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Smart gating porous particles as new carriers for drug delivery

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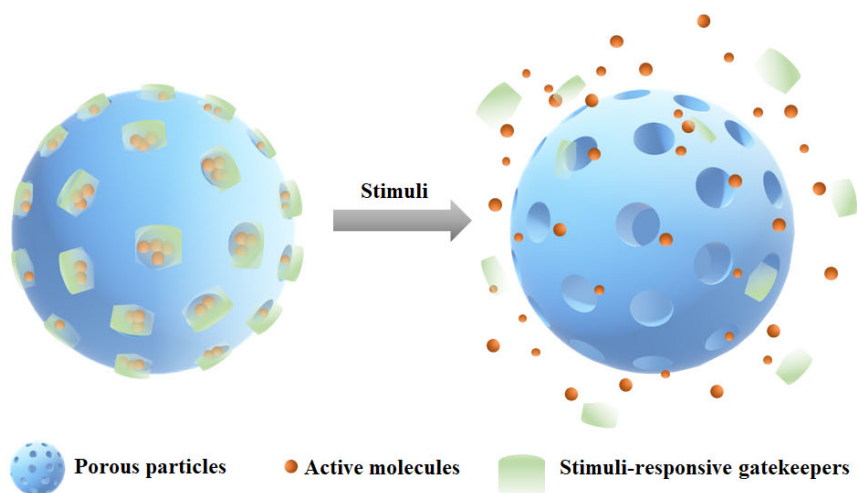
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Abstract

The design of smart drug delivery carriers has recently attracted great attention in the biomedical field. These smart carriers respond to physical and chemical changes in their environment, including changes in pH, temperature, light, and specific agents. The porous structure of the particles plays an important role in facilitating the diffusion of drug molecules and cell attachment. Smart gatekeepers provide advanced functions such as “open-close” switching by grafting stimuli-responsive polymers onto the particle’s pores. These controlled delivery systems enable drugs to be targeted at specific rates/time-programmes and sites of the human body. This review proposes the integration of porous particles and stimuli-responsive gatekeepers for effective drug delivery. The fabrication techniques of porous materials, gate structures, triggered targeting strategies, and controlled release mechanisms are detailed. Current ongoing research and future trends in drug delivery applications are highlighted.

Keywords Stimuli-responsive polymers; Drug delivery; Biomedicine; Gatekeeper; Porous particles

Graphical abstract



1. Introduction

Stimuli-responsive polymers have attracted growing interest over the last few decades for a diverse range of applications, e.g., drug delivery, gene delivery, sensors, and tissue engineering [1-3]. Inspired by natural living cells, stimuli-responsiveness is a crucial function for maintaining human body balance and self-healing. These polymeric “smart materials” correspond to biological environment stimuli such as pH [4], temperature [5], electric and magnetic fields [6], ion concentration [7], light [8], chemical, and biological stimulus [9]. Stimuli act as triggers that can be applied externally and remotely to achieve the controlled release of active molecules from drug carriers [10]. Sensitive materials may be swelled, collapsed, crosslinked or degraded in soluble media. This characteristic makes these smart polymers important agents for drug delivery systems, among other applications. Recent progress in the synthesis of smart polymeric carriers for drug delivery applications has been discussed, focusing on pH-, photo- and thermo-responsive polymers [11-14].

In the preparation of stimuli-responsive polymeric carriers for drug delivery applications, an important step is not only the selection of an appropriate stimuli-responsive polymer material according to final applications sought, including sites and modes of administration, but also the selection of an encapsulation method for the entrapment of therapeutic agents. Encapsulation entraps active ingredients inside reservoirs which enable the protection of active agents against light, oxidation, and enzyme degradation, and their controlled release [15]. The drug encapsulation process usually depends on the hydrophilicity or hydrophobicity of the molecules employed [16]. Several encapsulation processes exist and they may be divided into two main groups: (i) coacervation based on chemical techniques, e.g., suspension polymerization, emulsion polymerization, miniemulsion polymerization, and interfacial polymerization, (ii) physico-mechanical methods, e.g., spray drying, microfluidics and the layer-by-layer technique [17-19]. Generally, stimuli-drug carriers are synthesized using polymer matrices or other structures including nanogels, micelles, core/shell-like particles and capsules. The external stimulus provokes carrier disassembly or disintegration. When the particles swell or break down into polymer chains, they become porous, allowing drug release [20].

Conventional particles for drug delivery are usually spherical in shape with a variety of morphologies, e.g., solid particles, core/shell particles, and porous particles [21-23]. In order to control the release of active agents, solid and core/shell structures provide slow release, while

porous structures present a high initial burst release due to high particle porosity [22]. Owing to the release behavior, porous particles are suitable for application as stimuli-responsive gatekeepers for drug delivery systems. Porous particles have been fabricated with a variety of pore sizes, densities, and morphologies. The large surface area of porous structures facilitates drug diffusion and cell attachment, with improved absorption/adsorption properties of hydrophobic or hydrophilic drugs into microcapsules [24]. Porous particles can be fabricated by both inorganic and organic materials. Mesoporous silica materials are excellent carriers for drug delivery due to the high loading efficacy of the drugs inside the pore channels and easy functionalization [25, 26]. Pore size is also an important factor for permeability; large pores generally enhance permeability [27]. Synthetic polymers have been employed in the synthesis of porous particles by many techniques, including microfluidics, seed polymerization, and double emulsion polymerization [28]. Recently, porous biodegradable materials e.g., poly(lactide) [29, 30], poly(lactic-co-glycolide) [22, 31], poly(caprolactone) [32], and Eudragit®RS100 [33], have been prepared [34, 35]. These biodegradable polymers show outstanding attributes of biocompatibility, high stability in blood, and degradability in the body. The degradation kinetics of polymers are dependent on functional groups, polymer structure, molecular weight, and the body's biological environments (e.g., pH, temperature and enzymes) [36].

The main focus of this review is to highlight the utility of stimuli-responsive polymers as gatekeepers to control the drug diffusion through the porous carriers. Smart gating porous particles serves the purposes to trigger the drug delivery system by an external- or internal- stimuli and improve the surface properties of the bare particles. Functional gates can be switched to transport drug molecules from inside the particles to the surrounding environment [37]. An external stimulus immediately triggers therapeutic drug release at a target site. Current studies have focused on the development of sensitive tunable gates, prepared by surface-initiated polymerization and the layer-by-layer method [38]. This review explores new trends of stimuli-responsive porous particles, fabrication techniques, the drug release mechanisms, and briefly practical use in biomedical field. This is one of the promising candidates with potential opportunities for stimuli-responsive drug delivery.

2. Porous particles for drug delivery applications

Porous particles are a group of drug carriers which are widely reported in drug delivery applications and tissue engineering, due to their large surface area, high porosity, uniform and

tunable pore structures, and surface modifiability [39-41]. Porous particles are mainly prepared by using templating agents, porogens, self-forming pores and specific chemical synthesis [40].

2.1 Preparation of porous particles

Recently, several reviews on porous micro/nanoparticles introduced the features and synthetic techniques involved. These materials are classified based on their pore formation mechanisms, including a self-forming technique, and the use of templates or pore forming agents. In addition, specific preparation processes are also employed to produce porous particles, such as microfluidizer and spray drying techniques. The main advantages and limitations of each porous particle formation technique (i.e., synthesis of mesoporous silica nanoparticles, double emulsion solvent evaporation, templates, and pore-forming agents, microfluidics and spray drying techniques) regarding the properties and performance of drug delivery systems are summarized in Table 1.

Table 1 Advantages and limitations of pore forming techniques for drug delivery.

Techniques	Advantages	Limitations	Ref.
Synthesis of mesoporous silica nanoparticles (MSNs)	<ol style="list-style-type: none"> 1. Large porosity and surface area. 2. More stability and uniform particles. 3. Ease of surface modification. 4. High drug loading capacity. 	<ol style="list-style-type: none"> 1. Possible interactions with the reticuloendothelial system and accumulation in the body. 	[39-42]
Double emulsion solvent evaporation	<ol style="list-style-type: none"> 1. Encapsulation of both hydrophilic and hydrophobic active agents in a single carrier. 	<ol style="list-style-type: none"> 1. Two-step process. 2. Polydispersity and variable pore sizes. 3. Instability. 4. Difficult to scale up 	[19, 43, 44]
Templates and pore forming agents	<ol style="list-style-type: none"> 1. Uniform pore size and structure. 2. Good repeatability in same pattern. 3. Easy setup and scalability. 4. Various kinds of templates and porogens. 5. Easy to remove templates by solvent or calcination. 	<ol style="list-style-type: none"> 1. The elimination of the template may lead to the collapse of parts of the pore structure. 2. Leaching of pore-forming agents may also remove encapsulated active agents. 	[40, 45-48]
Microfluidizer	<ol style="list-style-type: none"> 1. Monodisperse particles. 2. Finely controlled pore sizes. 3. Good reproducibility. 4. Low reagent consumption. 5. Combination with UV curing during continuous flow lithography. 	<ol style="list-style-type: none"> 1. Droplet size depends on channel dimension. 2. More complex operation. 3. High cost of chip fabrication. 	[49-52]
Spray drying	<ol style="list-style-type: none"> 1. Continuous and rapid operation. 2. Wide range of raw materials. 3. Precisely controllable size. 4. Self-pore forming or use of templates/porogens. 	<ol style="list-style-type: none"> 1. High cost and complex equipment. 2. Excessive heat production. 3. Particle shrinkage during evaporation. 	[47, 53-56]

2.1.1 Mesoporous silica nanoparticles (MSNs)

A well-known group of inorganic porous particles is silica-based because of their large surface area, high porosity, stability, biocompatibility, and nontoxicity. MSNs have mesopores with a size ranging between 2 and 50 nm. This attracts great interest from pharmaceutical research, and for drug delivery systems. In 1968, Stöber and Fink discovered how to synthesise monodisperse silica nanoparticles [57], although mesoporous silica materials were first used as drug delivery systems in 2001 [58]. Generally, MSNs are synthesized by the sol-gel method, using cationic surfactant templates, cetyltrimethylammonium bromide (CTAB) [59]. Figure 1 shows the structure of polymerized tetraethylorthosilicate (TEOS) in the presence of CTAB micelles. The MSNs type MCM-41 is performed by cooperative self-assembly between the CTAB micelles and the surface silanol groups. The surfactant is removed by either calcination or extraction, finally the nanopores are achieved [41, 60].

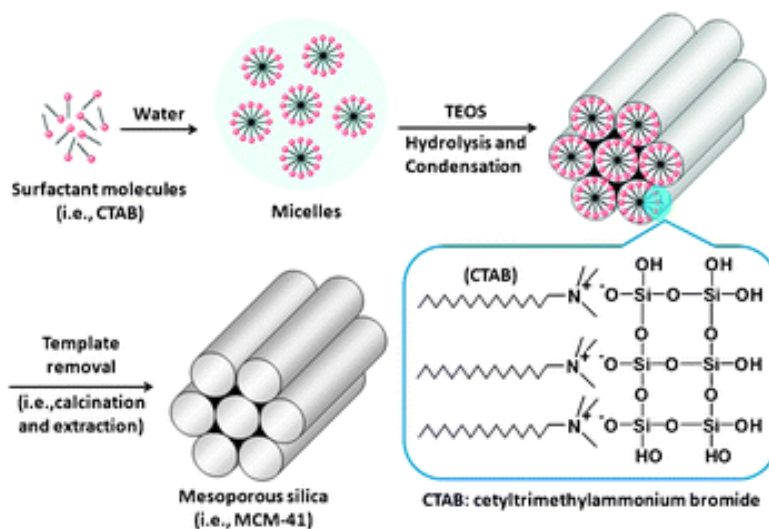


Figure 1 Schematic diagram of the formation of mesoporous silica type MCM-41. Reprinted with permission from ref. [41].

