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Review Article

Stimuli-responsive Bio-based Polymeric Particles and their Use in Biomedical Applications

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Abstract: Stimuli-responsive bio-based polymeric particles are of great interest for use in various applications, especially in biomedical fields. The materials are powerful tools for controlled drug delivery and precision medicine applications. They are useful in a large variety of physiological conditions for normal microenvironments and diseased sites. In this review, recent advances in the development of fabrication processes for stimuli-responsive bio-based polymeric particles with various morphologies and functionalities, are highlighted. Furthermore, the potential use of the materials as smart drug-delivery carriers is discussed. Finally, the respective prospects and limitations inherent in these material systems are addressed.

Keywords: Stimuli-responsive, Bio-based polymeric particles, Drug delivery, Biomedical application

1. Introduction

The development of polymeric micro-/nano-particles has attracted vast attention for applications in various fields, especially as pharmaceutical products, drug delivery carriers, cosmetic products, insecticides, paints, and textile products. This is due to their excellent ability to protect active compounds until reaching a specific target site. However, these materials are mainly produced from conventional polymers. This imposes adverse effects on the environment, due to their non-degradable nature, leading to waste accumulation and contamination in the ecosystem [1,2]. The development of "green" products from renewable raw materials, instead of fossil-based materials, is of interest in the research and industrial communities. Bio-based polymeric materials are produced through biological, chemical, or physical methods, from renewable resources, including crops or other plants and their residues. Cellulose, starch, proteins, polysaccharides, natural rubber, lignin, chitin, and chitosan are important examples of bio-based polymers, which can be degraded by microorganisms after use. The majority of chemosynthetic bio-based polymers are in the group of aliphatic polyesters, which contain hydrolyzable ester groups, such as polylactic acid (PLA), polybutylene succinate (PBS), and polycaprolactone (PCL) [3-6].

A broad range of degradable bio-based polymeric particles with diverse sizes, architectures, and surface properties has been designed and fabricated, due to recent advances in their fabricating technology. Besides, various functional groups have been employed to design multi-functional bio-based polymeric particles. Nowadays, stimuli-responsive polymers or smart polymers have been intensively studied for a diverse range of applications, e.g., drug delivery, tissue engineering, biosensing, smart coatings, and artificial muscles [2,7-9]. These materials are capable of

altering their chemical and/or physical properties upon exposure to external stimuli, including temperature, light, electrical or magnetic fields, and chemicals. Stimuli-responsive polymers are unique as they can mimic some parts of natural systems, which respond to various environments within the living systems. This makes these smart polymers important agents for drug delivery systems, among other applications.

In this review, recent research work on the preparation of stimuli-responsive bio-based polymeric particles with various morphologies and functionalities is highlighted. The effects of types of polymers and fabrication techniques on the properties of the resulting particles are discussed. Their applications as smart drug delivery carriers are emphasized.

2. Preparation of stimuli-responsive bio-based polymeric particles

Standard processes for the fabrication of polymeric particles have been developed by employing various techniques, including surface-initiated polymerization, emulsion, layer-by-layer (LbL), spray drying, and microfluidic techniques. Among these, double-emulsion solvent evaporation is an effective method that is commonly used to fabricate polymer-based porous particles. The double emulsion may be either water-oil-water ($W_1/O/W_2$) or oil-water-oil ($O_1/W/O_2$) emulsions [10,11]. Biodegradable poly(lactide-*co*-glycolic acid) (PLGA) porous carriers for donepezil (Alzheimer's disease drug) were prepared *via* the double-emulsion solvent evaporation method [12]. The particles were produced by a two-step emulsification mechanism. In the first step, an inner aqueous phase (W_1) of ammonium bicarbonate solution was homogenized with an organic phase (PLGA dissolved in dichloromethane) to obtain a primary emulsion. In the second step, the W_1/O emulsion was emulsified with an outer aqueous phase (W_2) containing polyvinyl alcohol (PVA) as a stabilizer, using an overhead stirrer to prepare a water-oil-water (W/O/W) emulsion, followed by solvent evaporation. The resulting porous PLGA microspheres, with a diameter ranging from 45–150 μm, as shown in Figure 1, were then loaded with donepezil drug. However, an initial burst release of donepezil from the porous PLGA particles was observed. To reduce this initial burst release, their surface pores were decorated with a sodium alginate coating, using a spray-ionotropic gelation method. The final pore-closed PLGA microspheres showed an in vitro sustained release for approximately 3 weeks. From predictions of plasma drug concentration profiles using a convolution method, the mean residence time of the pore-closed PLGA was 2.7-fold longer than that of the native porous PLGA carriers.

