Expert Opinion

Triggered drug delivery from biomaterials

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Importance of the field: Conventional dosing methods are frequently unable to deliver the clinical requirement of the patient. The ability to control the delivery of drugs from implanted materials is difficult to achieve, but offers promise in diverse areas such as infection-resistant medical devices and responsive implants for diabetics.
Areas covered in this review: This review gives a broad overview of recent progress in the use of triggers that can be used to achieve modulation of drug release rates from implantable biomaterials. In particular, these can be classified as being responsive to one or more of the following stimuli: a chemical species, light, heat, magnetism, ultrasound and mechanical force.
What the reader will gain: An overview of the potential for triggered drug delivery to give methods for tailoring the dose, location and time of release of a wide range of drugs where traditional dosing methods are not suitable. Particular emphasis is given to recently reported systems, and important historical reports are included.
Take home message: The use of externally or internally applied triggers of drug delivery to biomaterials has significant potential for improved delivery modalities and infection resistance.

Keywords: biomaterials, light, pH, smart materials, stimulated delivery, thermal, triggered delivery

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1. Introduction

Conventional methods of administering drugs, such as in an oral dosage form, intravenous injection, suppository, and so on, often represent a compromise in terms of achieving a therapeutic concentration over the clinically required duration of action. Frequently, regular dosing is required to maintain the circulating drug concentration within a therapeutic, and non-toxic or subclinical, range [1]. Also, a range of conditions, such as diabetes, patients requiring breakthrough pain relief, ulcer patients requiring inhibition of gastric acid secretion and angina suffers requiring nitrate therapy, require rapid establishment of relatively high drug concentrations.

The widespread incidence of infection in medical polymers has also seen the advent of drug-eluting polymers, which have similar demands in terms of the ability to respond to the onset of infection, or provide prophylaxis against infection for sustained periods. Simple passive elution strategies have already found application in this area in, for example, gentamicin-eluting bone cements, paclitaxel-eluting coronary stents and silver-impregnated catheters. However, the development of 'smart' responsive polymers holds much promise for next-generation biomaterials, which give unprecedented control over drug dosing and offer the ability to give pulsatile or sustained release modes. The unifying principle behind triggered drug delivery from an implantable polymer is that a stimulus, which may be applied externally or originate within the system itself, induces either a physical change in the structure of the polymer itself, thereby modulating the rate at which an embedded drug is

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Article highlights.

- Conventional dosage methods often represent a compromise in terms of achieving a therapeutic concentration over the clinically required duration of action, but 'smart' responsive polymers can give unprecedented control over drug dosing and offer the ability to give pulsatile or sustained release modes.
- Chemical triggers, such as pH, glucose or the presence of particular enzymes, can be judiciously exploited to couple their presence to either a change in polymer shape, which modulates release rate, or bond cleavage to liberate a drug conjugated to the biomaterial.
- The ability to manipulate light in terms of its wavelength, intensity, site of application and duration allows for precise control with regards to the location, dose and time at which a therapeutic agent is released, if the liberation of drug is linked to a photochemical event.
- Temperature-sensitive hydrogels can swell or contract around physiological temperature and thereby module release rates.
- Magnetism, ultrasound, pressure and electric fields are important external triggers that have been widely exploited for triggering drug release.
- In addition to organising systems according to stimulus, two approaches are used predominantly: either the trigger serves to modulate the physical dimensions of the material in which drug has been incorporated, or the trigger directly causes cleavage and subsequently elution of drugs from polymeric media.

This box summarises key points contained in the article.

released (**Figure 1**), or acts directly to induce cleavage of the drug from a drug-polymer conjugate, from which the drug subsequently elutes (**Figure 2**). Such systems are typically still at *in vitro* development stages, and this review serves to give a broad survey of recent developments in these stimulus-responsive systems. Stimuli that can be exploited include a chemical species, light, heat, magnetism, ultrasound and mechanical force.

2. Chemically responsive biomaterials

Numerous polymeric biomaterials that respond to the various chemical stimuli which contact that biomaterial have been exploited for improved site-specific drug delivery. These aim to deliver an appropriate therapeutic concentration to the site, thus limiting side effects caused by toxic or subtherapeutic concentrations of drug. Stimuli such as glucose, pH, enzymes and ionic strength have all been exploited to develop these chemically triggered systems.