The effects of pH, co-surfactant, basic solvent, and mixtures of alcohol/water on the pore size, morphology and uniformity of the nanoparticles have been examined [60]. The morphology of MSNs was transformed by varying synthesis parameters with the use of dual soft surfactant templates. Varying the amount of dodecanol (C_{12} -OH) and reaction temperatures resulted in six different types of MSNs: spherically shaped, shell-like, rugby ball-like, peanut-like, hollow, and yolk-shell structures (Figure 2) [61]. In addition, chemical and physical interactions on the surface

of MSNs can be triggered between silanol groups and functional groups present on the drug molecules, such as amino, hydroxyl, or carboxyl groups [62, 63].

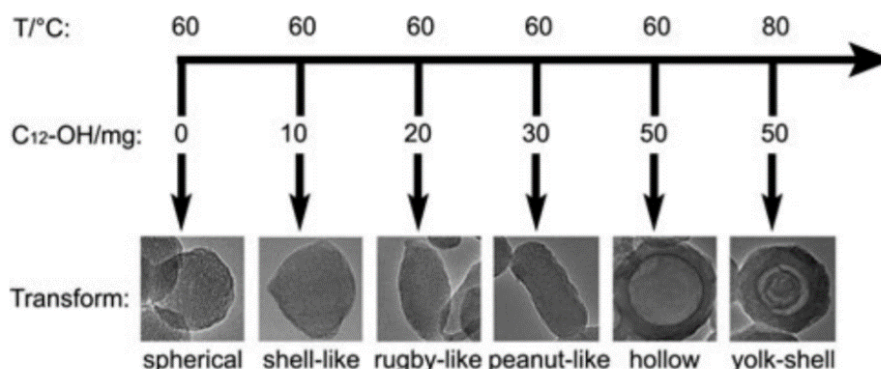


Figure 2 Schematic illustration of MSN morphologies generated by varying the amount of dodecanol and reaction temperature. Reprinted with permission from ref. [61].

2.1.2 Double emulsion solvent evaporation technique

The multiple step emulsion method consists of self-pore formation without porogens or templates. This method is generally combined with solvent evaporation for producing porous microspheres. Basically, the double emulsion may be a water-oil-water (W/O/W) or an oil-water-oil (O/W/O) technique. Figure 3 illustrates the pore-forming process via $W_1/O/W_2$ double emulsion. The process is composed of 3 steps: (i) a water-in-oil (W_1/O) emulsion formation by dispersing the inner aqueous phase (W_1) in an organic solvent (O), (ii) the formation of a double emulsion ($W_1/O/W_2$) by emulsifying the primary emulsion in the aqueous continuous phase (W_2), and (iii) the evaporation of the solvent [19, 64]. By using this technique, water soluble drugs have been encapsulated by W/O/W double emulsion. The important properties of microspheres, such as droplet size distribution and double emulsion stability, can be controlled by carefully adjusting the parameters, e.g., polymer and surfactant concentrations, phase ratios, and the mixing intensity.

Various drug-loaded microspheres derived from biodegradable polymers, including poly(lactic-co-glycolide) (PLGA), poly(lactic acid), poly(caprolactone) (PCL), and ammonio methacrylate copolymers (Eudragit RS100) have been prepared using the double emulsion technique. Iqbal *et al.* prepared biodegradable poly(caprolactone) (PCL) porous particles using the double emulsion solvent evaporation process with an ultrasound-assisted method; it involved a two-step emulsification process [65]. In the first step, the inner aqueous phase (W_1) was homogenized with an organic phase (PCL in dichloromethane) to obtain the primary emulsion. In

the second step, the primary emulsion was emulsified with the outer aqueous phase (W_2) containing polyvinyl alcohol (PVA) as a stabilizer using power ultrasound, followed by solvent evaporation. This method is generally combined with solvent evaporation for producing porous microspheres. The particle size is decreased by increasing the ultrasonic exposure time and amplitude, and the outer aqueous phase volume. Additionally, the particle size is also dependent on the amount of PCL and the PVA concentration [65]. Eudragit RS100 sponge-like particles were also prepared by a similar method. The well-defined porosity of the particle can be attributed to the double emulsion solvent evaporation process, as described above. The nature of the Eudragit RS100 consists of a hydrophilicity of ammonium groups which can interact with water molecules. During the solvent evaporation and precipitation, the hydrophilic cavities are generated [66].

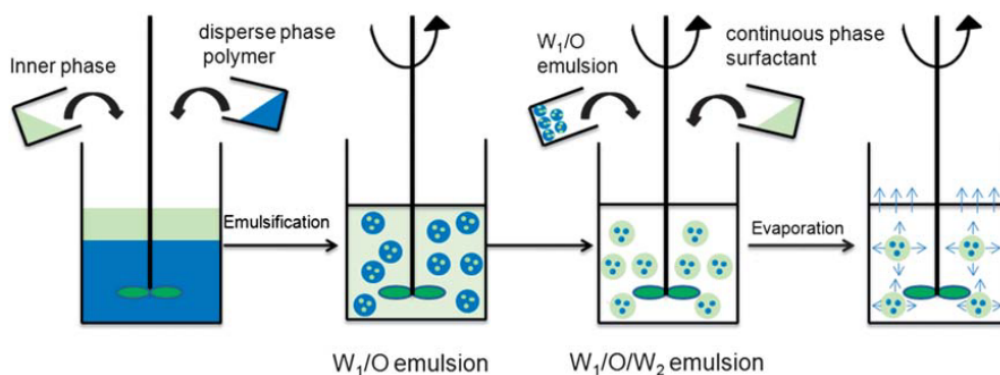


Figure 3 Double emulsion solvent evaporation method. Reprinted with permission from ref. [64].

2.1.3 Templates and pore forming agents

Templates or porogens are commonly employed for effectively controlling morphology and pore size via template removal for pore generation. Pore generation mechanisms that use templates or porogens are different, as summarized in Figure 4. Templates can be divided into two groups, depending on their physical properties, which are hard and soft templates [45, 67]. Hard templates are commonly used in the synthesis of nano/micro-structured materials, such as hollow particles, nanorods, nanowires, and nanotubes, for example polystyrene spheres [68], carbon nanospheres [69], anodic aluminum oxides, mesoporous oxides, and carbon nanotubes [70]. In the synthesis process, a polymer precursor is absorbed on the surface of the hard template, with no interaction or aggregation with the precursors in the synthesis process, due to the high stability of the hard template. The removal of the template leads to the formation of the pore structure. However, during the pore formation step, structure collapse may occur. In contrast, soft templates can self-assemble

to form micelle-like structures, and inter- or intramolecular interactions occur (e.g., hydrogen bonding, covalent bonding, or ionic bonding) during the reaction. This creates cavity structures after the templates are removed by an appropriate solvent [45]. A precursor is deposited around the micelles or the template surfaces. The commonly-used soft templates are surfactants (CTAB for MSNs synthesis [60], and PEO–PPO–PEO (Pluronic F127) [71]) and amphiphilic block polymers (e.g., poly(styrene)-block-poly(ethylene oxide) [72], poly(styrene)-block-poly(4-vinylpyridine), and poly(styrene)-block-poly(acrylic acid) [73]). The templated synthesis of porous particles typically involves the following steps: (i) preparation of the template, (ii) the synthesis of polymer particles consisting of host materials and templates (generally synthesized by colloidal methods, including emulsion polymerization, microemulsion polymerization, soap-free emulsion polymerization, suspension polymerization, dispersion polymerization, the dipping method, layer-by-layer assembly, as well as combinations with the spray drying technique), and (iii) template removal by calcination or etching [46, 47].

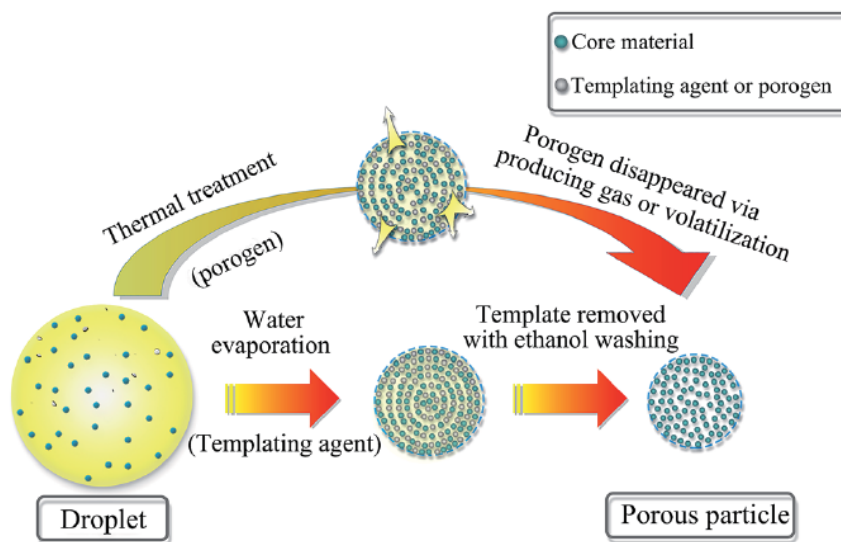


Figure 4 Schematic diagram of porous particles formation by removing templates or pore forming agents producing the cavitation. Reprinted with permission from ref. [40].

Pore-forming agents are commonly employed in the pore formation step by gas foaming or volatilization in the system. These agents are called “porogen and osmogen”. Types and structures of the pore-forming agents impose strong effects on the resultant porous particle’s morphology, porosity, surface area, pore volume, and mechanical stability. As porogen is inert and can be homogeneously dissoluble within an organic phase, its removal leads to both external and

internal pores [48]. Three main requirements may be listed for porogens selection: (i) non reactivity with the precursor, (ii) solubility in the solvent, and (iii) miscibility with other substances (e.g., monomers, initiator and crosslinker) [74, 75]. Low molecular weight polymers (e.g., polyethyleneglycol, PEG) or surfactants are usually used as porogens. Nevertheless, few articles have reported the use of carbon dioxide gas as a porogenic agent. However, the fabrication of porous particles can be achieved by using ammonium bicarbonate (NH_4HCO_3) as porogen, which spontaneously produces CO_2 and NH_3 to generate pores [76]. Another type of pore-forming agent is osmogene, a water-soluble component whose osmotic pressure acts as a driving force to produce tiny pores. Osmotic agents can generally generate osmotic pressures ranging from 8 to 500 atm [77]. The presence of high osmotic pressure as a result from inorganic salts or carbohydrate compounds (e.g., fructose, sucrose, and dextrose) is used to fabricate porous materials for use in oral controlled delivery [78]. Pore-forming agents are classified by their pore-generation mechanisms: salt leaching, gas foaming, and phase separation, by either porogen or osmogen, as shown in Figure 5. The types and amounts of pore-forming agent are important factors in controlling pore structures and sizes. A large amount of pore-forming agent produces large pore granules, while its type affects pore formation mechanisms [74, 79]. Table 2 lists the examples of using pore forming agents in the preparation of porous microspheres.

