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Encapsulating Wall Materials for Micro-/Nanocapsules

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Abstract

Wall materials play a vital role in the development of micro-/nanocapsules to protect the bioactive compounds against external factors. The encapsulation process and the type of polymers exert a direct impact on the development of bioactive micro-/nanocapsules, which greatly reflect in encapsulation efficiency, solubility, stability, surface permeability, and release profile of desired bioactive compounds. Among the polymers, biodegradable polymeric materials have been the focus for various applications in food, pharmaceutical, and cosmetic industries. Thus, this chapter focuses on different encapsulation techniques and the importance of biodegradable polymers employed as wall materials for developing stable and safe micro-/nanocapsules. Among the natural polymers, protein- and polysaccharide-based polymers are widely used. Similarly, the most commonly used synthetic polymers are polycaprolactone, poly(lactic-co-glycolic acid), and polyethylene glycol. Synthetic polymers have been classified based on their exogenous and endogenous responsive natures. At the end, we have also discussed on the applications of biodegradable polymers employed in the development of micro-/nanocapsules. To compile this chapter and to provide adequate information to the readers, we have explored various sources, such as reviews, research articles, books, and book chapters including Google sites.

Keywords: biodegradable polymers, microcapsules, nanocapsules, responsive polymers

1. Introduction

Encapsulation is a process in which tiny particles or droplets are surrounded by a coating to form capsules. Microcapsules and nanocapsules are small spheres with a uniform wall around it. The material inside the capsule is referred as the core, internal phase, or fill, whereas the wall is called as the shell, coating, or membrane. The core material may be liquid or solid, active constituents, stabilizers, diluents, excipients, and release-rate retardants or accelerators.

Encapsulation can be done for multiple reasons. The primary purpose of encapsulation is either for sustained or prolonged drug release. For orally delivered drugs, this method has been widely used for masking taste and odor to improve patient compliance, reduce toxicity, and gastrointestinal irritation. This method can be used to convert liquid drugs to a free flowing powder form, prevent vaporization of volatile drugs, alter the site of absorption, and to prevent incompatibility among the drugs. The drugs which are sensitive to oxygen, moisture, light, or pH changes can

be stabilized by encapsulation. Depending on the applications, the wall material of the capsules is designed to serve the desired specific purpose.

Thus, the wall material is the most vital component in any capsule. The selection of appropriate wall material decides the physical and chemical properties of the resultant micro-/nanocapsules. The wall material should have the properties like being inert toward core active ingredients, stabilize the core material, film-forming, pliable and tasteless, non-hygroscopic, moderate viscosity, economical and soluble in an aqueous media or solvent, or melting, the coating may be flexible, brittle, hard, and thin, controlled release at the specific site under specific conditions.

Understanding the importance of polymers as wall materials, we have attempted to give a review of wall materials used in micro- and nanocapsules for the sustained/controlled delivery of drugs. A detailed account on encapsulation techniques is given. The biodegradable materials employed as wall materials are discussed adequately. The advantages of biodegradable materials including their limitations are covered in the chapter. The release profiles were discussed based on both exogenous and endogenous responsiveness of the wall materials. At the end of the chapter, future prospects and challenges of the wall materials are highlighted.

2. Encapsulation techniques

Microencapsulation of active compounds can be achieved by physical and chemical methods. Though these techniques are neither purely physical nor purely chemical, they are classified as physical and chemical methods based on the pre-dominant or primary principle involved. In **Table 1**, we have listed commonly used physical and chemical methods used for encapsulation.

Physical methods	Chemical methods
Air suspension coating	Solvent evaporation
Coacervation	Polymerization
Centrifugal extrusion	
Pan coating	
Spray drying	
Fluidized bed technology	

Table 1.
Encapsulation techniques.

3. Polymers as wall materials

3.1 Natural polymers

Natural polymers are broadly classified into protein-based polymers and polysaccharide-based polymers. Albumin and gelatin are the examples of protein-based polymers. Polysaccharide-based polymers are agarose, alginate, hyaluronic acid, dextran, chitosan, etc. These natural polymers are highly biodegradable and biocompatible in nature.

3.1.1 Protein-based polymers

3.1.1.1 Albumin

Albumin is a biodegradable and water soluble protein and thus plays an important role in the circulating system. It is involved in osmotic pressure regulation, binding, and transport of nutrients to the cells that can be obtained from a variety of sources including egg white, bovine serum, and human serum. It is stable in the pH range of 4–9 and can be heated at 60°C up to 10 h without any deleterious effects [1]. It undergoes degradation by protease enzymes, which helps the microcapsules to release the drugs in the small intestine. It also facilitates the release of therapeutic cargo from nanocapsules inside the endosomes.

3.1.1.2 Gelatin

Gelatin is biodegradable, inexpensive, easily sterilized, non-pyrogenic, non-toxic, non-immunogenic, and easy to be crosslinked or modified chemically. Gelatin has many ionizable groups, such as carboxyl, amino, phenol, guanidine, and imidazole, which are potential sites for conjugation or chemical modifications. Chemical crosslinking agents like glutaraldehyde improves the integrity and performance of the gelatin and provides gelatin with greater stability, shape, and increased circulation time *in vivo* [2]. The degree of crosslinking determines the release of drugs from the gelatin capsules. Thus, gelatin is regarded as a safe excipient approved by the US FDA for pharmaceutical applications.

3.1.2 Polysaccharide-based polymers

3.1.2.1 Chitosan

Chitosan, the second most abundant polysaccharide in nature, is a promising biopolymer widely used in biomedical and pharmaceutical fields like wound dressing, tissue engineering and drug delivery. It is produced from chitin which is the structural element found in the exoskeleton of crustaceans like shrimps, lobsters, and crabs. Chitosan has been reported to exhibit many therapeutic properties, such as activation of immune response, cholesterol lowering activity, anti-hypertensive activity, inhibition of growth of microorganism, pain alleviation, and promotion of hemostasis and epidermal cell growth [3]. This is all due to the favorable pharmaceutical properties of chitosan, such as biocompatibility, low production cost, ability to bind some organic compounds, susceptibility to enzymatic hydrolysis, and nontoxicity.

Chitosan is considered as the most important polysaccharide-based polymer owing to its cationic character based on its primary amino groups, which are responsible for its versatile properties, such as mucoadhesion (improves pulmonary drug delivery), controlled drug release, transfection, *in situ* gelation, and efflux pump inhibitory properties and permeation enhancement [4]. The major drawback is its poor solubility at physiological pH due to partial protonation of the amino groups in the presence of proteolytic enzymes and thereby causing presystemic metabolism of drugs in intestinal and gastric fluids. To overcome these inherent drawbacks, various derivatives of chitosan, such as carboxylated, different conjugates, thiolated and acylated chitosan have been used in drug-delivery systems [3].

