microbalance	L-malic acid	1.3 E-9*	[51]
Optical			
QD phosphorescence	Bovine hemoglobin	3.8 E-8	[43]
LSPR spectroscopy	Neutrophil gelatinase-associated lipocalin	1.3 E-8	[45]
QD-MIP ELISA	α-Amylase	7.0 E-14*	[44]
Electrochemical			
Square wave voltammetry	Tramadol	4 E-9	[38]
Cyclic voltammetry and electrochemical impedance spectroscopy	D-glutamic acid	2 E-10	[41]
	Hepatochlor	8.0 E-12	[42]
Electrochemical impedance spectroscopy	HPV derived E7 protein	4.7 E-14*	[39]
	Human ferritin	2.2 E-17*	

*Values reported in mass concentration converted here to molar concentration