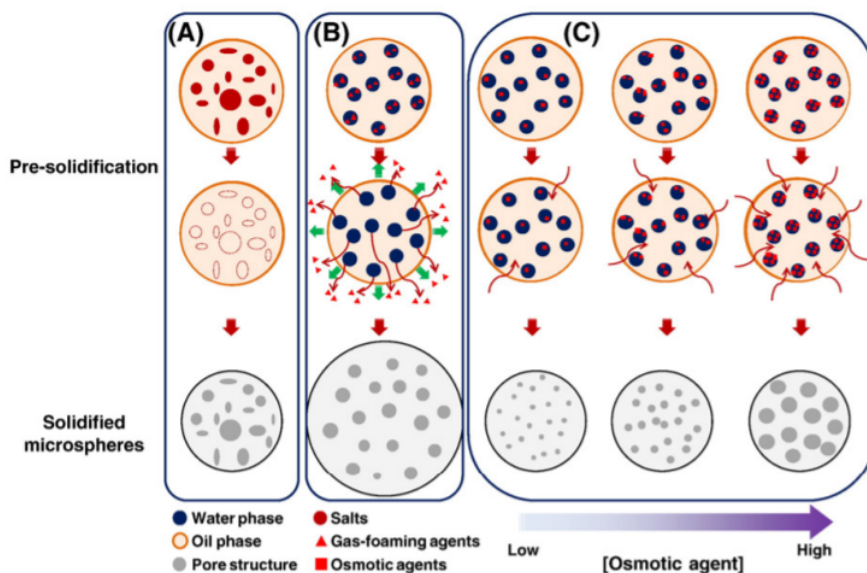


Figure 5 Schematic illustration of porous particle preparation by using different types of pore-forming agents: (a) salt leaching, (b) gas foaming, and (c) osmogen. Reprinted with permission from ref. [79].

Table 2 Examples of pore-forming agents, polymeric shells, encapsulated active ingredients, and methodologies.

Types	Pore forming agents	Polymer	Methodology	Active ingredient	Ref.
Porogen	Dibutylphthalate	PMMA	Seed swelling polymerization	-	[80]
	PEG-PPG-PEG	PMMA	O/W emulsion	-	[81]
	PEG-PPG-PEG	PLGA	O/W emulsion	Human growth hormone	[82]
	PBS	PLGA	W/O/W double emulsion	-	[83]
	Ammonium bicarbonate	PLGA	W/O/W double emulsion	-	[84]
	Ammonium bicarbonate	PLLA	Emulsion precipitation	Insulin	[85]
	Ammonium bicarbonate, sodium hydroxide	PLGA, PLA	Microfluidic method	6-Coumarin	[49]
	Ammonium bicarbonate	Leucine	Spray drying	Meloxicam	[86]
	α -cyclodextrin/PEG	PLGA	W/O/W double emulsion	Rhodamine B or melatonin	[87]
	Surfactants: sorbitan trioleate, sorbitan sesquioleate, sorbitan oleate, Pentaoleic acid hexaglycerin ester, polyoxyethylene sorbitan monooleate	PGMA	Suspension polymerization	-	[88]
	Supercritical CO ₂	P(TRIM)	Suspension polymerization	-	[89]
Osmogen	Bovine serum albumin	PLGA	W/O/W double emulsion	Insulin and vascular endothelial growth factor	[79]
	Sodium chloride	PLGA	W/O/W double emulsion	Risedronate sodium	[90]
	Sodium chloride, and calcium chloride	PLA	W/O/W double emulsion	Brilliant blue	[91]
	Sodium chloride, potassium chloride, and sucrose	PLGA	O/W emulsion	Insulin	[22]

2.1.4 Microfluidics and spray drying techniques

Among conventional porous particle preparation methods, the microfluidics-based technique represents a challenging means of producing porous particles with controlled final morphologies. An important component of microfluidic devices is a capillary system designed for droplet generation and controlling particle structures. Generally, a capillary device consists of coaxial assemblies fabricated from glass-based structures or polydimethylsiloxane (PDMS) [50, 51, 92]. Its capillary design must be simple and highly robust. The immiscible fluidic phases involve the breakup of droplets dripping under flow velocity through a small channel, generating monodisperse particles. The influence of tip size and flow rates also affect particle size [51]. In the microfluidics method, pore formation techniques are classified into 5 systems, including polymerization with and without porogens, using templates, flow reaction, self-assembly, and flow lithography [50]. Figure 6 illustrates the comparison of porous microsphere preparations using a

conventional double emulsion solvent evaporation and a microfluidics device. The resultant porous microspheres exhibit higher porosity and controllable particle size with a narrow size distribution using the microfluidics method, compared to the double emulsion method. In the microfluidics process, the rate of dispersion is a key factor in controlling particle size, in which the diameter of PLGA particles decreases from 77 to 43 μm at flow rates of 0.3 and 0.6 mL/min, respectively [49]. In addition, microfluidic emulsion polymerization is combined with UV irradiation in continuous flow photolithography, leading to fast response time and the stability of immobilized bioactive molecules in the resulting particles [93].

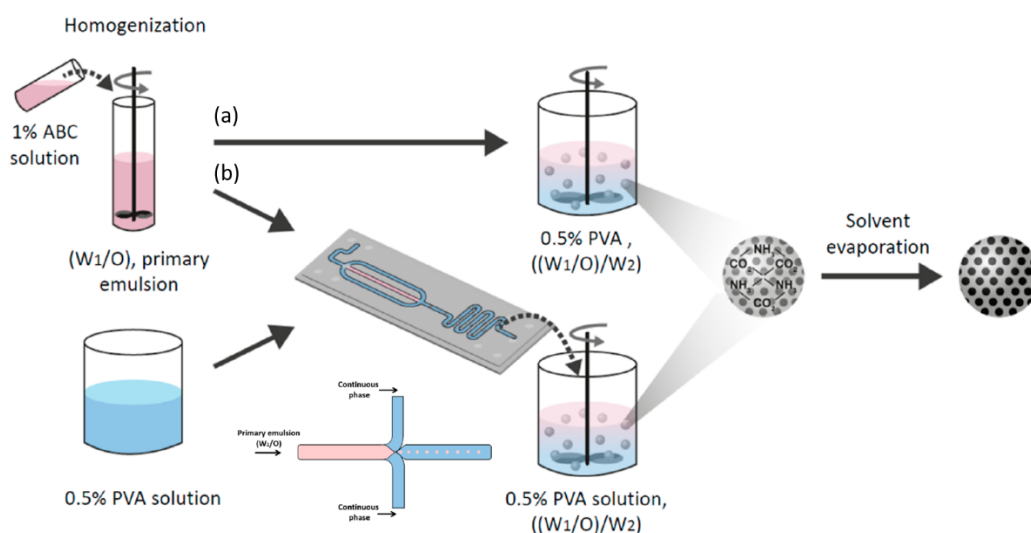


Figure 6 Schematic illustration of porous particle preparation by (a) $W_1/O/W_2$ double emulsion solvent evaporation, in comparison with (b) the microfluidic method, along with its flow chip capillary design. Reprinted with permission from ref. [49].

In the large-scale production of particles with relatively narrow unimodal size distribution, spray drying has been shown to be an attractive method for fabricating pharmaceutical particles. The particles obtained have low density and precise particle diameters with a controlled morphology. The spray drying method typically involves 3 steps of processing: (i) atomization, (ii) droplet-to-particle conversion, and (iii) particle collection [55]. Initially, precursors, including polymer, porogens, and templates are homogeneously mixed before spraying. Then, the precursor droplets are sprayed and rapidly vaporized to form solid particles by the driving force of the atomizer, for example, ultrasonic or fluid nozzles. Finally, the porous particles are obtained [47, 55]. The template used is removed by solvent leaching or heat treatment [94]. Porous hyaluronic

acid particles with controllable pore size were fabricated by using a spray drying method and polystyrene templated particles. The obtained particles were 0.5 to 5 μm with pore sizes in the range of 100 to 300nm [94]. Further modifications of the process conditions or the addition of pore-forming agent can produce particles with various shapes, such as spherical particles, hollow particles, porous particles, mushroom-like, and doughnut-shaped particles [55]. Peng *et al.* studied the key factors of outlet temperature and ammonium carbonate concentrations for the spray drying of porous particles. The average particles size of obtained particles was about 5 μm . The formation of porous particles was achieved by varying the outlet temperatures at 65, 75, and 85°C. Non-porous particles were formed at the lowest temperature due to slow evaporation, while pressure and the fast evaporation rate of the highest temperature led to the collapse of shell structures. Increasing the porogen content also affects the pore size and pore structure (closed pores, interconnected pores, and pore fusion). Optimized conditions to produce nanoporous particles with a mean pore size of 6 nm were observed at an outlet temperature of 75 °C and 25wt% porogen [95].

2.2 Morphology and properties of porous particles

Pores size and size distribution, structure, surface area, and volume also affect the loading efficacy and the release rate of drug molecules. Porous materials can be prepared by organic polymers, inorganic materials (e.g., silica, metal oxides, and silver), or hybrid materials (magnetic core-porous shell nanoparticles) [96, 97].

2.2.1 Pore size

Pores size is an important factor associated with drug loading capacity and molecules diffusion, due to steric hindrance and interaction inside the cavities [98, 99]. Porous particles are classified according to their pore size: micro (less than 2 nm), meso (2-50 nm), macro (50-200 nm) and giga (larger than 200 nm) [100]. Mesoporous silica nanoparticles (MSNs) with three dimensional structures have unique properties and tunable pore size. The effect of pore size of an MSNs loaded with an anticancer drug (doxorubicin, DOX) was reported [101]. A pore size difference from 2.3 to 8.2 nm resulted in the increase of loading capacity from 8 up to 21% [101]. In case of pore diameter smaller than the drug molecule, the drug cannot access into the cavity. This suggests that increasing pore size lead to easier drug absorption and entrapment inside the pores. In addition, the chemical bonding or surface charge between drug and porous particles also affect the loading capacity. In this study, DOX and MSNs dissolved at neutral pH (PBS pH = 7.4)

were positively charged of amino groups and negatively charged of silanol groups, respectively. Therefore, the electrostatic interaction between DOX and MSNs enhanced the loading capacity of DOX [101]. Sharma *et al.* investigated the four morphologies of PLA microspheres, which are non-porous, microporous, mesoporous, and macroporous structures for biotherapeutic release in lung. Variable pore sizes of microspheres explored the different mechanisms of release. Macroporous microspheres (pore sizes ≥ 100 nm) demonstrated high initial burst release and complete release from the porous structure, while non-porous, microporous, and mesoporous structures showed low encapsulation efficiency and slow release [102].