Chitosan is produced by the deacetylation of chitin. The degree of deacetylation is related to chitosan's crystallinity and degradation rates. Chitosan's solubility can

also be improved when the primary amino group is protonated at low pH. The viscosity of chitosan solution increases with increasing the concentration of chitosan [5]. These properties and the ease with which it can be modified makes chitosan a versatile and bioactive polymer for its use in encapsulation.

3.1.2.2 Hyaluronic acid

Hyaluronic acid (HA) is a nonsulfated glycosaminoglycan, comprising a relatively simple linear structure of alternating units of D-glucuronic acid and N-acetyl-D-glucosamine, linked via β -1,3- and β -1,4-glycosidic bonds. Hyaluronic acid is biodegradable, biocompatible, nontoxic, and non-immunogenic glycosaminoglycan distributed widely in connective, epithelial, and neural tissues.

The cluster of differentiation (CD) protein CD44 is the main HA binding receptor. CD44 is involved in the interaction between HA and the surface of specific cells, in cell proliferation, in cellular adhesion processes (aggregation and migration), angiogenesis, in cell survival and endocytosis of HA. CD44 receptor is also overexpressed in many types of tumors and this overexpression is related to tumor invasion and tumor metastasis, which makes HA a promising candidate for intracellular delivery of imaging and anticancer agents exploiting a receptor-mediated active targeting strategy. HA also interacts with hyaluronan receptor for endocytosis (HARE), lymphatic vessel endothelium receptor-1 (LYVE-1), and intracellular adhesion molecule-1 (ICAM-1), serum-derived hyaluronan-associated protein (SHAP), Brevican and Neurocan (brain and nervous tissue-specific HA and proteoglycan binding proteins), hyaluronan-binding protein 1 (HABP1) and toll-like receptors (TLRs), and all of which have specific functions. This is known as receptor-ligand interaction, which can be exploited to achieve receptor-mediated active targeting strategy [6, 7]. HA has been bioconjugated with anticancer drugs, like paclitaxel, doxorubicin, cisplatin, etc. and anti-inflammatory drugs like methotrexate, dexamethasone, methylprednisolone, etc. to achieve receptor-mediated endocytosis [8]. HA polymer has also been used in the treatment of osteoarthritis, in ocular and plastic surgery, and in tissue engineering.

3.2 Synthetic polymers

Over the past 5–6 decades, biodegradable polymers have gained tremendous attention due to their growing applications in biomaterials, drug-delivery systems, tissue engineering, and medical devices. Chemists, biologists, physicians, and engineers have collaboratively made significant advancements in these applications. The most commonly used synthetic polymers in micro-/nanocapsules for drug-delivery applications are poly(ϵ -caprolactone), poly(lactic-co-glycolic acid), and polyethylene glycol.

3.2.1 Poly(ϵ -caprolactone)

Poly(ϵ -caprolactone) (PCL) is a semicrystalline aliphatic polyester with glass transition temperature and melting temperature of about -60 and 60°C , respectively [9]. PCL mixes well with other polymers to form blends that impart good physical and chemical properties to achieve desired properties like swelling, porosity, and stability in different media. Microencapsulation or nanocapsulation with PCL has many advantages like modulation of drug release, control of drug penetration/permeation into the skin, and improve photochemical stability and pharmacological response. Due to its long degradation times, PCL has found many applications in tissue engineering and prolonged drug release. PCL is approved by the US Food and

Drug Administration (FDA) and has found numerous applications in implants and surgical absorbable sutures due to its biocompatibility and slow biodegradability.

3.2.2 Poly(lactic-co-glycolic acid)

Poly(lactic-co-glycolic acid) (PLGA) is the most extensively studied degradable polymer to date. PLGA is an aliphatic polyester and it undergoes hydrolysis in the body to produce biodegradable metabolite monomers such as lactic acid and glycolic acid. During metabolism in the body via the Krebs cycle, carbon dioxide, and water are removed and thereby toxicity is minimized [10]. PLGA is approved by the US FDA for use in drug-delivery systems due to its biodegradability with tissue and cells, drug biocompatibility, suitable biodegradation kinetics, mechanical properties, and ease of processing. Thus, PLGA based microcapsules and nanocapsules are the most viable candidates for drug-delivery systems, anticancer agents, bio-imaging, and vaccine immunotherapy.

3.2.3 Poly(ethylene glycol)

Polyethylene glycol (PEG) is also the most widely used “stealth” polymer in drug delivery. It is approved by the US FDA and considered to be safe. Coating of nanocapsules with PEG generates a hydration layer due to its hydrophilic nature and forms a steric barrier. This steric hindrance effect helps the nanocapsules to avoid interactions with neighboring capsules and blood components like immunogenic cells [11]. PEG coating on nanocapsules shields it from aggregation, opsonization, and phagocytosis by reticuloendothelial system. The lack of immunogenicity confers PEG-coated nanocapsules with prolonged systemic circulation time which in turn leads to enhance absorption due to enhanced permeation and retention effect. PEGylation has become a mainstay in fabrication of drug-delivery systems that require high doses of toxic drugs with prolonged duration of action.

4. Sensitive polymers

The design of polymeric drug-delivery systems has matured to exploit local biochemical changes in pathological states to trigger drug release. In a classical example, organs or tissues with cancer are characterized by a shift in homeostasis which include, but are not limited to, surge in specific enzymatic activity, shift toward acidic pH, reductive or oxidative states, or a buildup of reactive oxygen species. These homeostatic disturbances can be exploited for the development of targeted therapies that can be activated under certain conditions to trigger drug release. Being aware of these intracellular and extracellular changes allows us to design smart polymer microcapsules and nanocapsules. In addition to these homeostatic disturbances, external physical parameters, such as temperature, ultraviolet light, ultrasound, or magnetic energy, can also be used to trigger drug release from polymer capsules. Thus, in this chapter, we have attempted to summarize the effects of adding biologically responsive moieties to the polymer structure in order to achieve more targeted controlled therapeutic outcomes. They are exogenous and endogenous factors.

4.1 Exogenous factors

Exogenous stimuli result in manipulation of capsule structure from outside the body, such as heat, light, or ultrasound induction.

4.1.1 Temperature sensitive

Temperature sensitive polymeric capsules have been designed to release the drug payloads at the target site due to an induced change in temperature acting as a trigger. The polymers are selected or designed so as to change their physical and chemical properties in response to temperature change. Most tumors and inflammatory conditions tend to exhibit a localized rise in temperature as a result of increased blood flow due to vasodilation or angiogenesis, leukocytic infiltration, increased metabolic activity, and increased cell proliferation and high cell turnover in pathological tissues. Besides this inherent temperature differential between healthy and diseased tissue, external sources can be employed to induce a localized temperature change.