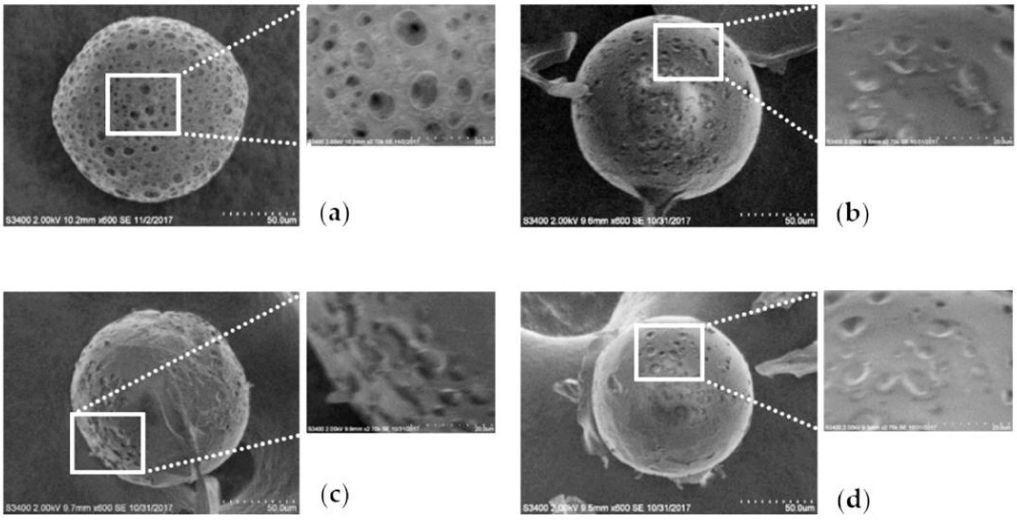

Figure 1 Scanning electron micrographs of (a) PLGA microspheres without sodium alginate coating and the microspheres with pore-closed materials derived from sodium alginate solutions with different concentrations: (b) 1%, (c) 1.5%, and (d) 2%. Reproduced with permission from ref. [12].

Biodegradable/biocompatible poly(lactide-*co*-glycidyl methacrylate), P(LA-*co*-GMA) copolymers were fabricated into microparticles with crosslinked structures by employing a thermal-curing reaction of the GMA units *via* suspension polymerization [13,14]. This is a heterogeneous system, in which the suspending agent was dissolved in distilled water as an aqueous phase. The organic phase consists of a monomer and an initiator. An active ingredient was then added into the aqueous phase with continuous stirring at an optimized speed, generating polymeric particles. The advantages of the suspension process include mild reaction conditions, due to the presence of the suspension medium, high purity of the products, and low viscosity, and hence, low energy consumption. Particles with hollow structures and tunable morphology were obtained by varying the curing time at 1 and 2 h, in which a longer curing time led to an increase in the crosslinking density. In a separate study, particles of P(LA-*co*-GMA) copolymers having a spherical shape with rough wrinkled surface morphology and bimodal size distribution (1 and 10 μm) were prepared via a phase inversion emulsification (PIE) process. The PIE technique has been widely used in the fabrication of polymeric particles that are used in cosmetic products and biomedical materials. Most importantly, this process consumes a low amount of energy for generating particles, with a narrow particle-size distribution [14,15]. In this process, two phases of emulsions, consisting of water-in-oil (W/O) and oil-in-water (O/W), are required. First, a W/O emulsion is formed. The water phase is then continuously added until the amount of water is higher than the oil phase. The W/O emulsion is finally irreversibly converted into an O/W phase. The effects of co-surfactant concentrations and the aqueous phase addition rate on the efficiency of the particle formation were evaluated. The addition of sodium dodecyl sulfate (SDS) co-surfactant at slow addition rates led to narrow size distribution and high stability of the microspheres. This is due to the formation of effective structures of polyvinyl alcohol (PVA) surfactant and SDS at the oil/water interface. The semi-crystalline particles possessed a network structure with a high gel content of 50%. The crosslinking efficiency was promoted by mixing the copolymers and the initiator homogeneously in the droplets, covered by surfactant molecules.

Generally, the layer-by-layer (LbL) assembly technique has been widely used to fabricate polymer film materials with tunable architectures and properties. This technique involves the alternating deposition of different interacting materials onto a substrate, in which the driving forces for LbL film formation range from electrostatic interactions to hydrogen bonding, charge-transfer interactions, host-guest complexes, and coordination bonding [16,17]. Recent advances in this technique include the possibility of all-aqueous processing, operationally simple control over the thickness of the resulting films through several deposition cycles, and the possibility of creating stratified films. With the LbL technique, stimuli-responsive bio-based polymeric particles can also be produced. J. Chen *et al*. fabricated core-shell (stacked) nanoparticles having dual pH- and reduction-sensitive drug-delivery properties by applying a facile LbL assembly technique [18]. Nanoparticles with various sizes (which can be further shrunk by specific enzymes or ultraviolet light) were also designed to have interchangeable charges under tumor stimuli, leading to enhanced penetration into the cells (Figure 2). The core-shell nanoparticles are composed of a dimethylmaleic anhydride-modified methoxy poly(ethylene glycol-*b*-l-lysine) ($mPEG_{113}$-*b*-PLL_{25}/DMMA) shell and a positively-charged and disulfide-crosslinked nanogel $PZLL_{10}$–P(LP_7-*co*-LC_5) core. The shell to core ratio is a key factor for controlling the sizes of the nanoparticles. The thickness of the shell was about three times the diameter of the core, which might be due to the electrostatic interaction and the rigid α-helical conformation of the polypeptide-based shell. The authors demonstrated that the size of the obtained nanoparticles was reduced from 145 to 40 nm, whereas the surface charges were converted from -7.4 to 8.2 mV at an acidic tumor area. This was likely because $mPEG_{113}$-*b*-PLL_{25} was released after cleaving the DMMA groups. In contrast, the disulfide crosslinking maintained the stability of the particles and prevented an undesired premature drug release before the release of the $mPEG_{113}$-*b*-PLL_{25} shells. This accelerated the cleavage of disulfide bonds and intracellular drug release after cellular uptake. The small size of the particles (40 nm) and positively charged surfaces was favorable for tumor accumulation and penetration, as well as cellular uptake.