2.2.2 Pore structure

In terms of geometry, pores are divided into two types. An open pore is interconnected to the external surface, and acts as a passage to allow active molecules passing through the outside. In contrast, a closed pore is a void isolated from the external surface [103]. Open pores show outstanding properties, such as low density, high surface area, and fast release rate. They are more effective carriers for drug delivery systems since they show higher transfer capacity than closed pores. Bae and coworkers reported the influence of different morphologies of open-pore and closed-pore microspheres on their release profiles of dexamethasone. PLGA microspheres were prepared by using a double emulsion solvent evaporation method by adapting hydrogen peroxide as a porogen to produce the internal pore. A high amount of hydrogen peroxide promotes porous structures with an initial burst release of 60%, and complete release in 28 days, while the internal closed pore particles were produced at a low concentration of porogen and presented a slow release rate [104]. As shown in Figure 7, the synthesis method strongly affects pore morphology. Porous microspheres were prepared by double emulsion solvent evaporation using ammonium bicarbonate as a porogen [105, 106]. A specific combination of polymer molecular weight, volume ratio of aqueous to organic phases, homogenization speed, and porogen concentration led to cage-like microspheres with high porosity ($> 93\%$) and large pore size. This structure is a three-dimensional porous PLGA scaffold (Figure 7a) [24]. Porous PLGA microspheres with a sponge-like skeleton was also obtained by ammonolysis. The diffusion of ammonia transferred to an aqueous phase resulted in numerous voids in both internal and external matrices (Figure 7b) [107]. Generally, the formation of golf ball-like microspheres can be achieved by using seeded polymerization and Pickering emulsion. Golf ball-like PLGA microspheres were fabricated by an oil-in-water emulsion with the addition of an organic phase-change material (PCM) for building

specific morphologies (Figure 7c) [108]. Volatile PCM droplets play a role as a nonsolvent located in the PLGA interphase [108]. Self-assembly hydrophobic/hydrophilic porous particles were synthesized by a double emulsion interfacial polymerization [108]. Heterostructure-enabled separation particles, produced from poly(styrene-divinyl benzene)-poly(acrylic acid) (PSDVB-PAA) were synthesized by a double emulsion interfacial polymerization process. The spherical porous particles were formed by turning the hydrophilic side chains of PAA to outside the particles and inside the voids, while hydrophobic chains of PSDVB constituted the matrix. The interconnected porous structure was obtained after interfacial polymerization (Figure 7d) [109].

2.2.3 Surface area

Surface area is a significant parameter that involves pore size and plays a key role in the absorption of active ingredients. For instance, porous chitosan microspheres were prepared by a water/oil emulsion using agarose as a pore-forming agent [110]. These porous microspheres provided a higher surface area of $246 \text{ m}^2 \text{ g}^{-1}$, compared to $55.65 \text{ m}^2 \text{ g}^{-1}$ for non-porous microspheres, as investigated by the BET method. The modified surface property of chitosan porous particles presented a hierarchical or interconnected porous structure and excellent adsorption of 302 mg.g^{-1} bovine hemoglobin within 15 min [110]. Cong *et al.* studied the effect of Span 80 on the morphologies of poly(glycidyl methacrylate-divinylbenzene) (PGMA-DVB) microspheres by using seed emulsion polymerization [75]. The pore size distribution and BET surface area of the product depended on the amount of Span 80: those without Span 80 exhibited the smallest pore size (10 nm) and a surface area value of $325 \text{ m}^2 \text{ g}^{-1}$. In contrast, those produced with 0.6 ml of Span 80 presented a microporous morphology with an average pore size of 12 nm and a surface area of $192 \text{ m}^2 \text{ g}^{-1}$ [75].

2.2.4 Pore volume

Pore volume is directly related to surface area and drug loading capacity. Qiao and coworkers reported that by increasing the amount of pore-forming agent, a large number of voids were obtained. The increase in the porogen weight ratio from 0 to 15 % led to an increase in the pore volume from 0.02 to $0.11 \text{ cm}^3 \text{ g}^{-1}$ [110]. Another study of an MSN loaded with an anticancer drug showed that the surfactant concentration promoted the change of the pore volume from 0.48 to $1.55 \text{ cm}^3 \text{ g}^{-1}$. [111] The largest pore volume and the highest surface area also led to the highest drug loading content of 57.2% [111].

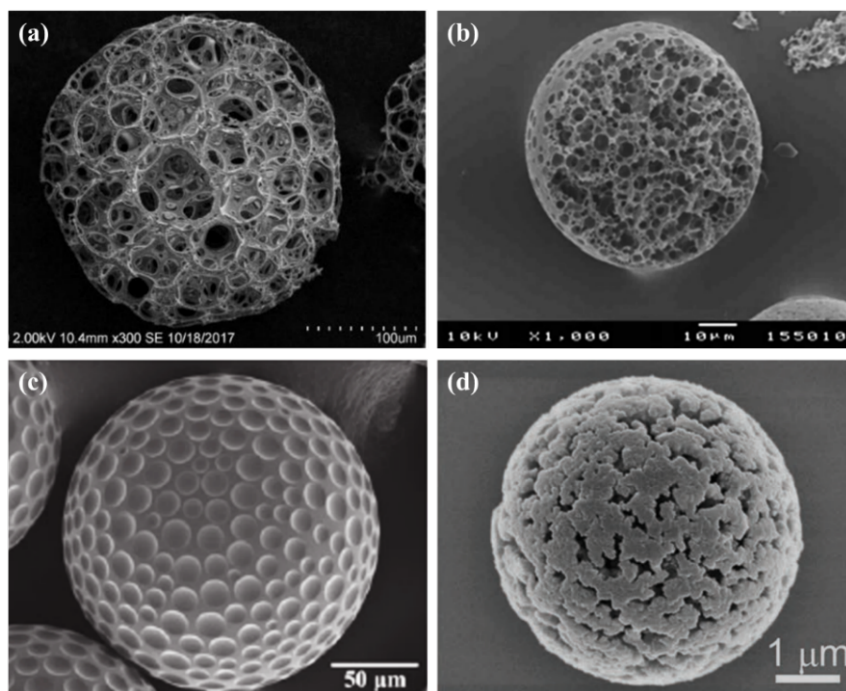


Figure 7 Examples of interconnected porous particles: (a) cage-like PLGA microsphere, Reprinted with permission from ref. [24]; (b) sponge-like PLGA microsphere, Reprinted with permission from ref. [107]; (c) golf ball-like microsphere, Reprinted with permission from ref. [108]; (d) interconnected pore network of PSDVB-PAA microspheres, Reprinted with permission from ref. [109].

3. Stimuli-responsive gating porous particles

Smart drug delivery carriers have been designed to accomplish controlled release formulations, as this can respond to physiochemical stimuli in their environment. Functional responsive porous particles can be monitored and their drug-release through the specific target can be controlled. Porous particles can effectively encapsulate drug molecules, magnetic nanoparticles, and fluorescent agents. The outer surface can be modified with specific antibodies, ligands targeting the cell surface, and anti-adhesive molecules. Furthermore, they can be synthesized or functionalized by responsive molecules for the precise control of open/closed pore structures at specific sites (Figure 8). The stimuli particles can respond simultaneously depending on the inherent stimuli of the human body or external stimuli, including pH, temperature, enzymes, redox reagents, light, and magnetic field. Multifunctional integrated stimuli responsive polymers also improve their therapeutic efficacy and their capacity to deliver in a regulated manner for specific

treatments. Table 3 summarizes the list of currently reported articles on stimuli-responsive porous particles.

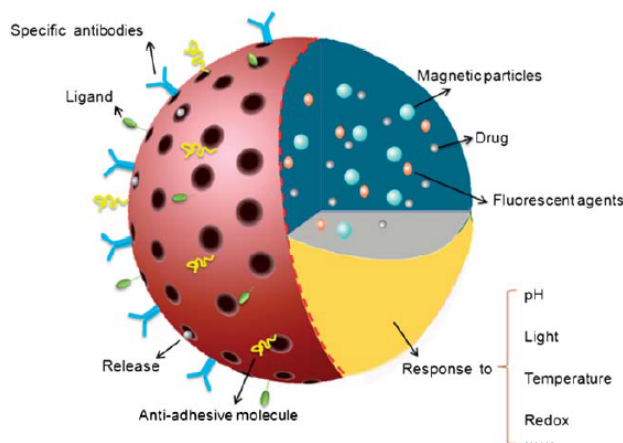


Figure 8 Schematic demonstration of multifunctional stimuli-responsive porous particle-loaded therapeutics and controlled release to specific target. Reprinted with permission from ref. [64].

3.2 Types of gating structure

The major types of gating structures are described by using MSNs as a core model, as illustrated in Figure 9 [39, 41]. Various gatekeepers show the “open/close” mechanism for preventing drug diffusion before delivery to the target. The gatekeepers are functionalized or bonded onto the surface of the porous carriers. Originally, the drug molecules are blocked, and unable to pass out of the pore host. The stimuli environment triggers the deformation of the gatekeeper, resulting in drug release [112]. The major types of gating structures include:

Structure I: Nanoparticles (NPs). Small size NPs (mostly inorganic NPs, e.g., Au NPs, Ag NPs, CdS NPs, Fe₃O₄ NPs, and ZnO NPs) are attached to the external pores of MSNs by ionic bonding interaction. External stimuli, such as pH, redox potential and temperature can break these chemical bonds.

Structure II: Macrocyclic organic molecules. Organic molecules (cyclodextrin, cucurbit [6]uril, and dibenzo-24-crown-8) with bucket or crown shapes act as cages to immobilize stalks on the pores of MSNs. The cage can then be disassembled by external stimuli to release the encapsulated drug.

Structure III: Liner molecules. Stimuli sensitive linear polymers are grafted around the surfaces of external pores. The molecules act as a switch gate to open/close pores when the system is stimulated.

Structure IV: Multi-layer shell coating. Stimuli-responsive polymers, biomolecules or polyelectrolyte multilayers are coated on the surface of MSNs by a layer-by-layer (LbL) deposition technique.[113] In the stimuli environment, the multilayer polymer chains are broken into small fragments, leading to drug diffusion.

Structure V: Pore modification. Only the interior pores of MSNs are modified by specific functional groups, stimuli-responsive polymers or nanoimpellers. These act as obstructions to trap the drug inside the pores.