Polymers have been discovered that undergo conformational changes upon temperature variation. These conformational changes could result from a change in hydration states. A majority of temperature sensitive polymers are hydrophilic below a certain temperature and are hydrophobic above a specific temperature. The temperature at which this phase transition occurs is called the lower critical solution temperature (LCST) [12]. The temperature range at which the capsule releases the cargo can be tuned by modulating the balance between hydrophilic and hydrophobic groups in the polymer. It is desirable for a temperature-sensitive capsule to release its cargo at a temperature range of 37–42°C. It is considered to be the optimum working range to attain maximum physiological benefit without any toxic affects due to protein denaturation above 42°C.

Poly(N-isopropylacrylamide) (PNIPAAm) is the most extensively investigated temperature sensitive polymer. It exhibits a LCST of approximately 33°C in aqueous solution, below which PNIPAAm is water soluble and above which it becomes water insoluble. The LCST of PNIPAAm-based polymers can be tuned by copolymerization with hydrophilic or hydrophobic moieties. Incorporation of hydrophilic moieties increases the LCST of the resultant PNIPAAm copolymer and incorporating a hydrophobic moiety would decrease the LCST [13]. However, questions still linger over the biocompatibility of PNIPAAm, which make it an unsavory choice based on the known neurotoxicity of acrylamide monomer and the hydrolysis of PNIPAAm under acidic condition, which yield highly toxic amine molecules [14].

Poly(N-vinylcaprolactam) (PNVCL) is a temperature sensitive polymer that provides a favorable alternative. In contrast to PNIPAAm, PNVCL is biocompatible with extremely low cytotoxicity and does not release toxic small organic amine compounds upon hydrolysis. PNVCL was well tolerated with the Caco-2 and Calu-3 cell lines up to 10 mg mL⁻¹. Further *in vivo* studies are needed to study organ toxicity and elimination to give an in-depth evaluation on its potential. PNVCL-containing materials have been scrutinized for cell immobilization, tissue engineering, anticancer drug delivery, protein separation, etc.

Aliphatic polyesters are attractive thermoresponsive biocompatible and degradable materials for the development of nanocapsules. ϵ -Caprolactones are biocompatible temperature-sensitive aliphatic polyesters that exhibit a slow biodegradability profile. Cheng et al. [15] synthesized a thermoresponsive poly { γ -2-[2-(2-methoxyethoxy)-ethoxy]ethoxy- ϵ -caprolactone}-b-poly(γ -octyloxy- ϵ -caprolactone) (PMEEECL-b-POCTCL) diblock copolymer with a LCST of 38°C. It combined the biocompatibility and biodegradability properties of polycaprolactone with the thermo-responsive properties of oligoethylene glycol-substituted polymers. The thermally sensitive diblock copolymer PMEEECL-b-POCTCL was able to sense the elevated local temperature due to faster metabolism or induced hyperthermia and then release Nile Red and Doxorubicin in a controlled manner (**Figures 1 and 2**). The PMEEECL-b-POCTCL block copolymer also

showed relatively low cytotoxicity. Rainbolt et al. [16] synthesized amphiphilic diblock copolymers comprising poly[γ -(2-methoxyethoxy)- ϵ -caprolactone] and thermosensitive poly{ γ -2-[2-(2-methoxyethoxy)ethoxy]ethoxy- ϵ -caprolactone} (PMECL) as the hydrophobic and hydrophilic blocks, respectively. By controlling the ratio between the monomers MEEECL and MECL, and by varying the number of pendant ethylene oxide units, they were able to achieve highly tunable LCSTs in the range of 31–43°C. PMEEECL-*b*-PMECL copolymers possessed fully biodegradable backbones. The fundamental lack of chemical functionality in the parent aliphatic polyesters makes it difficult to modify the polymer backbone.

Aliphatic polycarbonates have been employed to produce thermoresponsive biocompatible and degradable materials. Kim et al. [17] synthesized thermoresponsive block copolymers by the ring opening polymerization of cyclic carbonate monomers

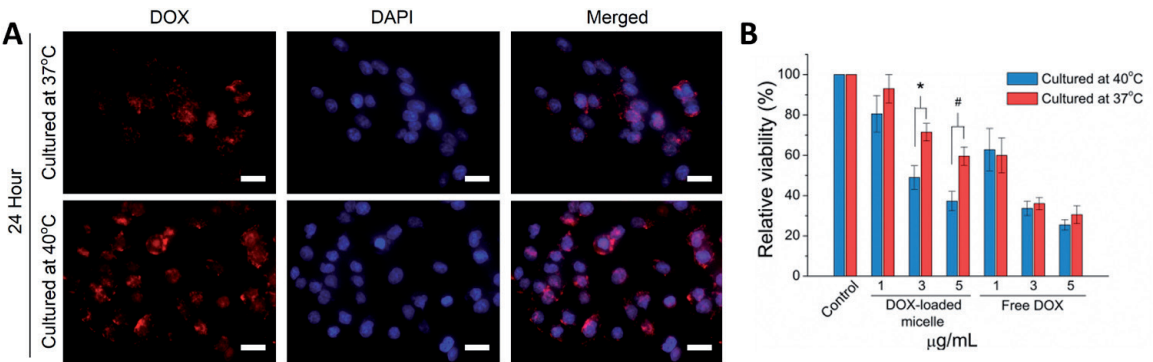


Figure 1. (A) CLSM images of MCF-7 cells treated with DOX-loaded PMEEECL-*b*-POCTCL micelles at either 37 (below LCST) or 40°C (above LCST) for 24 h. For each panel, images from left to right show cells with DOX (red fluorescence), DAPI (blue fluorescence), and overlays of both images. The scale bar indicates 20 μm. (B) The viability of MCF-7 cells incubated with various concentrations of DOX-loaded PMEEECL-*b*-POCTCL micelles and free DOX at either 37 or 40°C after 24 h of incubation ($n = 6$). * and # indicate a significant difference between the two participating groups ($p < 0.05$). Reprinted with permission from Ref. [8]. Copyright 2012 American Chemical Society.