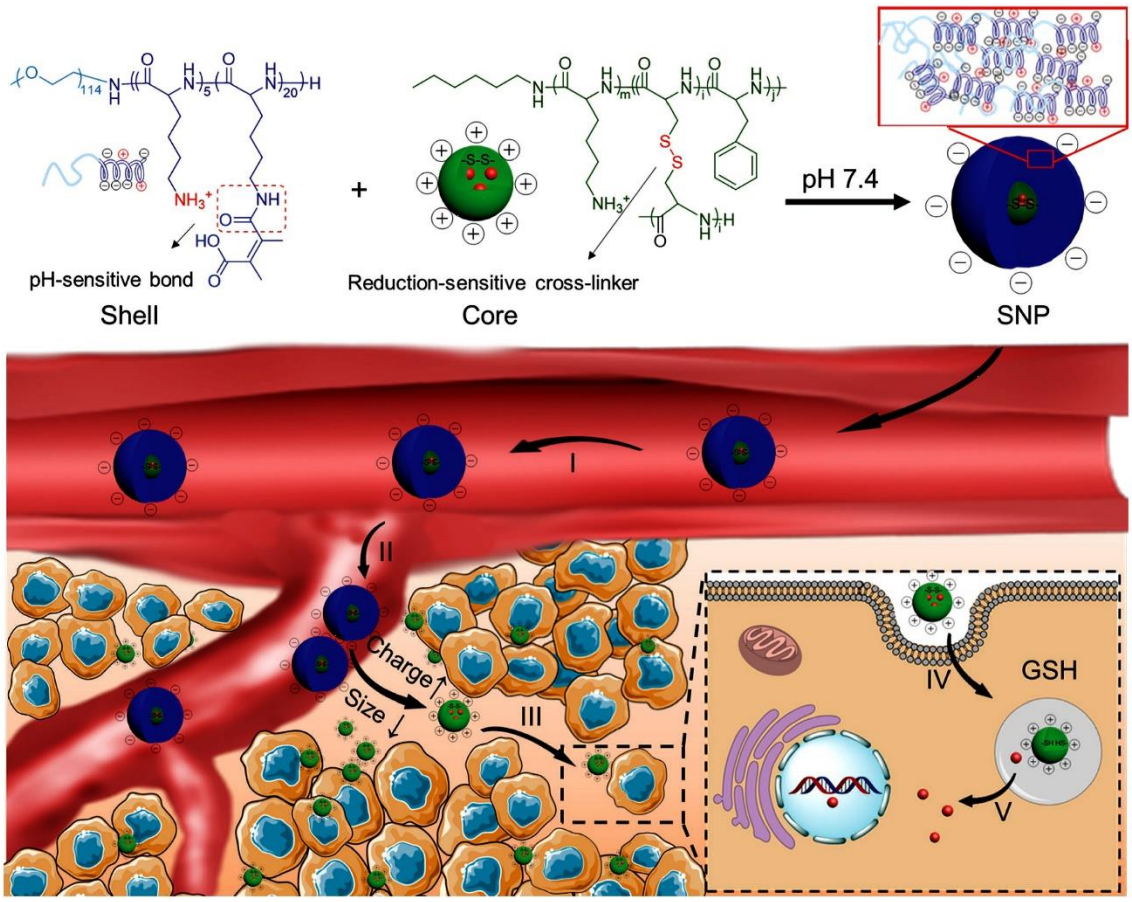

Figure 2 Formation of positively charged and disulfide-crosslinked polypeptide core-PEGylated and negatively charged shell nanoparticles by applying a facile LbL assembly technique. Due to the tumor-microenvironment-mediated multi-transformation, the nanoparticles could lead to a perfect cascade of drug delivery. I) Long circulation, II) enhanced accumulation, III) deep penetration, IV) promoted internalization, and V) accelerated drug release. Reproduced with permission from ref. [18]. Copyright 2017 John Wiley and Sons.