2.1 pH-triggered release

Variation in proton concentration (which determines pH) occurs throughout the different body fluids, from acidic conditions in the stomach to a basic environment in the intestines and at the onset of urinary catheter infection. pH-responsive polymers contain hydroxyl, carboxylate, sulphate, or amine pendant groups that either donate or accept protons and dissociate depending on the pH of the environment. Polyacids such as poly(acrylic acid) (PAA) or poly(methacrylic acid) (PMAA) contain carboxyl functionalities that dissociate in basic pH environments. This dissociation results in negatively charged COO^- moieties within the network; these repel each other causing the chains of the polymer to elongate, resulting in an increased pore size of the polymer network. This allows a greater influx of water, resulting in enhanced swelling of the polymer [2]. The opposite effect occurs for polybases, which accept protons in acidic environments, for example poly(*N*,*N*′-dimethylamino ethyl methacrylate) (PDMAEMA). Therapeutic agents are released from each system through diffusion out of the swollen matrix or by a 'squeezing' effect of a polymer in swollen state collapsing and compacting. Control over the swelling and pore size of pH-responsive polymers is achieved through combining different proportions of polyacid/base monomers in the copolymer matrix, or through the incorporation of hydrophobic elements, which results in more repulsive electrostatic forces needing to be surpassed before swelling. Numerous systems have been developed as drug delivery systems in this field, and comprehensive reviews have been published elsewhere [3,4].

Medical device-associated infection (MDAI) is a recognised problem that can lead to increased morbidity to patients and cost to the healthcare sector. Several strategies have been used to combat MDAI with varying degrees of success. The classic example of how pH-responsive polymers could be used to prevent biofilm formation on medical devices is on urinary catheters. In an infection of the urinary tract, bacteria produce urease, which converts urea in the urine to ammonia, raising the pH of the environment. pH-responsive polymers composed of PAA or PMAA and, for example, 2-hydroxymethyl methacrylate or poly(ethylene glycol), can be engineered to trigger release of antibiotic only in response to infection by swelling in an alkaline environment. This may lead to more effective catheter coatings than passive eluting or silver-based systems, which in recent detailed reviews have suffered from drawbacks such as 'burst' release followed by prolonged periods of subtherapeutic drug levels that can lead to the development of resistant bacterial strains [5-7].

An alternative strategy involves pH-triggered release of a drug from the backbone of a polymeric biomaterial, whereby a therapeutic agent is covalently bonded to the polymer, primarily through a hydrolytically labile ester bond. Release of the therapeutic is achieved through the hydrolysis of the ester bond linking the drug to spacer, which accelerates at elevated pH. Early work in this area was aimed at improving delivery of non-steroidal anti-inflammatory (NSAID) drugs, where release of free NSAID was greater in more alkali environments, which reduces the ulcerative adverse effects associated with NSAIDs [8,9].

It has recently been demonstrated that not only does the pH of the medium in contact with the biomaterial play a

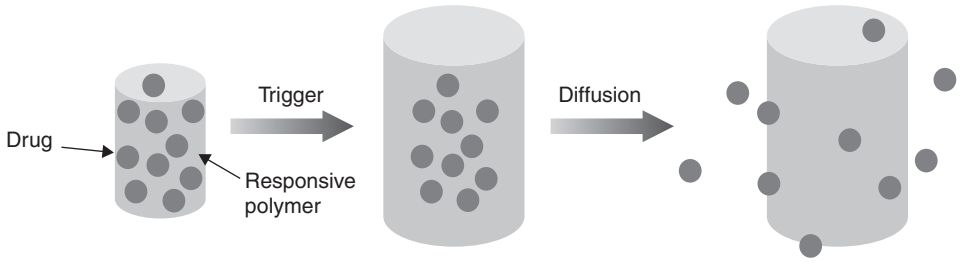

Figure 1. Schematic representation of triggered release from a polymer that undergoes a change in morphology as a result of an applied stimulus.

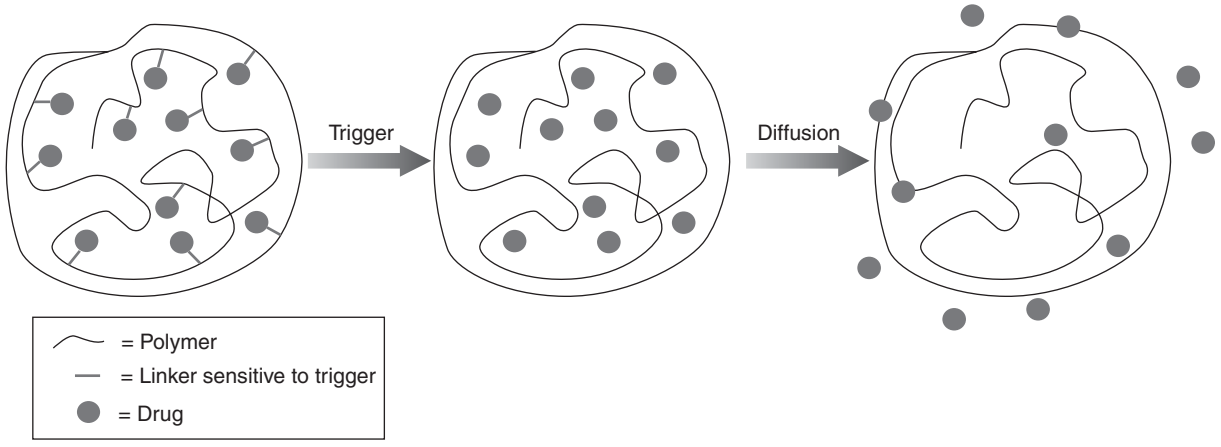

Figure 2. Schematic representation of triggered release from a polymer to which drug is conjugated by means of a linker that is labile to the applied trigger.