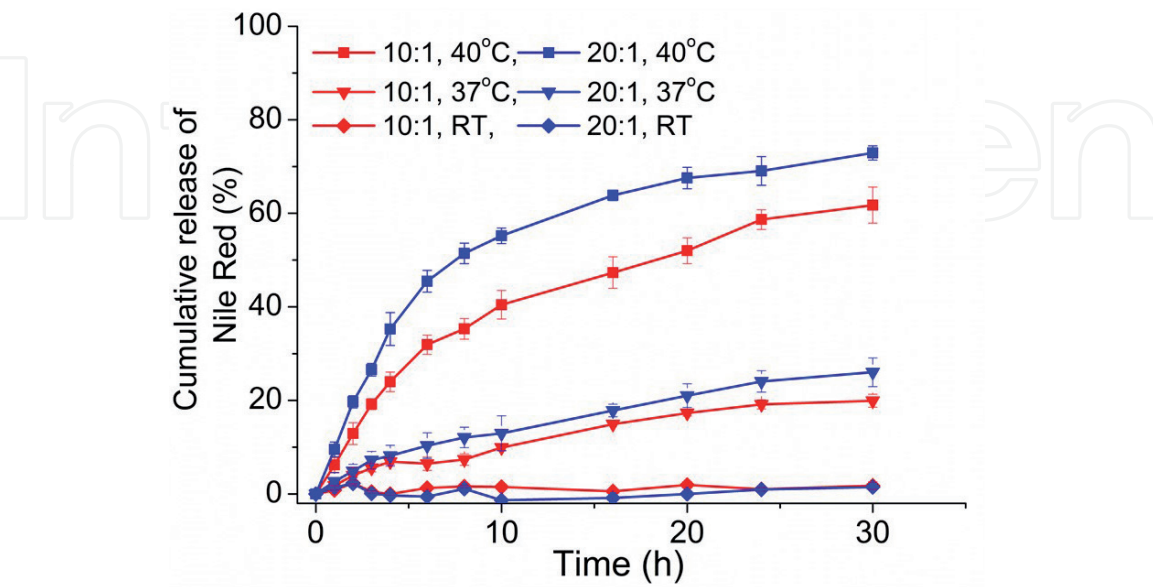


Figure 2. Cumulative Nile Red release from PMEEECL-*b*-POCTCL micelle at room temperature, 37 (below LCST) and 40°C (above LCST) in PBS. Reprinted with permission from Ref. [8]. Copyright 2012 American Chemical Society.

functionalized with hydrophilic and hydrophobic groups. The methyltrimethylcarbonate (MTC) family of cyclic carbonates derived from 2,2-bis(methylol)propionic acid (bis-MPA) was exploited as a synthetic building block for functional biodegradable monomers. These polycarbonates derived from cyclic carbonates can be prepared with a range of pendant functional groups that requires only a single functionalization reaction and a simple purification step. Polycarbonates are stable *in vitro*, while they degrade enzymatically *in vivo*. The LCST of these copolymers varied in the range of 36–60°C, depending on the molecular weight of hydrophilic poly(ethylene glycol) (PEG) chains, compositions of copolymers and molar ratios of hydrophilic to hydrophobic monomers. TRC350-10,30,60, (thermosensitive polycarbonate block copolymer where 10, 30, and 60 refers to degrees of polymerization of MTC-C₂, MTC-PEG and MTC-C₁₂, respectively) which possessed a LCST of 36°C, was identified as a useful model polymer with higher Paclitaxel release at the body temperature (37°C) as compared to a temperature below the LCST. Ajiro et al. [18] developed a thermosensitive biodegradable homopolymer with a poly(trimethylene carbonate) (PTMC) backbone and oligoethylene glycol (OEG). The LCST ranged from 31 to 35°C and was influenced by the molecular weight and polymer concentration.

Some of the other commonly studied thermoresponsive polymers that are focused on LCST-typed polymers are typically based on poly(N,N-diethylacrylamide), poly(methyl vinyl ether) (PMVE), poly(2-ethyl-2-oxazoline) (PEtOx), poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO), etc.

4.1.2 Ultrasound sensitive

Ultrasound (U/S) is defined as high-frequency pressure waves produced by mechanical oscillations in response to an alternating current applied across piezoelectric materials. Ultrasound devices operate with frequencies from 20 kHz up to several gigahertz. Ultrasonic devices are used to detect objects and invisible flaws and measure distances. Ultrasound is non-invasive and can penetrate deep into tissue of the body. Low-frequency U/S does not damage or heat the tissues, though it is difficult to focus because it produces a larger area of focus. High-frequency U/S can be focused on smaller areas. A high-intensity focused ultrasound (HIFU) beam can target tumors and can harmlessly penetrate the skin and other tissues. Thus, HIFU can be used to treat a variety of tumors.

Ultrasound causes thermal and non-thermal effects on interaction with organic tissue. The hyperthermia is due to the absorption of acoustic energy by fluids and tissues. Thus, U/S can heat the drug carriers, the drugs, and the treated tissues. Hyperthermia induced by the application of U/S is used as an adjuvant in cancer chemotherapy and in physical therapy.

The non-thermal effects of U/S are related to cavitating bubbles. Acoustic cavitation is the interaction of acoustic waves and gas bubbles. Ultrasound reacts with air bubbles and makes them oscillate in response to the negative and positive pressure cycles. The air bubbles oscillate and undergo compression and rarefaction at low acoustic amplitudes, and the frequency of their oscillation resonates with the frequency of the applied U/S. An increase in acoustic pressure results in nonlinear and violent oscillations that ultimately collapse the bubbles (inertial or transient cavitation). The collapse of bubbles and resultant high shear force was demonstrated to enhance drug uptake by cells (*in vivo* and *in vitro*), by temporarily increasing the membrane permeability, and can also dismantle nanocapsules, triggering the release of therapeutic payloads [19].

Husseini et al. [20] extensively studied Pluronic P105 micelles and their release kinetics in relation to U/S exposure. They studied properties like drug release kinetics, pluronic, and drug concentration, the duration of exposure, frequency,

intensity, and power density of U/S used. Drug release (doxorubicin and ruboxyl) was most efficient at 20 kHz ultrasound and the data suggests an important role of transient cavitation in drug release. Zhang et al. [21] developed amphiphilic block copolymer PLA-b-PEG encapsulating hydrophobic Nile Red dye. High intensity focused ultrasound (HIFU), as a non-contact and remote control approach, can trigger the release of the encapsulated cargo. The release behavior of Nile Red can be tuned by adjusting the HIFU time, intensity, and location or reactor. An irreversible release due to the degradation of PLA-b-PEG chain resulting from the transient cavitation in the HIFU focal spot was proposed.