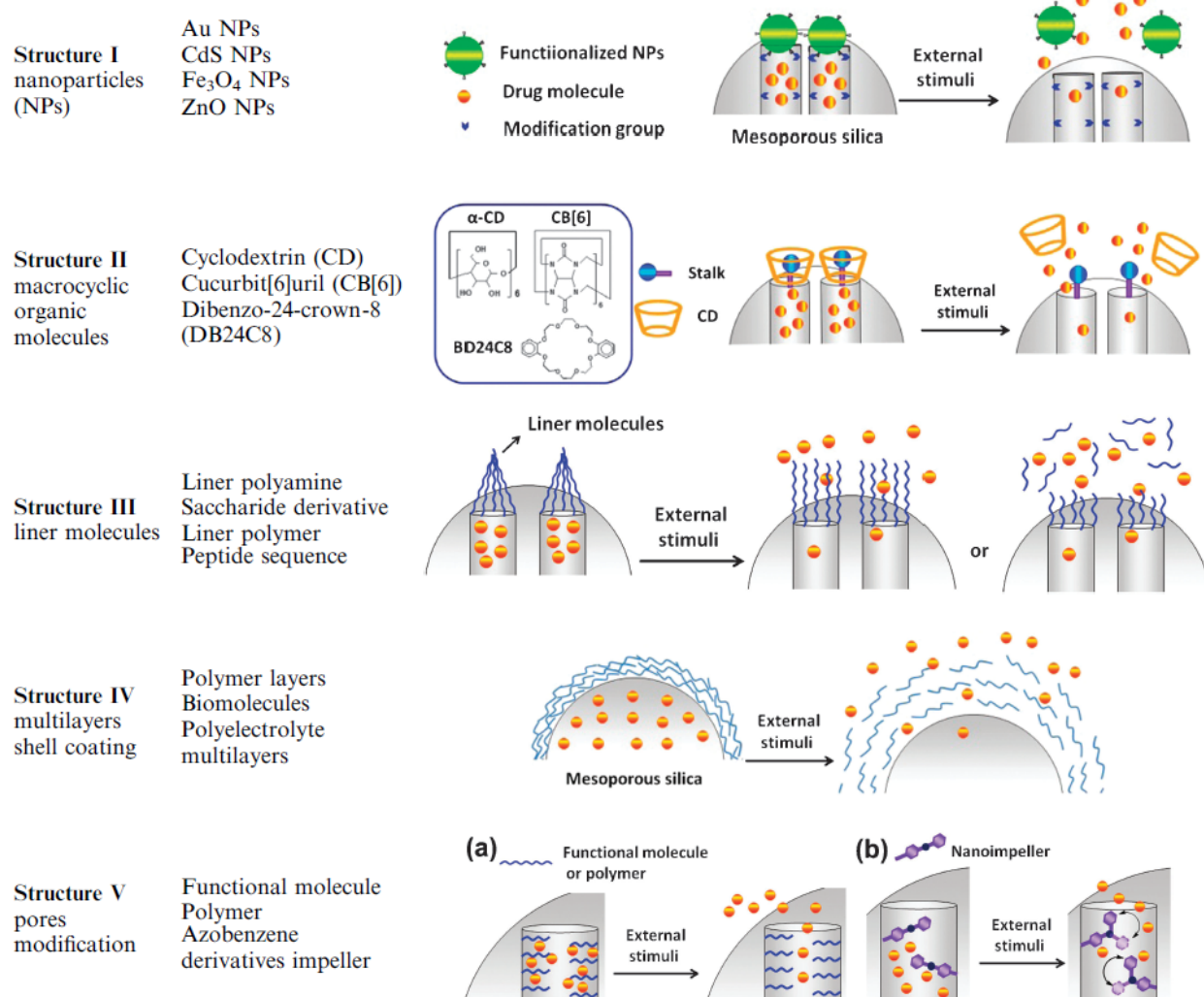


Figure 9 Schematic gating structures of mesoporous silica particles illustrated by types and examples of stimuli-responsive gates. Reprinted with permission from ref. [41].

The development of stimuli-responsive drug delivery systems increases drug carrier performance for remotely controlled action at the target site. Stimuli-responsive polymers can undergo structural transformation, self-assembly or chemical cleavage when triggered [114]. Stimuli-responsive drug delivery systems are categorized into two types: exogenous and endogenous stimuli. Exogenous stimuli are triggered by external factors, such as heat, light, magnetic field, and ultrasound. These stimuli are easily triggered for remotely-controlled drug delivery to the target after the administration of drug-loaded particles. This ensures that the carriers can release the drug at the target site at the right time [115]. On the other hand, endogenous stimuli provide significant benefits for diseased tissues in the microenvironment, including pH variation, redox state, different levels of glutathione (GSH), blood glucose level, and specific enzyme triggers [114, 116]. Therefore, endogenous stimuli-responsive drug delivery systems can reduce side effects, and serve as more effective therapeutics [117].

3.3 Exogenous stimuli-responsive gates

Drug delivery is triggered by external physical stimuli. Common exogenous stimuli, such as temperature, light, magnetic nanoparticles, and ultrasound can induce shrinking or swelling transitions of the polymer gates utilized to obtain “close to open” switching pores.

3.3.3 Thermo-responsive gates

The thermo-responsive polymeric gate is one of the most attractive candidates, because of its specific sol-gel phase transition temperature. The difference between the environment and the body's temperatures stimulates the switchable trigger to allow drug release. Generally, the polymers in this case are categorized into two classes: polymers with a low critical solution temperature (LCST) undergo hydrophilic to hydrophobic transition, whereas polymers with an upper critical solution temperature (UCST) exhibit the opposite transition [5, 118, 119]. Varieties of temperature-sensitive polymers have been examined for use in drug delivery, synthetic or natural polymers; poly(*N*-isopropyl acrylamide) (PNIPAM), poly(*N*-vinylcaprolactam) (PVCL), poly(*N*-vinylalkylamide), poly(2-hydroxyethylmethacrylate) (PHEMA), pluronic, chitosan, hyaluronic acid, polypeptide, and gelatin [120]. PNIPAM is a well-known and largely employed thermo-responsive polymer. This polymer is water soluble with an LCST of around 32°C. Below its LCST, PNIPAM is swollen, due to hydrogen bond formation between amide groups and water molecules, hence the pores are closed. When the temperature is increased above the LCST, the

polymer segments become hydrophobic and shrink, leading to pore opening and the release of the encapsulated drug to the medium (Figure 10a) [27, 120, 121]. In addition, further modifications of PNIPAM properties can be achieved, in particular its LCST can be increased by the copolymerization of PNIPAM with different monomers, according to specific applications [122, 123]. Jadhav *et al.* developed thermoresponsive polymeric gates from random copolymers of NIPAM with acrylamide (AM), i.e., (poly(NIPAM-co-AM) copolymers) grafted in the inner MSN pores. The LCST value of the copolymers was raised to 41°C. Antioxidant rutin was encapsulated in these thermoresponsive gate particles. When the temperature was increased to 45°C, above the LCST of the copolymers, the sensitive polymer chains collapsed to open the pores, resulting in the release of rutin [123].

3.3.4 Light-responsive gates

Light- or photo-responsive gates can achieve drug release by external light irradiation at a specific wavelength, such as ultraviolet (UV), visible light, and near-infrared (NIR). According to their isomerization mechanisms, photo-responsive polymers are divided into reversible and irreversible behaviors [8]. Reversible photo-responsive polymers can transform into cyclic *cis-trans* isomers without bond cleavage, for example, azobenzene can change from *trans* to *cis* configurations, in response to UV light at 351 nm, with the distance of *para* carbon atoms decreasing from 9.0 to 5.5 Å (Figure 10b) [27, 124]. Yuan *et al.* reported the photosensitive gating of MSNs using azobenzene-modified DNA molecules. The modified photoresponsive gate is immobilized at the pore mouth of MSNs. Rhodamine 6G, a model drug, was encapsulated within the porous particles to evaluate their controlled release behavior. Under visible light (450 nm), drug release was not observed due to the closed pore structure. However, drug release occurred when the gate was exposed to a UV range of (365 nm) [125]. Another azobenzene derivative was employed to act as a valves by bonding onto the outer surface of porous particles to prevent drug release. Azobenzene can bind with cyclodextrin (CD) in the *trans* configuration through van der Waals interaction, and debind in the *cis* configuration when being irradiated with UV light [126, 127]. Regarding irreversible photo-responsive polymers, during light induction the chemical bond is cleaved to switch from hydrophobic to hydrophilic isomers, such as spiropyran, coumarinyl and *o*-nitrobenzyl.[8] Despite the advantages, the use of light irradiation to trigger drug release may be limited by the depth of light penetration at deep tissue sites [128].

3.3.5 Magnetic-responsive gates

Magnetic nanoparticles (MNPs) have attracted interest in biomedical applications, due to their targeted delivery platform and capacity for controlled therapeutic release, by applying an external magnetic field. Superparamagnetic nanoparticles are typically used as magnetic-responsive gates by nanocapping (structure I) or incorporation with other responsive polymers, such as pH-responsive or temperature responsive polymers [124, 129]. For example, pH-responsive nanocomposites of magnetic mesoporous silica were developed for hyperthermia cancer treatments [6]. In this system, β -thiopropionate-poly(ethylene glycol) acts as a pH gatekeeper, and can be hydrolyzed for fast release behavior at pH 5.8 [130]. The dual-responsive gating particles of MNPs and temperature-responsive PNIPAM can control the close/open gates through the application of a magnetic field, as the MNPs generate thermal energy, inducing conformation changes of the thermo-responsive polymer (Figure 10c) [131].

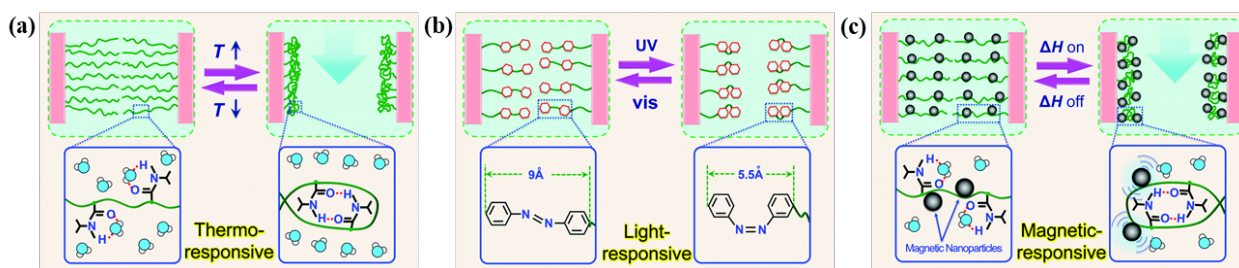


Figure 10 Smart gating model in the presence of external stimuli: (a) temperature, (b) UV light, and (c) magnetic field. Modified and reprinted with permission from ref. [27].

3.2.4 Ultrasound responsive gates

Ultrasound is a powerful physical modality for drug delivery and medical treatment. Ultrasound enhances the permeation of active ingredients through deep tissues with controlled frequency. Moreover, it can induce thermo-induction, mechanical stimulus or gas vaporization (bubble) for safety therapy [132]. The ultrasound parameters, including frequency, power, cycle, and exposure time are optimized for triggering drug release at a specific target. Paris *et al.* studied the utilization of 2-tetrahydropyranyl methacrylate (THPMA) as an ultrasound-responsive polymer gatekeeper for MSNs. When ultrasound was applied, a phase transformation of THPMA occurred, changing it from hydrophobic to hydrophilic form. Figure 11 shows that the hydrolysis of ultrasound-responsive polymer leads to gate opening, resulting in the release of fluorescein to the medium, by employing ultrasound at 1.3 MHz and 100 W for 10 min [133].

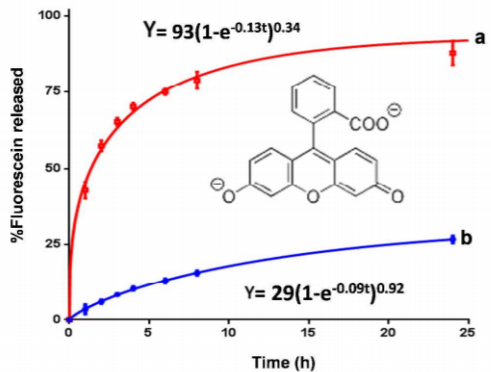


Figure 11 The release profiles of fluorescein from hybrid mesoporous silica nanoparticles in PBS solution: with (a) ultrasound exposure and (b) without ultrasound. Reprinted with permission from ref. [133].

3.4 Endogenous stimuli-responsive particles

The stimuli-responsive carriers are sensitive to biochemical origins and cellular levels in changing endogenous stimuli, such as pH, redox, enzyme, and glucose. The stimuli can trigger drug release at targeted tissues.

3.4.3 pH responsive gates

Among various types of stimuli, pH-sensitive drug carriers are those most commonly used for the development of controlled release systems. Different locations of human organs have distinctly different pH values, for example the gastrointestinal system of the stomach (pH \approx 1.0-3.0), intestine (pH \approx 6.5-8.0), and blood (pH \approx 7.4). Pathogenic conditions, such as tumors and bacterial infections, lead to changes in pH level from neutral to slightly acidic (pH \approx 6.8) [41, 134]. The development of porous particles can be achieved through surface functionalization with pH-responsive triggers as gatekeepers by using polyelectrolytes, supramolecular valves, pH-sensitive linkers, and acid-decomposable inorganic materials [124, 134, 135]. pH-sensitive carriers have the ability to differentiate slight pH changes in some diseases, such as tumors, and inflamed tissues. Lin *et al.* designed pH-sensitive MSNs using acetelated-dextran as a gate for the controlled release of anticancer drugs. In a neutral environment (pH 7.4), hydrophobic dextran acted as a gate to block drugs entrapped inside MSNs. In acidic conditions, however, hydrolyzed dextran transforms into hydrophilic state, which triggers the release of DOX [136].