Vast attention has been focused on developing stimuli-responsive polymeric gels with unique properties, such as biocompatibility, biodegradability, and biological functionality, for potential use in biomedical applications [8,19–24]. Hydrogels are polymeric cross-linked three-dimensional networks with the ability to absorb and retain large amounts of water. They provide good biocompatibility while maintaining their shape. For applications as active delivery vehicles, stimuli-responsive elements can be incorporated into hydrogel structures, permitting an "intelligent" delivery of the active agents. These hydrogels may swell or collapse in response to changes in environmental conditions (temperature, pH, ionic strength, electric field, mechanical stress, or enzymes). They are suitable for use as "smart" materials for various biomedical applications. Also, these responsive hydrogels can be prepared by combining thermo-responsive polymers with natural-based polymeric components. Some polysaccharides have been combined with thermo-responsive materials, such as chitosan, pullulan, alginate, cellulose, and dextran.

Karakasyan *et al.* employed a droplet-based microfluidic technique in the production of monodisperse thermo-responsive alginate-*b*-polyetheramine copolymer microgels for drug delivery applications [25]. The microfluidic soft lithography technology is a new effective route for the fabrication of stimuli-responsive bio-based polymeric particles with high throughput. The microfluidic approaches offer several advantages over conventional flow control technology. These approaches can be used to produce monodispersed spherical and non-spherical polymeric particles

(spheres, cylinders, vesicles, and complex multicompartment vesicles with internal symmetry). These particles have a diameter ranging from several tens to several hundreds of μm and a diverse range of shapes. In this case, grafted-alginate microgels with average sizes varying from 60 to 80 μm were produced, depending on the type of alginate and the degree of substitution. The droplet-based microfluidic technique offers exquisite control of both the dimensions and physical/chemical properties of the grafted-alginate microgels. The thermosensitivity of the microgels was demonstrated, in which a 10 to 20 % reduction in size was obtained when the temperature was increased above the lower critical solution temperature (T_{LCST}) of poly(ether amine).

Based on microfluidic soft lithography technology, glutathione (GSH)-responsive biological polymeric nanoparticles of amphiphilic poly(ethylene oxide-block-methacrylate) having disulfide pendants with multicompartment vesicles were prepared by a two-phase microfluidic reactor at various flow rates [26]. The tunable shear forces within the microchannels provided effective control over the size distribution, morphology, and internal structures of the polymer nanoparticles. Moreover, distinct GSH-triggered responsivities of the polymeric nanoparticles were achieved under different conditions of the microfluidic flow. This shows the roles of the linkage location and the shear forces in controlling the rates of the particle and inner-compartment growth, upon GSH exposure. In addition, with the microfluidic strategy, different properties, including drug encapsulation efficiency, release rate, and *in vitro* cytotoxicity, can be produced with variable flow-directed shear forces within high-shear "hot spots" of two-phase segmented microfluidic reactors. This provides processing control over self-assembly, leading to polymer nanoparticles with controllable structure and properties, including drug encapsulation efficiencies, release rates, and *in vitro* cytotoxicity.

Chitosan is a typical bio-based polymer that is sensitive to pH, as a result of the charges imparted to its amino groups via protonation and deprotonation processes [27–29]. Chitosan and its derivatives have been widely used in biomedical applications, e.g., controlled drug delivery, wound healing, and tissue engineering [30–33]. Various techniques have been employed for the preparation of chitosan nanoparticles, such as ionic gelation, micro-emulsion, reverse micelle, and coacervation. Among these, ionic gelation is considered a facile technique with mild conditions (non-solvent) [34]. The method utilizes electrostatic interactions between cationic chitosan and negatively charged molecules, like sodium triphosphate (TPP), to generate particle structures. Chitosan can simultaneously form a gel structure when in contact with TPP, as a result of the formation of inter- and intra-molecular ionic crosslinking between the amino and phosphate groups. Several studies have been performed, and several guidelines (sometimes conflicting) on tuning the particle average size and polydispersity have been revealed. The average particle size, for instance, has generally been shown to increase with the concentration of the parent chitosan solution and the chitosan molecular weight. Likewise, the chitosan/TPP particle size and the colloidal stability were demonstrated to be sensitive to TPP: chitosan ratio [35–37]. Due to their simple, convenient, and controllable fabrication procedures, chitosan/TPP particles are at the leading edge of chitosan-based complexes and have been intensively studied for biomedical utilization [38]. The inherent biological properties of the particles and the ability to incorporate hydrophilic and hydrophobic drugs into the particle-matrix have made chitosan/TPP particles an attractive drug-delivery system.