2-Tetrahydropyranyl methacrylate (THPMA) is a mechanolabile functional group that can hydrolyze in response to U/S exposure. A novel approach was demonstrated by Xuan et al. [22] to amplify the effect of HIFU on the disassembly of block copolymers (BCP). By introducing a small amount of ultrasound-labile functional group into the thermosensitive block copolymer, the ultrasound-induced reaction of THMPA increased the LCST due to a polarity enhancement. Thus, the BCP becomes soluble in water and results in the disassembly without any changes in the solution temperature. The validity of this new mechanism was shown by synthesizing and investigating a diblock copolymer of PEO₁₁₂-b-P(MEO₂MA₁₈₉-co-THPMA₂₁). A ¹³C NMR spectral analysis provided critical evidence to show that the hydrolysis of THPMA groups occurs under HIFU irradiation and that the BCP disassembly originates from an increase in the LCST due to the ultrasound-induced conversion of hydrophobic comonomer units of THPMA onto hydrophilic methacrylic acid (MAA). This general approach of modulating the LCST by ultrasound can be applied by further exploring other ultrasound-labile moieties in the block copolymer design.

The ester bonds and disulfide bonds have been known to have U/S responsiveness. The disulfide bond has a relatively low dissociation energy ($E_{S-S} \sim 268 \text{ kJ mol}^{-1}$) and longer bond length ($l_{S-S} \sim 2.03 \text{ \AA}$) compared with those of the C-C bond ($E_{C-C} \sim 347 \text{ kJ mol}^{-1}$; $l_{C-C} \sim 1.54 \text{ \AA}$) [23]. Li et al. [24] synthesized biodegradable block copolymer (PEG-S-S-PLA) containing the central labile disulfide linkage between polyethylene glycol (PEG) and poly-L-lactic acid (PLA) segments. When the BCP are subjected to HIFU, the labile disulfide bonds are cleaved, and the amphiphilic structures are broken, which further leads to the disruption of BCP and the release of the encapsulated cargo. HIFU disrupts PEG-S-S-PLA structure because of the HIFU-induced site specific degradation of PEG-S-S-PLA.

Tong et al. [25] synthesized pluronic type copolymer PEG-COO-SS-PPG containing disulfide and mechanolabile ester bonds at the junction points of PEG and PPG blocks. They demonstrated that HIFU caused polymer degradation of the BCP and was substantiated by decrease in molecular weight. The molecular weight of PEG-COO-SS-PPG decreases with increase in HIFU exposure time. They also concluded that the cavitation was the primary reason for the cleavage of ester bonds and polymer degradation, and not the U/S-induced thermal effect. The disulfide bonds in the copolymer PEG-COO-SS-PPG possessed redox responsive property. Thus, the copolymer featured ultrasound and redox dual responsiveness exhibited relatively slow redox-induced release behavior and fast HIFU-induced release behavior. Ultrasound triggered mechanochemical cleavage occurred preferentially at the central ester bond rather than at the disulfide bond.

Wang et al. [26] developed a diblock copolymer composed of poly(ethylene oxide) and poly(2-tetrahydropyranyl methacrylate) (PEO-b-PTHPMA) that could be hydrolyzed by high-frequency ultrasound (1.1 MHz). HIFU beam could induce the hydrolysis reaction of THPMA at room temperature resulting in the cleavage of THP groups leading to the formation of carboxylic acid dimers and hydroxyl groups. As shown in **Figure 3**, it was found that upon exposure to a high-intensity focused ultrasound (HIFU) beam at room temperature, the pH value decreased

over irradiation time. It was also found that with increase in ultrasound power output, the pH decrease was more significant, thus demonstrating ultrasound triggered polymer degradation.

Ultrasound triggered drug release has many advantages. It provides the ability to control the time of drug release from the carrier. This is especially desirable when it is required to release the majority of the drug instantly and simultaneously to achieve a rapid high and lethal concentration. It would also be prudent to keep in mind that whenever ultrasound is utilized, its parameters, such as the power density, acoustic frequency, continuous or pulsed U/S, and pulse duration, have to be optimized to reach the desired therapeutic effect while minimizing the damage to the adjacent health tissues [19].

4.1.3 Light sensitive

Capsules capable of undergoing physical or chemical changes in response to light irradiation offer spatiotemporal control over the release of encapsulated therapeutic payloads. Chemical and physical processes that can be initiated by light irradiation at a specific wavelength can be either reversible or irreversible. These processes can involve formation or cleavage of bonds, interconversion of isomers, electrostatic charge switching, and rearrangement of chemical reactions. Light-triggered polymeric capsules can be developed by the incorporation of functional groups that interact with light which are triggered to disintegrate and release the encapsulated payload via light irradiation.

The suitability of these capsules for any biomedical application is dependent on the radiation wavelength required. The radiation required should be benign to live tissues, exhibit minimal absorption, and interaction with the biological components and offer substantial tissue penetration for *in vivo* applications. X-Rays and γ -rays have short wavelengths and possess high energy that would damage normal tissues, making them unsuitable for this purpose. UV radiation with its broader wavelength and less energy is more suited for developing light-sensitive capsules. Azobenzene and spiropyran have been known to undergo UV light-triggered photoisomerization. Incorporation of these functional groups into the polymer chain (in the backbone or as pendant groups) has helped to develop UV light-triggered capsules.

Under UV light radiation, Azobenzene undergoes photoisomerization from apolar *trans* to polar *cis* isomeric form. This isomeric transition can be reversed by

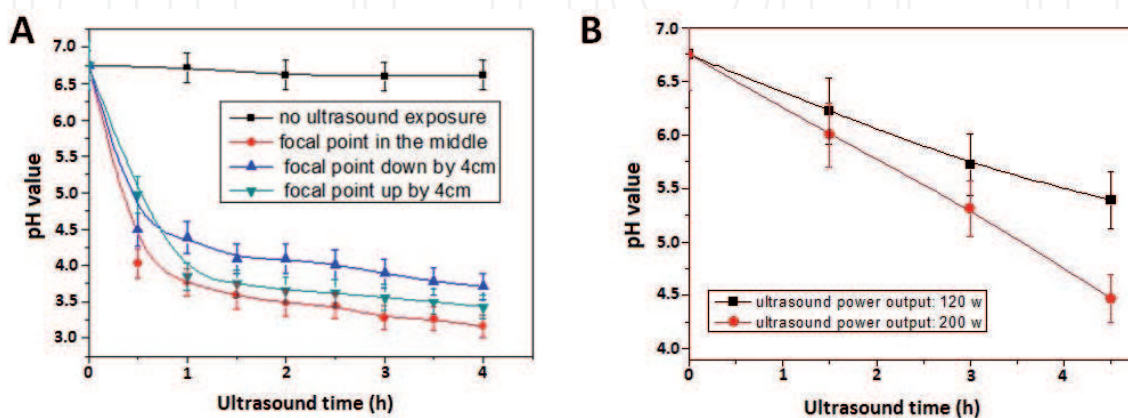


Figure 3.