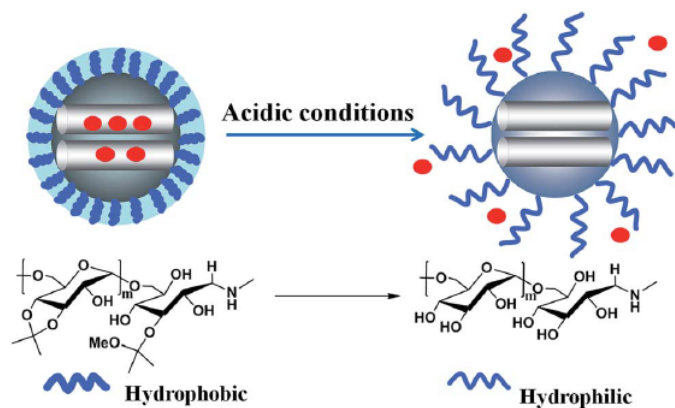


Figure 12 Schematic illustration of the pH triggered drug release of acetalated-dextran/mesoporous silica nanoparticles. Reprinted with permission from ref. [136].

3.3.2 Redox responsive gates

Among the variety of stimuli-responsive species for drug delivery systems, redox-responsive carriers can effectively trigger the targeted intercellular environment. In this regard, glutathione (GSH) is the most abundant reducing agent; the cleavage of GSH produces disulfide bonds (S-S). The stability of the disulfide linkages can block the encapsulated drug from the external environment, while their reduction in the tumor environment leads to bond breaking and drug release. Disulfide bonds acquire redox sensitivity [137]. The presence of high concentrations of GSH also affects the release rate of drug molecules due to completely cleaved disulfide bonds at the pores [138]. Redox-gatekeepers have been developed by using nanoparticles, supramolecules, and polymers for covering the pore structure [124]. Wang *et al.* successfully fabricated redox-responsive MSN by using polyethylene glycol (PEG) as a gatekeeper. PEG was grafted onto the external surface pores of modified MSN (SS-MSN) by condensation reaction between hydroxyl groups of PEG and carboxyl groups of SS-MSN through disulfide bonds, resulting in PEG-SS-MSN. Intracellular GSH is adequate to break disulfide bonds for releasing dyes (Figure 13) [139].

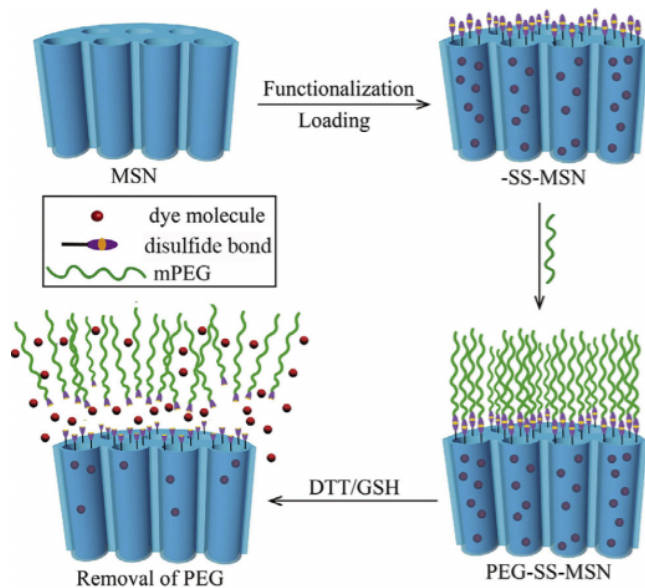


Figure 13 Schematic illustration of drug loaded redox-responsive carriers based on silica and PEG gatekeepers. Reprinted with permission from ref. [139].

3.3.3 Enzyme-responsive gates

Enzymes are biological catalysts produced by particular microorganisms. They can break down polymeric bonds, causing the disassembly of nanocarriers and allowing drug release in drug-delivery applications. Enzyme-responsive systems have been applied in the form of responsive gatekeepers on the nanovalves of porous silica nanoparticles [124, 140]. Nanoparticles can be modified with specific enzyme-labile linkages to trigger drug release and control the initial response time of the system. Sensitive peptide gatekeepers, i.e., succinic acid–glycine–phenylalanine–leucine–glycine (SGFLG) sequence and transferrin were grafted onto MSN surfaces to encapsulate an anticancer drug (DOX) and photosensitizer (chlorine e6), as shown in Figure 14 [141]. Sensitive polypeptide gatekeepers induce gate opening and controlled drug release towards their degradation in a cathepsin D (protease) and low pH environment. In addition, this smart particle promotes photosensitivity to generate reactive oxygen species under NIR irradiation for specific chemotherapy and photodynamic therapy in cancer treatments. Other enzyme-responsive nanoparticles were reported to improve diagnostic features for cancer treatments and inflammation. For example, supramolecular cyclodextrin, [142-144] and gold nanoparticles [145] combined with specific sensitive linkers were utilized to block nanopores.

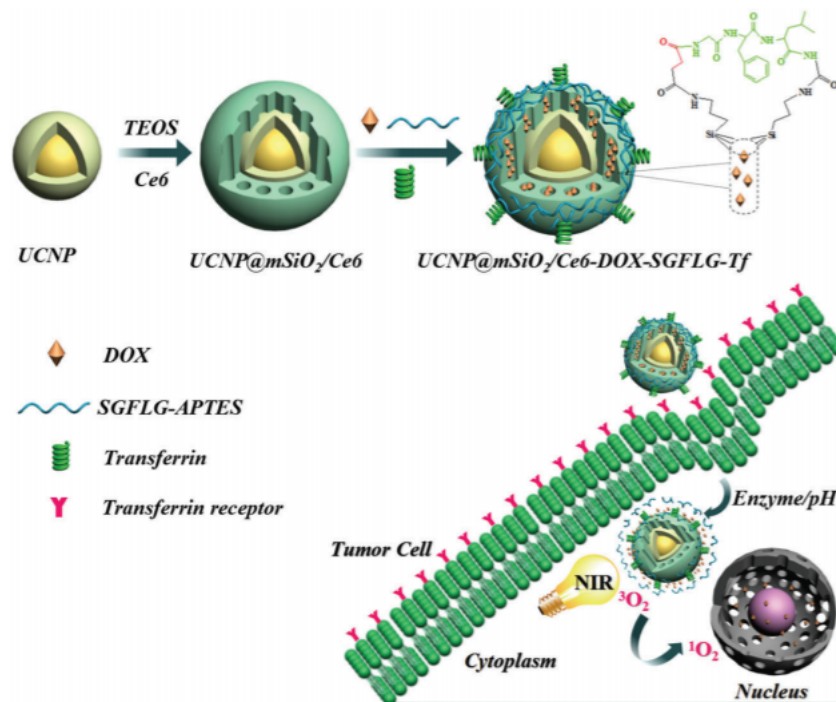


Figure 14 Dual enzyme/pH-responsive nanoparticles of DOX-loaded MSN with a SGFLG peptide gatekeeper. Reprinted with permission from ref. [141].

3.3.4 Glucose-responsive gates

Smart insulin delivery is a highly promising treatment for diabetes, which is a metabolic disorder leading to hyperglycemia. Glucose responsive compounds play an important role in the detection of the blood glucose level. They are mainly classified into 3 classes, including phenylboronic acid, concanavalin A, and glucose oxidase [146]. Phenylboronic acid (PBA) is a typical synthetic compound sensitive to rapid physicochemical changes in glucose response. PBA reacts reversibly with *D*-fructose, *D*-galactose and 1,2-*cis*-/1,3diols, resulting in transformation from hydrophobic to hydrophilic form. This trigger can effectively induce the release of insulin [147]. Concanavalin A (Con A) is a lectin that contains four sugar-binding sites: α -*D*-mannopyranose, α -*D*-glucopyranose, and the other ono-reducing sugars. This sensitive compound combines with Con A and other substances on the particles, resulting in the break down of their chemical structure and insulin release [148]. However, Con A possesses poor biocompatibility and instability.[146] A well-known enzyme for monitoring the blood glucose level is glucose oxidase (GOx). This consists of two subunits bonded with two prosthetic groups of flavin adenine dinucleotides. Cyclodextrain modified glucose oxidase (CD-GOx) was used as a gatekeeper grafted onto MSN for fluoresein isothiocyanate-labeled insulin (FITC-Ins) delivery [149]. Figure

15 represents the design of the complex gatekeeper between CD-GOx and benzimidazol groups. When the particles are triggered by glucose in a medium, glucose is hydrolyzed into gluconic acid by the glucose oxidase enzyme, with the protonation of benzimidazol groups. This promotes the dethreading of gatekeeper complexes, leading to delivery insulin.

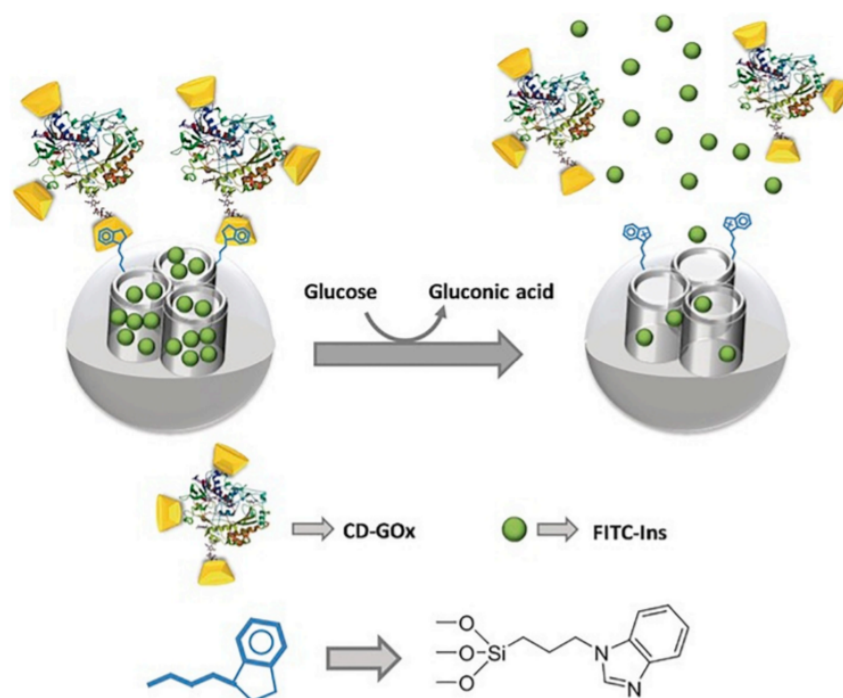


Figure 15 The glucose responsive drug delivery of fluorescein isothiocyanate-labeled insulin-based mesoporous silica nanoparticles. Reprinted with permission from ref. [149].

Table 3 Stimuli-responsive polymers and their corresponding stimulus.