Plant-based spores are also considered as natural robust microcapsules for drug delivery applications [39,40]. Such spores provide a ready-made capsule scaffold with high structural uniformity, a large internal cavity, porous shell, and tough outer shell structures that can stay intact even in severe environments. The materials have high resistance to strong acids and bases and are difficult to dissolve in organic solvents. The demonstrated potential of natural spores for encapsulation applications motivates their further exploration, especially as delivery vehicles for various active compounds. Different natural spores have unique architectures that are formed by natural bio-templating processes. Their high degree of uniformity and robustness make these ideal biomaterials for encapsulation purposes, especially considering environmentally-friendly encapsulation, which can bypass the need for harsh chemical treatments. There are several reports on the use of *Lycopodium (L.) clavatum* spores as microcapsules for drugs and vaccine antigens to translocate the intestinal epithelium into the body [41,42]. While these materials can survive harsh acidic treatments, enzymes in the body can degrade them. These materials provide potentially safe natural carriers for oral drugs and vaccine deliveries. Cho et al. demonstrated the effective encapsulation of macromolecules into natural *L. clavatum*

spores by three different microencapsulation techniques, e.g., passive, compression, and vacuum loading methods (Figure 3) [43].

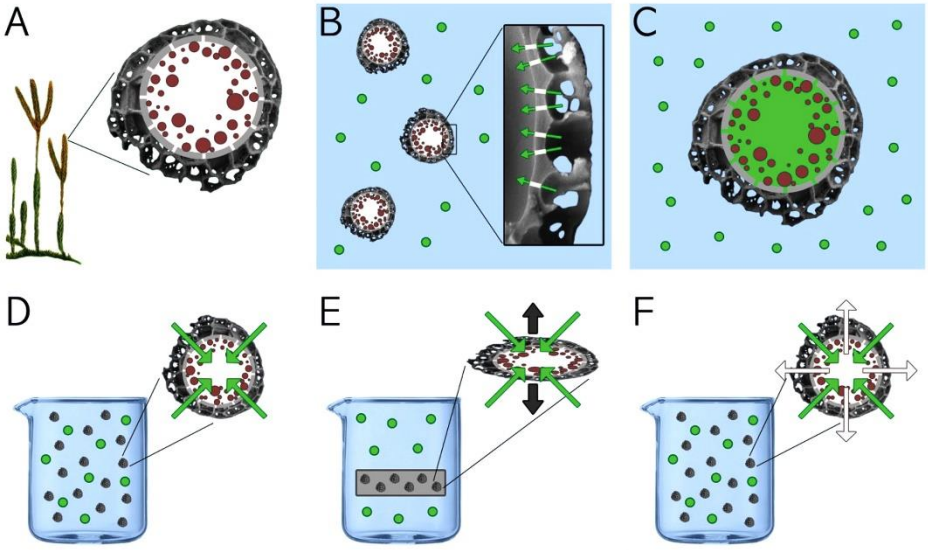

Figure 3 Structures and processes for encapsulating macromolecules by natural spores. (A) Spore microstructure depicting uniform ridges distributed on the surface with natural sporoplasm constituents contained inside. These spores originate from a vascular plant with spirally arranged leaves. (B) Natural spores suspended in a macromolecule-containing solution for the uptake of macromolecules. The enlarged inset depicts macromolecular entry *via* nanochannels located within the *L. clavatum* microstructure. (C) Spores encapsulating macromolecules (indicated as green) with the natural sporoplasm constituents. (D) Passive macromolecule loading technique involving the incubation of natural spores in the aqueous macromolecule solution at 4 °C under stirring at 500 rpm. (E) Compression of dried spore powder and incubating the resulting spore tablet in a macromolecule solution for the uptake of macromolecules by the spores. (F) A vacuum loading technique involving the application of a vacuum to a suspension containing natural spores and macromolecules. The macromolecules enter the spores through the nanochannels located within the surface microstructures of the natural spores. Reproduced with permission from ref. [43]. Copyright 2015 John Wiley and Sons.

In a passive loading process, *L. clavatum* spores were suspended in bovine serum albumin (BSA, a model hydrophilic macromolecule) solution while shaking at 500 rpm at 4 °C. For the compression loading process, a compressed tablet was prepared by using a hydraulic press at 5-ton pressure for 20 s, before soaking in a BSA solution. For the vacuum loading method, a suspension of BSA and *L. clavatum* spores was placed in a freeze-drier, where a 1 mbar vacuum was applied. Optimum encapsulation was achieved with the use of the vacuum loading process. The encapsulation of macromolecules was confirmed by confocal laser scanning microscopy, in which the localization of fluorescein isothiocyanate-conjugated BSA (FITC-BSA) was observed to be within the natural spore cavity. To obtain a tunable release profile, a biocompatible alginate coating was applied by homogeneously mixing BSA-loaded natural spores with alginate solutions. After coating, the spores were fused inside the alginate microbeads, indicating that alginate acts as a barrier to retard the macromolecular release from the spores. Dyab *et al.* also studied the encapsulation of erythromycin and bacitracin antibiotics into natural spores by using a passive diffusion process, followed by a vacuum loading technique [44]. The two antibiotics were successfully encapsulated, leading to a 16.2% loading capacity and a 32.4% entrapping efficiency.