(A) Change in pH as a function of ultrasound irradiation time. By repositioning the tube reactor, the location of the focal point of the ultrasound beams can be varied (ultrasound power, 200 W). (B) Change in pH as a function of ultrasound irradiation time for PEO-b-PHPMA, using two different ultrasound power outputs. Reprinted with permission from Ref. [27]. Copyright 2009 American Chemical Society.

storage in the dark or by irradiation with visible light. The change in hydrophilicity and the transition from *trans* to *cis* conformation can cause disintegration of the nanocapsules derived from polymers bearing azobenzene groups, leading to payload release.

Xiao et al. [28] developed photo-switchable microcapsules based on host-guest interactions between α -cyclodextrin (α -CD) and azobenzene. Confocal laser scanning microscopy was used to observe the photo-dissociation of capsules irradiated by UV light, as seen in **Figure 3**. These microcapsules exhibited controlled release behavior. Blasco et al. [29] developed linear-dendritic block copolymers which formed polymeric vesicles that are triggered by low intensity UV light, therefore limiting the possible toxic effects to organic tissue when exposed to UV radiation. The cyano group at the para-position of the azobenzene moiety was substituted by an alkyloxy group. This modification was instituted to increase the polarity between *trans* and *cis* isomers. They demonstrated that structural modification with 4-isobutyloxyazobenzene incorporation facilitated the disruption of azobenzene aggregates of the membrane on exposing the vesicles to low intensity UV light when compared to its 4-cyanoazobenzene and azobenzene counterparts. Blasco et al. [30] continued this work to study the photo-responsiveness of these polymer vesicles with different percent of 4-isobutyloxyazobenzene (IBO) and hydrocarbon chains (C18) randomly distributed at the periphery of the dendron. Results indicated that by diluting the azobenzene content at the periphery of the dendron, the *trans*-to-*cis* photoisomerization rate can be substantially accelerated and the light-induced release activity can be tuned. Vesicles with a 50/50 IBO/C18 ratio suffered the most significant changes upon UV irradiation. Yi and co-workers [31] developed a new class of UV responsive polyelectrolyte microcapsules. Upon exposure to UV light, the azobenzene moieties in the multilayers self-organized in the form of J aggregates due to the influence of polycation [poly(diallyldimethyl ammonium) chloride, (PDADMAC)]. The SEM images presented in **Figure 4** revealed that the re-orientation of azobenzene within

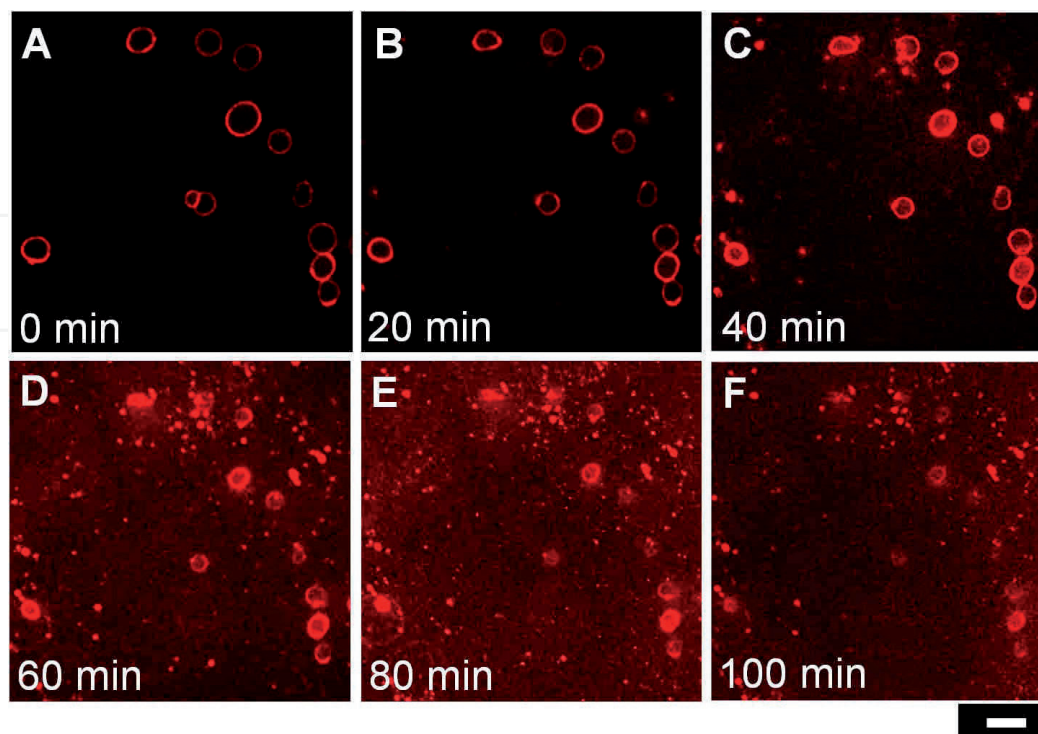


Figure 4. Snapshots of the photodissociation of microcapsules (A)–(F). The time interval between the snapshots is 20 min. Scale bar 15 μm . Reprinted with permission from Ref. [19]. Copyright 2011 American Chemical Society.

shell formations led to great damage of capsule integrity, illustrating the progress of capsules swelling and their disruption further. After 2 h of UV irradiation, the capsule debris was split into needle-like formations. This UV-induced microcapsule disruption process was proven to be irreversible.

Among the class of synthetic photoresponsive molecules, spiropyran (SP) has been known to possess unique tunability, stability, and fast response time. Spiropyran can undergo a reversible transformation from colorless to pink-colored merocyanine (MC) upon UV irradiation with a marked increase in the polarity associated with the structural conversion from neutral to charge-separated zwitterions [32]. This solubility switching of spiropyran from hydrophobic to hydrophilic can induce the destabilization of polymeric nanocapsules. Moreover, this destabilization induces controlled release of model hydrophobic therapeutics by UV irradiation. The transition can be reversed by irradiation with visible light. Achilleos and coworkers [33] developed water-dispersible nanocapsules based on the formation of H-type π - π interactions between the merocyanine (MC) isomers within the sterically crowded environment of the polymer brushes upon UV irradiation, which enables the SP-to-MC isomerization of the photosensitive species. Disruption of the nanocapsules can be achieved remotely by applying a harmless trigger such as visible-light irradiation.

Besides azobenzene and spiropyran, drug carriers based on cinnamic acid, cinnamic ester, and coumarin are also capable of responding to UV irradiation. Additionally, 2-diazo-1,2-naphthoquinone (DNQ), o-nitrobenzyl ester, coumarinyl ester, and pyrenylmethyl ester groups, which undergo cleavage, have also been explored for the development of UV-radiation-responsive drug carriers [34].