Type of stimulus	Porous particle	Gatekeeper	Objectives	Ref.
Temperature	MSN	Poly(ethylene glycol)/poly(ϵ -caprolactone) multiblock copolymer	Copolymer gatekeeper response to heat-shock stimuli for DOX release.	[150]
Temperature	MSN	Poly(<i>N</i> -isopropyl acrylamide)	Preparation of PNIPAM-grafted mesoporous silica particles.	[151]
Temperature	Hollow MSN	Poly(<i>N</i> -isopropylacryl amide)	Synthesis of hollow MSN with PNIPAM coating.	[152]
Temperature	Gelatin	Poly(<i>N</i> -isopropylacryl amide)	Grafted PNIPAM with gelatin microspheres with reversible on/off switch for drug release.	[153]
Temperature	Alginate	Poly(<i>N</i> -isopropylacryl amide)	Preparation of smart polysaccharide particles with temperature dependent drug release.	[154]
Temperature -Magnetic	MSN	<i>N</i> -isopropylacrylamide/(Hydroxymethyl)acrylamide copolymer	Effect of grafting structure on fluorescein release behavior, rendering opposite profiles.	[122]

NIR light	MSN	Copper sulfide (CuS)	CuS-capped MSN acted as NIR-responsive and photothermally triggered DOX release.	[155]
NIR light	PLA	Polypyrrole	One-step preparation of NIR responsive porous particles with conductivity and photo-thermo conversion.	[156]
UV light	MSN	Cyclodextrin <i>o</i> -nitrobenzyl	Cyclodextrin and photocleavable linkers blocked in MSN pores under UV light.	[157]
Magnetic	PCL	Magnetic Fe ₃ O ₄ nanoparticles	Magnetic/ PCL porous particles produced by electrospray technique, and release rate enhanced by external magnetic stimuli.	[158]
Magnetic	MSN	Superparamagnetic Fe ₂ O ₃ nanoparticles	Switchable DNA/MNPs as caps for blocking fluorescein with on-off release behavior.	[159]
Ultrasound	MSN	polyethylenimine	Responsive nanocarriers exposed by ultrasound for treating tumor cells.	[160]
Ultrasound	MSN	2-Tetrahydropyranyl methacrylate	Ultrasound parameters studied for applying nanocarriers inside LNCaP cells with high fluorescein release rate.	[133]
pH	MSN	Acetalated dextran	Preparation of hydrophobic valves to entrap DOX inside mesoporous silica.	[136]
pH	MSN	Poly(phenyl(4-(hydroxymethyl)phenyl)carbamate)	pH responsive nanocarriers for potential cancer treatment.	[161]
pH	MSN	Chitosan	Chitosan hydrogel capped over pores; insulin penetrates through swollen hydrogel at pH 6.0, while blocked at pH 7.4.	[162]
pH	PLGA	Chitosan/alginate	Layer-by-layer pH sensitive self-assembly nanoparticles.	[163]
pH-Magnetic	MSN	β -thiopropionate-poly(ethylene glycol)	DOX vehicles combined magnetic targeting, and pore opening at pH 5.8.	[130]
pH-Ultrasound	MSN	polydopamine	DOX released at low pH values due to degradation of polymer, while ultrasound stimulated DOX released by cavitation effect.	[164]
pH-Magnetic-Ultrasound	MSN	Dibenzo-crown ethers	The release of DOX triggered by low pH and ultrasonic waves to break up electrostatic interaction between supramolecular and metal stalks.	[165]
Redox	MSN	Glutathione	Concentration of gatekeepers on MSN affects the release rate of salicylic acid due to disulfide bond cleavage.	[138]
Redox	MSN	Poly(ethylene glycol)	Gating efficiency of glutathione and polyethylene glycol on model drug release.	[139]
Redox	MSN	Transferrin	Transferrin-capped MSN nanocarrier designed to control drug delivery via conjugating disulfide bonds.	[166]
Redox-NIR light	MSN	Gold nanoparticles	Gold/MSN particles act as gatekeepers and absorb NIR irradiation for inducing photothermal therapy.	[167]
Redox-NIR light	MSN	<i>D</i> - α -tocopherol polyethylene glycol 1000 succinate and cypate	MSN gate designed for antitumor drug.	[168]
Redox-Enzyme	MSN	Oxidized glutathione Hyaluronic acid	Modification of sealing pore drug carriers, drug release by cleaving of disulfide bonds or decomposition of hyaluronic acid.	[169]
Enzyme	MSN	Cyclodextrin	Cyclodextrin gatekeepers are sensitive to the enzymatic activity of α -amylase and lipase.	[144]

Enzyme	MSN	ϵ -poly-L-lysine	Two different types of ϵ -poly-L-lysine anchored onto outer pore MSN with release behavior in the presence of proteases.	[170]
Enzyme	MSN	Saccharide derivatives	Novel saccharide derivatives functionalized on the pore outlets of MSN. Enzyme dependent opening of saccharide gate and dye release.	[171]
Enzyme	MSN	Gold nanoparticles-biotin	Fabrication of gold nanoparticle-biotin conjugate-capped MSN.	[145]
Enzyme-pH	MSN	Succinic acid-glycine-phenylalanine-leucine-glycine (SGFLG)	<i>In vitro</i> DOX release of peptide gatekeeper depending on cathepsin B enzyme concentration and pH value.	[141]
Glucose	PLGA	Poly(vinyl alcohol) and poly(acrylamide phenyl boronic acid-co-N-vinylcaprolactam)	Development of multilayer microspheres for controlling blood sugar level to treat diabetes.	[172]
Glucose	MSN	Glucose oxidase (GOD) catalase	Design of controlled release of insulin by multilayer coating on outlet pore particles.	[173]
Glucose	MSN	B-Cyclodextrin modified glucose oxidase	Development of glucose-sensitive compound for insulin-controlled release.	[149]
Glucose	MSN	Gluconic acid-modified insulin	Synthesis of a glucose-responsive MSN with double delivery system for both insulin and cyclic adenosine monophosphate.	[174]
Glucose-pH	MSN	Low molecular weight gelator	Controlled antidiabetic gel capped drug release by glucose and pH stimuli.	[175]

MSN = mesoporous silica, MNPs = magnetic nanoparticles, DOX = doxorubicin, PLGA = poly(lactic-co-glycolic acid), PNIPAM = poly(*N*-isopropylacrylamide), PLA = poly(lactic acid), PCL = Poly(ϵ -caprolactone).

4. Potential roles in practical applications

In the biomedical field, drug-loaded stimuli-responsive porous particles are being investigated intensively. The benefits of these particles are: (i) high drug loading efficacy, due to their high surface area and porosity; (ii) precise design of gatekeepers and their structures; (iii) stimuli-responsive drug release at specific targeted sites. The major challenges in drug delivery systems are to find strategies to achieve high drug loading capacity and stability in physiological environments. Stimuli triggered gatekeepers finally allow sustained release at optimal levels over prolonged time periods [176]. Most studies of drug-loaded stimuli-responsive particles involve an anti-cancer drugs, anti-inflammatory drugs, and inhalable drugs for pulmonary drug delivery. However, the biocompatibility of drug carriers is mainly necessary for clinical use because materials can interfere within the biological system. Particles may interact with the biological systems through various complex mechanisms at a cellular level and cause toxicity [177]. Surface modification of MSNs with hydrophilic polymers, like PEG gatekeepers can also reduce their protein adsorption and prevent nonspecific binding on surface particles [139, 178]. Therefore,

biodegradable drug carriers and non-cytotoxic materials for gatekeepers require further investigation.

The development of responsive-drug carriers for chemotherapy demands sufficient drug release at the tumor location. Multiple endogenous stimuli carriers can be triggered by changing the microenvironment, including mild acidity, increasing intercellular glutathione levels, and enzyme overexpression, which are characteristics of tumor tissues [179, 180]. Therefore, the combination of internal stimuli and external stimuli, such as pH, redox, enzyme, temperature, light, and magnetic-responsive drug carriers, are also required for improving drug controlled release performance [181]. A novel nanoporous platform presented multiple sensitive drug delivery systems with DOX-loaded MSN, coated with polydopamine (PDA) via disulfide bonds. PDA plays an important role as a photothermal therapy gatekeeper with outstanding characteristics, since it is highly pH sensitive, it is capable of absorbing NIR radiation, and it is biocompatible. At a neutral pH, therapeutic drugs were blocked in MSN, but released at lower pHs. Figure 16 illustrates a redox/pH/NIR multi-responsive drug carrier, and their synthesis processes. Sustainable release was achieved at pH 5.0 and with 10 mM of GSH. The results from an *in vivo* study in mice showed that a synergistic effect of photothermal treatment and prolonged drug release was achieved by applying NIR irradiation to these particles. This led to the effective inhibition of tumor growth [182]. In another responsive porous particle system, modified pH-/redox-responsive MSN was prepared. DOX was entrapped in the MSN pores which were capped by hyaluronic acid-grafted-cyclodextrin (HA-g-CD) as a gatekeeper. The *in vitro* results indicated the excellent targeting ability of HA-g-CD nanocapsules against CD44 overexpressed cancer cells, the rapid release of DOX by the hydrolysis of benzoic imine bonds at low pH, and the cleavage of disulfide bonds at high glutathione levels [183].

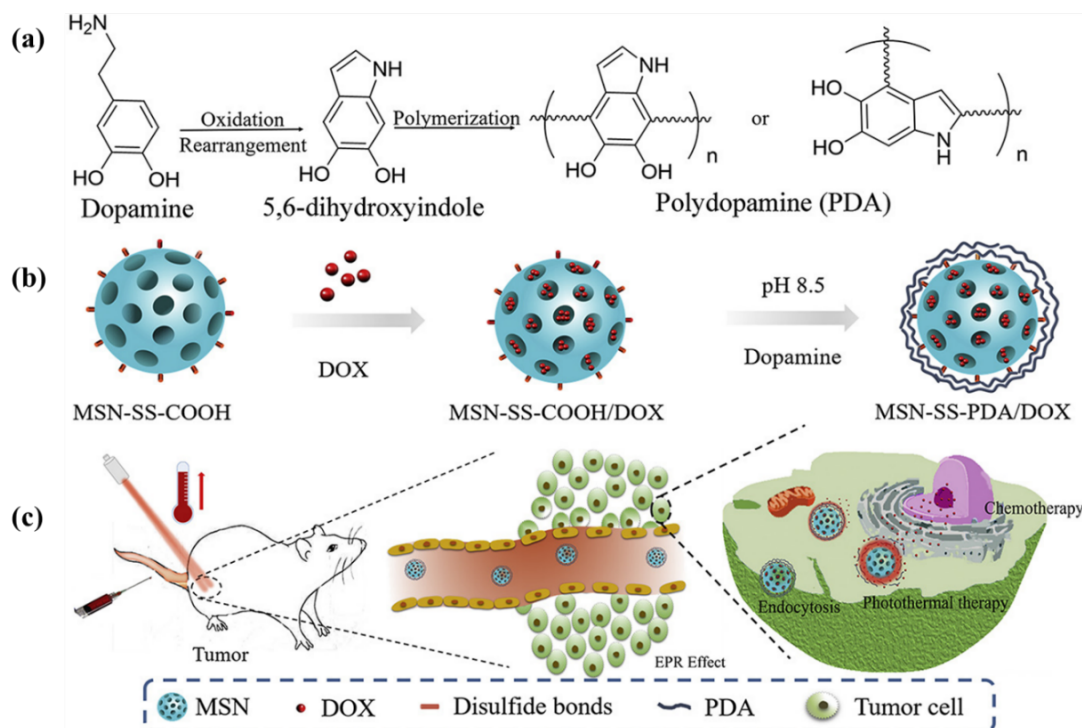


Figure 16 Schematic representation of: (a) the synthesis of polydopamine via oxidation polymerization, (b) the formation of stimuli-responsive MSN-SS-PDA/DOX particles, and (c) *in vivo* chemo-photothermal therapy on a tumor. Reprinted with permission from ref. [182].