To prevent allergy problems that are commonly associated with natural products, allergy-causing native biomolecules such as proteins are removed before the encapsulation of active ingredients in natural spores [41,45–47]. This involves the use of a mixture of glacial acetic acid and concentrated sulfuric acid, and a sequential systematic isolation method using acetone, potassium hydroxide, and phosphoric acid. By using such an extraction process, hollow uniform biodegradable microcapsules were obtained in a "green", sustainable, and easy fashion from natural renewable resources. Gill *et al.* developed a process for preparing *L. clavatum* spore microcapsules to be broadly applicable as a vaccination system. Natural *L. clavatum* spores were chemically treated by a conventional treatment method using acetone, potassium hydroxide, and phosphoric acid. This was followed by a series of washing steps to produce intact clean spores by a modified chemical cleaning process. The functional groups, e.g., hydroxyl, phenolic, and carboxylic acid groups were still observed. The resulting empty *L. clavatum* spores were then filled with foreign molecules up to 2000 kDa in size (Figure 4). Using ovalbumin (OVA) as a model antigen, *L. clavatum* (formulated with OVA) was orally fed to mice [48]. The results from confocal microscopy revealed that the *L. clavatum* microcapsules can translocate into mouse intestinal walls. The antibody response was not affected by pre-neutralization of the stomach acid and persisted for up to 7 months.

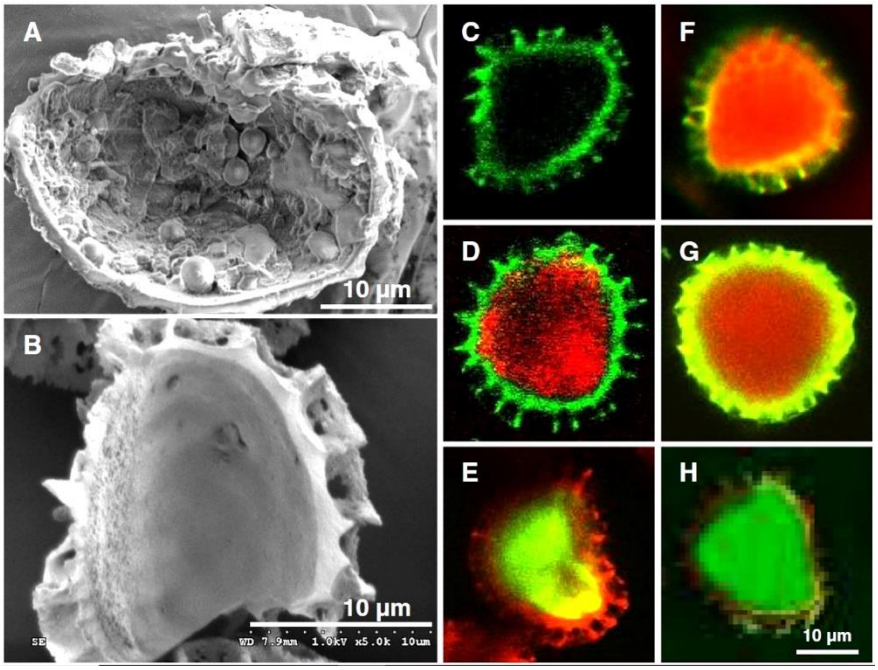

Figure 4 Interior structure of lycopodium spores at different stages of processing, and scanning electron micrographs of lycopodium spores manually cracked (A) before processing, showing cellular organelle and biomolecules in the core, and (B) after chemical processing, showing a clean core. Confocal micrographs of chemically processed lycopodium spores that are (C) empty, (D) filled with sulforhodamine (558 Da), (E) filled with dextran conjugated to fluorescein isothiocyanate (4000 Da), (F) filled with ovalbumin conjugated to Texas Red (45,000 Da), (G) filled with bovine serum albumin conjugated to Texas Red (67,000 Da), and (H) filled with dextran conjugated to fluorescein isothiocyanate (2,000,000 Da). Reproduced with permission from ref. [48]. Copyright 2014 Elsevier B.V.

Mackenzie *et al.* reported the use of renewable spore microcapsules for recovering oils from compressed seed extracts containing water. The materials were also used to scavenge contaminated oils from emulsions, in cases such as accidental spillage of toxic materials [49]. The possibility of encapsulating oil from oil-water emulsions is based on the unique fine-porosity characteristics of the spores, relative lipophilicity, and the presence of ionizable groups.

Extracted spore microcapsules possessing either a single-layered shell (exine) or double-layered shell (intine), were modified to increase their lipophilicity by acetylation and methylation of the available hydroxyl groups (alcohols, phenols, and carboxylic acids). Alternatively, a decrease in their lipophilicity was achieved by forming salts of the acidic functions (carboxylic acid and phenolic groups). The acetylated forms exhibited the most efficient oil-recovery efficiency in the emulsions.

Bio-based polymeric materials possess unique properties in biocompatibility, biodegradability, and biological functionality, which are suitable for various use. Vast varieties of these materials are available in the form of natural products or synthetic (co)polymers. In addition, further modifications are employed to the structures of the materials to broaden their applications. Thanks to the recent advances in their fabricating technology, additional stimuli-responsive characteristics can be achieved. As a result, various materials have been designed by equipping with smart, responsive multi-functionality for specific biomedical applications, especially as drug-controlled release materials.