4.2 Endogenous factors

Endogenous stimuli are generated as a result of inherent chemical biological pathology in diseased states, such as pH, reactive oxygen species, and elevated enzyme levels.

4.2.1 pH sensitive

pH variations between different tissue compartments have been exploited as a shining platform for the development of pH-sensitive drug-delivery systems. Normal extracellular tissue and systemic blood have a physiological pH of 7.4. However, tumor tissues having an abnormally high cell proliferation rate and the lack of nutrients leads to a high rate of glycolysis and accumulation of lactic acid, which lower the environmental pH by 0.5–1.0 unit as compared to healthy tissues. The intracellular organelles, like endosomes and lysosomes, have a more acidic pH of 4.0–6.5 [35]. This pH gradient can be exploited as an endogenous stimulus for the development of nanocapsules to selectively deliver and activate drug molecules while reducing their systemic side-effects. pH-responsive nanocapsules can be programmed by functionalizing the polymer backbone with hydrazones, amines, acetals, ketals, boronic acid, oximes, etc.

Literature indicated that hydrazone is the most extensively explored pH-responsive chemical bond due to its sharp responsiveness to pH changes. Ganivada et al. [36] synthesized a newly designed biodegradable copolymer (PVLPEG-PVLDOXI-PCL-PHOS- Fe_3O_4) that can be used as a nanocapsule. The magnetic nature of Fe_3O_4 is expected to behave as a smart nanocarrier for both magnetic resonance imaging (MRI) as well as efficient sustained delivery vehicle for doxorubicin. The acylhydrazine linker helps to release the drug under mild acidic conditions. Wang et al. [37]

developed a biodegradable endosomal pH-sensitive polymeric prodrug based on poly(5-methyl-5-allyloxycarbonyl-1,3-dioxan-2-one)-*graft*-12-acryloyloxy dodecyl phosphorylcholine (PMAC-*graft*-ADPC). Doxorubicin was conjugated to the polymer through hydrazone bonds. *In vitro* drug release studies showed that the release of doxorubicin was faster at endosomal pH (pH = 5.0) than at normal physiological environment (pH = 7.4), as shown in **Figure 5**.

Acetal is another acid-labile functional group that can be wielded to design smart polymeric nanocapsules. Tonhauser et al. [38] developed long chain branched and hyperbranched polyether polyols by copolymerization of an acetal-containing inimer, namely, 1-(glycidyoxy)ethyl ethylene glycol ether (GEGE) with ethylene oxide and glycidol. Owing to the presence of acetal group, a strong pH-dependence of the degradation kinetics was observed. At pH 4.5, $t_{1/2}$ (half-life) is approximately 76 h, while at pH 4, $t_{1/2}$ is almost one-third of this value with 26 h. Also, since no degradation was observed at pH 7 or higher, storage stability was guaranteed. Hu et al. [39] designed a series of well-defined three-armed star-block copolymers containing poly(ethylene glycol) monomethyl ether (mPEG) and poly(ϵ -caprolactone) blocks linked with acid-cleavable acetal groups to demonstrate the pH-dependent release of doxorubicin. Tomlinson et al. [40] proved that the pH responsiveness of acetal-labile polymer was due to polymer degradation. It was substantiated by a pH-dependent decrease in molecular weight at pH 7.4, 6.5, and 5.5.

β -Carboxylic amide is another acid-sensitive functional group that can be included as a pendant chain to incorporate its acid-sensitivity to the parent polymer chain. β -Carboxylic amides functionalized polymer chains are negatively charged and stable at neutral pH, but when the pH is decreased to 6, they quickly become positively charged due to the hydrolysis of β -carboxylic amides in acidic condition. After hydrolysis, the β -carboxylic amides form cationic primary amines. This charge reversal or charge conversion can have two main effects. In 1997, Behr [41] proposed the “proton-sponge” hypothesis describing that unprotonated amines can absorb protons as they are pumped into the lysosome, resulting in more protons being pumped in leading to an increased influx of chloride ions and water. This increases endosomal pH. A combination of osmotic swelling and swelling of the amine-functionalized polymer triggers endosomal escape, with subsequent release of its contents into the cytoplasm because of repulsion between protonated amine groups, which causes the rupture of the lysosomal membrane. Secondly, β -carboxylic amides modified

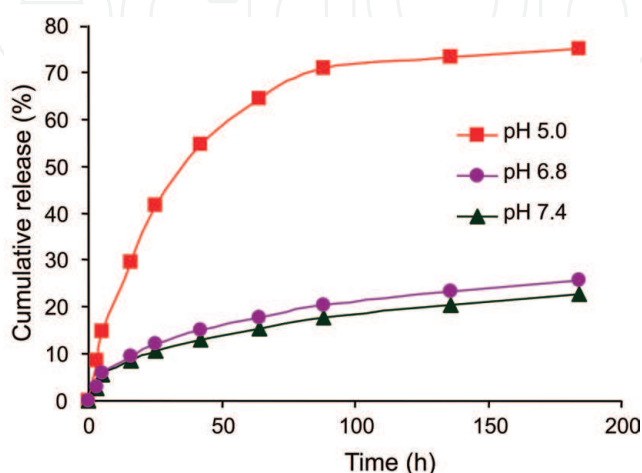


Figure 5.
 Time-dependent cumulative release of doxorubicin from PPC-Hyd-DOX-DA NPs at different pH values.
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polymer can exploit its negative charge interaction with cationic drugs like doxorubicin to achieve high drug-loading capacity and efficiency. The pH induces charge reversal in acidic condition, and generates a repulsive electrostatic force between positively charged amines and cationic drugs, leading to accelerated drug release. Quadir et al. [42] showed that PEG–polypeptide copolymers with amine pendant chains can be utilized as a pH-responsive drug-delivery vehicle. These nanosized vesicles were proved to be stable platforms for drug delivery that can successfully localize in solid tumors and release doxorubicin, mediated by the enhanced permeation, and retention effect by lowering the pH of the tumor microenvironment.

The pH difference between healthy and disease tissue, and between extracellular and intracellular compartments, has been exploited to fabricate the pH-responsive polymer nanocapsules for controlled drug release. This field is the target of extensive investigations being done worldwide.

4.2.2 Reactive oxygen species sensitive

Reactive oxygen species (ROS) are partially reduced chemically reactive metabolites of oxygen. These include superoxide anion, hydroxyl radical, hydrogen peroxide, peroxyxynitrite, and hypochlorous acid. ROS have important roles in cell signaling and homeostasis. However, high levels in certain pathological conditions can damage the cells by causing oxidations of lipids, proteins, and DNA. These have also been known to cause oxidative deactivation of specific enzymes by oxidation of co-factors. This is known as oxidative stress. Elevated levels of ROS have been implicated in a number of pathological conditions, including aging, male infertility, inflammation, infections, cancer, atherosclerosis, reperfusion injury, and diabetes [43]. This has sparked a lot of interest into finding ways to create ROS-eliminating strategies. This has been achieved by two mechanisms.