In case of pulmonary drug delivery, drug transfer with prolonged drug retention in the lung is required to achieve treatment efficacy. The number of cases of respiratory diseases, including lung cancer, asthma, pneumonia, idiopathic pulmonary fibrosis, and chronic obstructive pulmonary disease have increased in recent decades, due to smoking, genetic syndromes, and air pollution [184]. Inhaled drug carriers have the ability to transfer therapeutic drugs and provide sustained release to the target. Their particle size ranges widely from nano to micron sizes, depending on the target deposit site. For example, nanoparticles can diffuse through alveoli, while particles of 1-5 μm are deposited in the deep lungs. In contrast, particles with sizes larger than 10 μm are deposited in the oropharyngeal region [184, 185]. Porous particles are light particles with low density ($<0.4 \text{ g/cm}^3$) and suitable hydrodynamic diameters (1-3 μm) for improving deep lung deposition. Several biodegradable polymers were used to prepare inhalable porous particles, such as poly(lactic-co-glycolic acid), poly(lactic acid), chitosan, gelatin, alginate, etc [185, 186]. Figure 17 illustrates inhalable DOX-loaded PLGA porous microparticles with surface-attachment with TRAIL [187]. These particles were fabricated by a W/O/W double emulsion using ammonium bicarbonate as a pore-forming agent, while their surface was modified by strong ionic interaction

between TRAIL and poly(ethylene-*alt*-maleic anhydride) (PEMA). The inhalable microparticles showed excellent drug delivery to the lung over a 7-day period by leaching TRAIL and breaking ionic bonds around the particle surface, leading to DOX release.

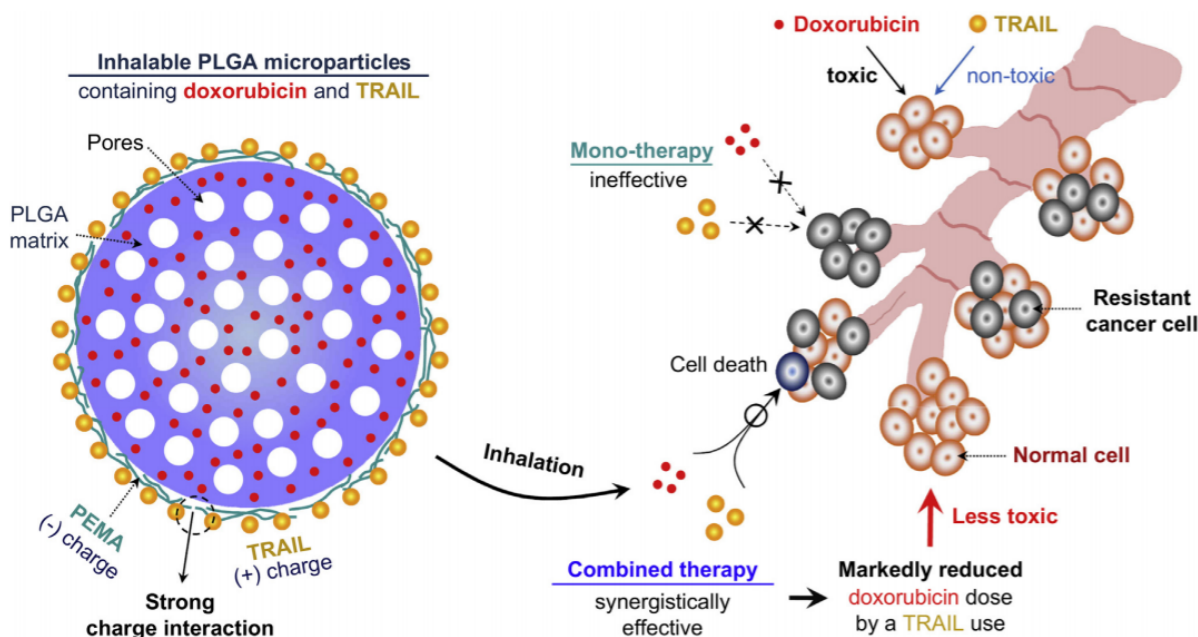


Figure 17 Schematic demonstration of inhalable TRAIL/Dox-loaded PLGA porous microspheres for anti-lung tumor treatment. Reprinted with permission from ref. [187].

Stimuli-responsive porous materials have been used prospectively in the clinical stages of tissue engineering and regenerative medicine. The three dimensional (3D) structures of porous particles serve as mechanical supports and they can transport nutrients or growth factors to injured tissues, for example skin, bone and cartilage, blood vessels, and nerves [188]. The high surface area of the porous structure can induce cell adhesion and regeneration [64]. Almost all types of bone diseases usually display the characteristic of increasing temperature ($\sim 2\text{-}3^{\circ}\text{C}$), due to inflammation, or decreasing pH due to osteolytic cancer. Thus, these disorders can be diagnosed by stimuli triggers, such as pH, temperature, redox, and enzymes [189-191]. Gan *et al.* investigated pH responsive chitosan-functionalized MSN for the dual-delivery of bone morphogenetic protein-2 (BMP-2) and dexamethasone (Dex), which are used to induce osteoblast differentiation. Crosslinked chitosan plays a role as a pH-responsive gatekeeper, immobilizing BMP-2 molecules onto the Dex-loaded MSN. In physiological state, BMP-2 was rapidly isolated from the chitosan-MSN surface, and bound to its specific cell receptors. However, in endocytosis, decreasing the pH of the environment stimulated Dex release through the dispersal of chitosan. Dex was then diffused

into the cytosol, (Figure 18). Finally, an *in vivo* study showed that osteogenesis was enhanced in the mouse ectopic bone [192].

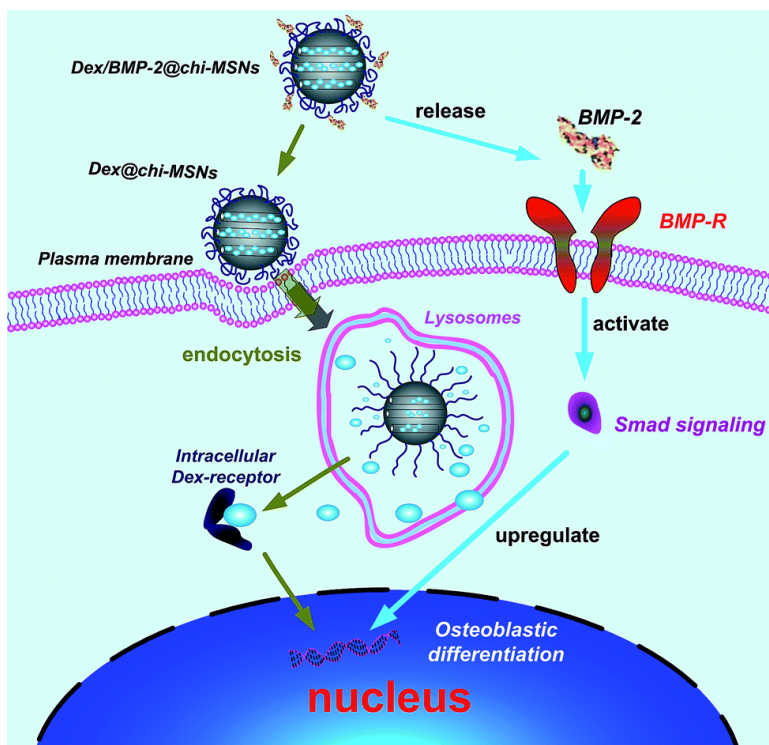


Figure 18 Schematic diagram showing a pH-responsive chitosan-functionalized MSN and the controlled release of BMP-2 and Dex on osteoblast differentiation. Reprinted with permission from ref. [192].

5. Conclusions

This review summarizes the research progress on stimuli-responsive porous particles for drug delivery applications. Porous structures can be approached by using pore-forming agents, or by self-forming using chemical synthesis, such as seed polymerization and the double emulsion technique. The controlled size of the particles and their pore size distribution are related to their specific target sites. Porous particles offer enhancements in drug loading capacity, colloidal stability, targeting ability, biological stability, and biodegradability in the human body. Biocompatible porous drug carriers have unique properties of high surface area, large pore volume, and easy-to-modify surfaces, all of which can also improve drug encapsulation efficacy and sustained release. Effective encapsulated drug approaches require increasing the surface area and the surface drug affinity of the carriers.

The design strategies of smart gates involve their fabrication during or after the particle formation steps. Changes in the environment or external driving forces, such as temperature, pH, redox, light, magnetic field, ultrasonication, and chemical variations induce changes in the conformations of stimuli-responsive polymers. Both exogenous and endogenous stimuli-gatekeepers display self-regulation in response to stimuli to block premature leakage or allow the release of entrapped drugs. Therefore, the surface modification, functionalization, and precise gate capping position are major challenges to produce the effective smart drug carriers. Stimuli-responsive particles permit further control of kinetic release over time at a specific target location. Several stimuli-capping materials, such as inorganic nanoparticles, macromolecules and polymers play a key role in blocking the outlet pores. A combination of dual or multi stimuli can be employed to obtain sequential or simultaneous responses, depending on the intended behavior inside the body, and the therapeutic approach. The behaviors of multifunctional particles can be monitored directly in real-time, during their controlled drug release or tissue regeneration in a complex *in vivo* microenvironment. Future efforts should focus on the fabrication of novel smart gating particles, as well as examine their detailed trigger mechanisms. Smart gating particles are promising candidates for application in future drug delivery methods and medical treatments.

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Abbreviations list

BMP-2, bone morphogenetic protein-2
CD, cyclodextrin
Con A, Concanavalin A
CTAB, cetyltrimethylammonium bromide
Dex, dexamethasone
DOX, doxorubicin
FITC-Ins, fluorescein isothiocyanate-labeled insulin
GOx, glucose oxidase
GSH, glutathione
HA, hyaluronic acid
KCl, potassium chloride

LCST, low critical solution temperature
 MNPs, magnetic nanoparticles
 MSNs, mesoporous silica nanoparticles
 NH_4HCO_3 , ammonium bicarbonate
 NPs, nanoparticles
 PBS, phosphate buffered saline
 PBA, Phenylboronic acid
 PCL, poly(ϵ -caprolactone)
 PCM, phase change material
 PDA, polydopamine
 PDMS, polydimethylsiloxane
 PEG, polyethylene glycol
 PEG-PPG-PEG, poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol)
 PEMA, poly(ethylene-*alt*-maleic anhydride)
 PGMA, poly(glycidyl methacrylate)
 PHEMA, poly(2-hydroxyethylmethacrylate)
 PLGA, poly(lactic-co-glycolic acid)
 PLA, polylactic acid
 PLLA, poly *L*-lactide
 PMMA, poly (methyl methacrylate)
 PNIPAM, poly(*N*-isopropyl acrylamide)
 PTRIM, poly(trimethylol propane trimethacrylate)
 PVCL, poly(*N*-vinylcaprolactam)
 SGFLG, succinic acid–glycine–phenylalanine–leucine–glycine
 THPMA, 2-tetrahydropyranyl methacrylate
 UCST, upper critical solution temperature

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