3. Drug delivery applications

Stimuli-responsive polymeric materials are powerful tools in drug delivery, to use for a large variety of physiological conditions in normal microenvironments and diseased sites. Recent progress in the synthesis of smart polymeric carriers for drug delivery applications has been focused on pH-responsive, thermo-responsive, and photo-responsive polymers.50–54 For pH responsiveness, polymers consisting of ionizable functional groups are capable of donating or accepting protons after environmental pH changes. Some common examples are (co)polymers of acrylic acid (AA) and N,N-dimethyl aminoethyl methacrylate. Poly(N-isopropylacrylamide) (PNIPAM) is one of the most extensively studied thermo-responsive polymers that exhibits a lower critical solution temperature (LCST) at ~32 ºC, which is close to physiological temperature. When the solution temperature is increased above its LCST, PNIPAM chains undergo a transition from an extended (solvated) random coil to a compact (desolvated) globular structure [55,56].

Serpe *et al.* synthesized P(NIPAM-*co*-AA) microgels, (AAc-MG), and P(NIPAM-*co*-acrylamido phenylboronic acid) (APBA-MG). The materials were used to construct reservoir devices by loading with model drug, i.e., positively charged methylene blue (MB) (Figure 5) [57]. At pH > 8.4, both the APBA-MG and AAc-MG were negatively charged, MB exhibited strong electrostatic interactions with negatively charged AAc and APBA-modified microgels. When the solution pH was decreased (pH 7), the APBA groups were neutralized, allowing MB to be released from the APBA-MG. MB was then released from the AAc-MG when the pH of the solution was below the AAc pKa (4.25).

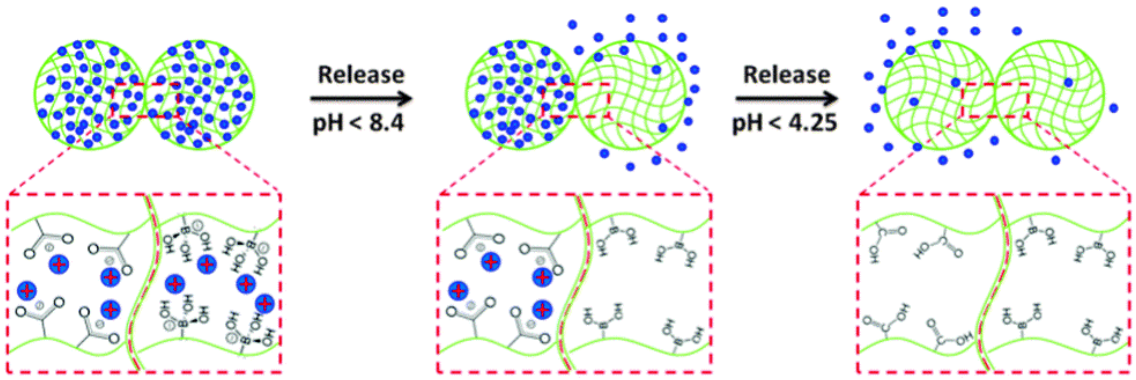

Figure 5 Schematic of the pH-triggered MB (blue dots) release from APBA-MG and AAc-MG. As each microgel is neutralized, the electrostatic interactions between the microgel and the MB are diminished, and the MB is released from the microgel. Reproduced with permission from ref. [57]. Copyright 2016 The Royal Society of Chemistry.

Stimuli-responsive clustered nanoparticles of platinum (Pt) pro-drug-conjugated poly(amidoamine-graft-polycaprolactone) (PCL-CDM-PAMAM/Pt) copolymer with PCL homopolymer and poly(ethylene glycol-*b*-*ε*-caprolactone), P(EG-*b*-PCL) copolymer, were prepared by a nanoprecipitation method (Figures 6A, 6B) [58]. The fabricated nanoparticles improved tumor cell penetration and therapeutic efficacy. At physiological pH, the clustered nanoparticles are about 100 nm with a raspberry-like structure containing 108 PAMAM and 719 platinum drugs (Figure 6C). To test their response to pH changes, the clustered nanoparticles were incubated in a phosphate buffer (PB) solution at pH 6.8 to mimic tumor acidity, over a predetermined period, whose morphological evolution was observed by TEM. After a 4-h incubation time, the raspberry-like morphology of the clustered nanoparticles was partially deformed, and small particles appeared in the solution (Figure 6C). After an additional incubation for 24 h, the raspberry-like structure was almost completely disintegrated and changed into a structure with a smooth surface that was analogous to the nanoparticles formed by PEG-PCL and PCL. This suggested that small PAMAM dendrimers were released upon cleavage of amide bonds at pH 6.8. Moreover, the nanoparticles were designed to release cisplatin, specifically in a redox environment. To observe the release of cisplatin, the nanoparticles were incubated in PB solutions (pH 7.4 and 6.8) and ascorbic acid solutions (5 mM, pH 7.4), to mimic an intracellular redox environment. The Pt drug release rate was examined via inductively coupled plasma mass spectrometry (ICP-MS). The nanoparticles showed minimal drug release in PB solutions regardless of the pH, whereas a rapid release was observed in the redox environment. This implies that blood plasma had minimal effects on the stability and pH responsiveness of the clustered nanoparticles.