The first mechanism involves a phase transition of the polymer backbone from hydrophobic to hydrophilic, thus making the capsule wall material soluble in solution and release the therapeutic payload. Sulfides and selenides are the two functional groups, when subjected to ROS, increase their solubility in water. Ma et al. [27] synthesized a diselenide-containing block copolymer and both the oxidizing and reducing groups were shown to have the capability to destroy Se-Se bonds. Poole et al. [44] developed ROS-responsive poly(propylene sulfide) (PPS) microspheres, which were successfully utilized for encapsulation and sustained delivery of curcumin in the diabetic mouse hind limb ischemia model of peripheral arterial disease. The PPS microspheres were biocompatible, improved cell survival under exogenous oxidative stress and reduced ROS levels both *in vitro* and *in vivo*.

The second mechanism involves the physical degradation of polymer backbone in response to ROS. Functional groups like boronic-esters, thioketals, and prolines have been proven to be ROS sensitive. Zhang et al. [45] synthesized 4-phenylboronic acid pinacol ester (PBAP) chemically conjugated onto hydroxyl groups of β -CD to synthesize oxidatively responsive β -cyclodextrin. ROS-sensitivity and superior biocompatibility of this boronic-ester functionalized cyclodextrin were validated via extensive *in vitro* and *in vivo* studies. Lee et al. [46] developed a ROS-degradable scaffold by crosslinking PCL with a ROS-degradable oligoproline peptide, KP₇K, which was further investigated in an *in vivo* model for long-term tissue engineering applications. The KP₇K-crosslinked polymer scaffolds underwent significant surface degradation in response to ROS.

In 2010, Wilson et al. [47] developed thioketal nanoparticles formulated via a polymer, poly-(1,4-phenyleneacetone dimethylene thioketal), that degraded selectively in response to ROS. Thioketal bonds were found to be stable to acid-, base-, and protease-catalyzed polymer degradation. In a murine model of ulcerative

colitis, orally administered thioketal nanoparticles, loaded with siRNA against the proinflammatory cytokine TNF- α , remained stable in the harsh environment of the gastrointestinal tract, protecting TNF-siRNA and preventing its release to non-inflamed mucosal tissues. However, at sites of intestinal inflammation, where infiltrating phagocytes produce unusually high levels of ROS, the thioketal bond crosslinked polymer degrades thus releasing TNF-siRNA to the site of inflammation. This led to controlled gene silencing to curtail TNF-mRNA levels in the colon and protect the mice from ulcerative colitis.

4.2.3 Enzyme sensitive

Enzymes are the key biological catalysts that play a vital role in all chemical, metabolic, and biological processes serving as the prime protagonists in the chemistry of living organisms at a molecular level. As their presence and activities are essential in maintaining the physiological homeostasis, enzyme dysregulation is associated with many diseases and pathological disorders, such as cancer, cardiovascular disease, inflammation, osteoarthritis, Alzheimer's disease, inborn errors of metabolism, etc. Therefore, altered expression level of specific enzymes can be exploited as a pristine biological trigger to achieve enzyme-mediated biomaterial responses and controlled release of biomolecules at the desired sites. Compared to typical catalyzed or non-catalyzed chemical reactions involved in polymer synthesis, enzyme-catalyzed reactions exhibit superior advantages, such as high selectivity and substrate specificity. These reactions can be conducted under quite mild condition (37°C, aqueous media, typically neutral or slightly acidic and alkaline pH). Another advantage is that enzyme-catalyzed reactions can be conducted *in vitro*.

Azobenzene is an artificial structural moiety that can be used to fabricate azoreductase-sensitive nanocapsules. The enzyme azoreductase is produced by microbial flora specifically present in the colon of the human intestine which makes it an elegant stimulus to create colon-specific drug-delivery systems. Rao et al. [48] developed an amphiphilic diblock copolymer with an azobenzene linkage introduced as an artificial enzyme active site at the junction of the diblock copolymer. The authors documented the enzymatic dissociation of the copolymer connection which released the two polymer segments following introduction of the enzyme azoreductase, in the presence of coenzyme Dihydronicotinamide-adenine dinucleotide phosphate (NADPH), leading to the cleavage of the azobenzene-based block copolymer linkage. The authors thus established the potential applications of azobenzene linkages in the realm of colon-specific drug-delivery systems.

Gelatinase is a mixture of two types of matrix metalloproteinase (MMP) enzymes that is highly expressed in tumor tissues. Dong et al. [49] developed a pH and enzyme-responsive complex composed of doxorubicin, CpG DNA fragments, cationic gelatin, and pH-sensitive alginate. Since gelatinase is relatively highly expressed in liver, a PEGylated pH-responsive alginate was introduced to reduce the liver accumulation of doxorubicin and thus attenuate its hepatotoxicity. The gelatinase and DNase present in high concentration in the cytoplasm of tumor cells helped to dissociate the cationic gelatin and CpG DNA fragments and enhanced the drug release.

5. Future Prospects and Challenges

Wall materials are already playing an important role in the development of micro-/nanoformulations, which have been applied as drug-delivery systems. These drug-delivery systems have greater potential for many applications, including anti-tumor therapy, gene therapy, AIDS-therapy, radiotherapy, delivery of proteins, antibiotics,

virostatics, vaccines, and as vesicles to cross the blood-brain barrier. Nanocapsules particularly provide massive advantages regarding drug targeting, delivery, and release. With their additional potential to combine diagnosis and therapy, they emerge as one of the major tools in nanomedicines. The major challenges are to improve their stability in a biological environment, to mediate the biodistribution of active compounds, improve drug loading, and establish greater interaction with the biological barriers. The cytotoxicity and the degradation products of the formulations developed from the wall materials remain a major problem. Thus, improvements in biocompatibility are the main concern of future research. These challenges can be suitably addressed by developing newer polymeric wall materials, which can be of better biocompatibility with the biological environment. Simultaneously, molecular modeling study would greatly contribute in understanding the interaction between the wall materials and drug, and this in turn with the biological environment. Finally, the success of this is largely dependent on the efforts of scientists, physicians, and engineers.

Acknowledgements


The authors thank the University Grants Commission (UGC), New Delhi and Department of Science and Technology (DST), New Delhi for providing the financial support respectively under UPE-FAR-I program [Grant No. 14-3/2.12(NS/PE)] and DST-PURSE-Phase-II program [Grant No. SR/PURSE PHASE-2/13(G)].

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