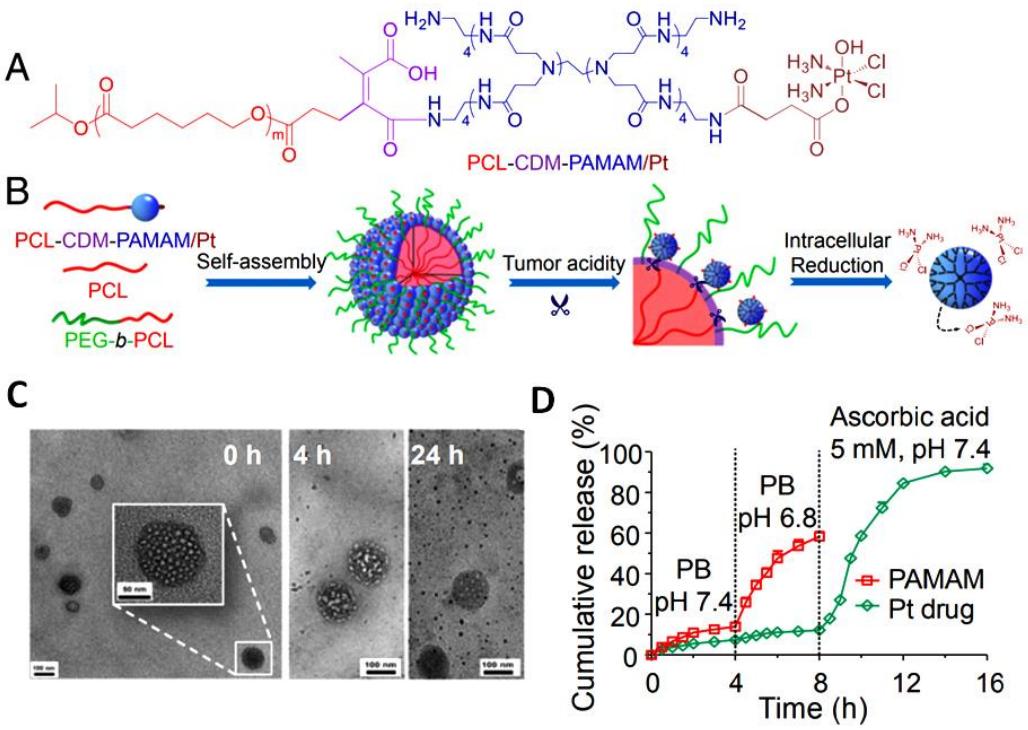

Figure 6 Preparation and physicochemical properties of clustered nanoparticles. (A) Chemical structure of PCL-CDM-PAMAM/Pt. (B) Self-assembly and structural changes of iCluster/Pt nanoparticles in response to tumor acidity and an intracellular redox environment. (C) TEM images of iCluster/Pt nanoparticles treated in PB at pH 6.8 for 0, 4, and 24 h (Scale bar: large images, 100 nm; inset image, 50 nm). (D) PAMAM (red line) and platinum drug (green line) released from iCluster under three different conditions, which include PB at pH 7.4 to mimic a neutral environment, PB at pH 6.8 to mimic a tumor extracellular environment, and ascorbic acid solution (5 mM, pH 7.4) to mimic an intracellular redox environment. PAMAM release was quantified by HPLC, whereas platinum release was determined by ICP-MS. Adapted with permission from ref. [58]. Copyright 2016 National Academy of Sciences.

4. Conclusions and prospects

Intelligent bio-based nanodevices and materials are of great interest to the research community and industry. Stimuli-responsive bio-based polymeric particles with outstanding properties of biodegradability, biocompatibility, and natural abundance are attractive materials in various fields, especially in biomedical applications. In this review, recent advances in the development of processes for the fabrication of such materials have been described in detail. The stimuli-responsive polymeric particles can be synthesized by a variety of techniques. They are widely employed in many applications as powerful tools for drug delivery. This has been emphatically discussed in this review. However, the number of research studies on processes for preparing stimuli-responsive materials from bio-based degradable polymeric particles for use in bio-nanotechnology (smart drug-delivery systems) has been limited and needs more systematic studies. The design and fabrication of bio-based polymeric particles as carriers for active compounds, which possess special structures and smart responsive properties, are of great interest. However, it is challenging to address these needs comprehensively. The incorporation of stimuli-responsive polymers into biological systems and nanoscale materials can further enable a variety of new functions and properties of the materials. In addition, a combination of bio-based polymers with other materials generates composite materials with attractive properties, such as biocompatibility, degradability, and nontoxicity.

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