role in the rate of hydrolysis of these linkages, but also that neighbouring groups within the molecule can control the rate of hydrolysis and subsequent release [10]. To demonstrate this principle, bone cements based on poly(methyl methacrylate) (PMMA) with covalently linked nalidixic acid-spacer conjugates were prepared and the effect of neighbouring group-controlled hydrolysis of the ester bond linking nalidixic acid to the spacer was demonstrated. The system relies on chemistry established by Fife and co-workers more than 30 years ago [11,12], whereby an intramolecular nucleophile such as a lone pair of electrons on a nitrogen atom, or a nitrogen-containing heterocycle such as imidazoyl or pyridyl, can accelerate the hydrolysis of a hydrolytically liable functional group. The study showed that the rate of release of nalidixic acid from the bone cements depended on the strength of the nucleophile and the relative stability of the required intramolecular intermediate, and that the use of neighbouring group participation can be applied to polymeric systems. Although steric effects of the length of the spacer group were not systematically examined in this study, it has been established by other groups that this can also allow control of the release rate of drugs from similar polymers by controlling steric access of the incoming nucleophile to the labile ester or amide to the carbonyl carbon, which controls release rate [13,14].

These systems benefit from being internally controlled by the chemical species triggering release (a high, or low, proton concentration), and do not need to have an external stimulus applied to give triggered release.

2.2 Biodegradable polymers

Polymer networks that undergo enzymatic degradation could be used in the delivery of antimicrobial agents to combat MDAI, or other therapeutics to treat disease states, from degradable medical devices.

Polymer matrices with covalently bonded fluroquinolone antibiotics that undergo enzymatic degradation by means of cholesterol esterase have been investigated as possible polymer coatings to inhibit biofilm formation. Woo *et al.* [15] developed such a matrix composed of polycaprolactone and ciprofloxacin, crosslinked using 1,6-dihexyl spacers. The matrix underwent degradation to render free ciprofloxacin; however, several extra degradation products were also produced,

attributed to the nonspecific cleaving action of the enzyme to render free ciprofloxacin. More recently, a biodegradable matrix of diisopropylcarbodiimide, poly(epsilon-caprolactone) diol and nalidixic acid showed a better release of the fluroquinolone antibiotic (release duration exceeded 6 months) [16].

Recent advances of biodegradable drug delivery systems include pH-sensitive biodegradable hydrogels. These dual-responsive systems have the advantage over typical pH-responsive polymer drug delivery systems by allowing an almost complete drug release. The primary method of controlled drug delivery is through the swelling of the polymer network and diffusion of the drug from the matrix; however, because the matrix is capable of being eroded by enzymes such as lipase, dextranase and esterase, there is less entrapment of the drug within the polymer network as the length of the diffusion path for the drug is decreased [17,18].

Tamoxifen citrate containing implants that undergo hydrolytic degradation have been investigated for tumour-specific delivery; these would provide a delivery method that would reduce the side effects associated with orally administered tamoxifen and improve patient compliance [19]. The authors demonstrated that at a loading of 10 wt%, tamoxifen can be delivered over a period of 70 days.

2.3 Glucose-triggered release

Diabetes mellitus is a major cause of morbidity and mortality in industrialised countries. The standard treatment for the disease is periodic injection of insulin (for insulin-dependent diabetics); however, poor control of blood glucose level and poor compliance associated with this method have turned attention to developing alternative treatments, specifically chemically synthesised closed-loop insulin delivery systems based on glucose-responsive hydrogels. Glucose oxidase (GOD) and lectin-modified hydrogels are examples of such systems. Ravaine *et al.* [20] recently reviewed approaches to this self-regulating closed-loop insulin delivery system, therefore our attention is focused on delivery through GOD-modified implantable hydrogel membranes. Such membranes incorporated with GOD and catalase have been shown to be effective in producing a glucose-responsive insulin delivery system. Glucose is oxidised to gluconic acid, the reaction being catalysed by GOD. The result is a decrease in pH of the microenvironment [21]. H_2O_2, a toxic by-product of this reaction, is converted to O_2 and H_2O by catalase, producing more O_2 to react with glucose and decrease the pH of the microenvironment to a greater extent. The use of a polybase such as *N*,*N*-dimethylaminoethyl methacrylate (DMAEMA), typically copolymerised with pHEMA to produce the membrane, gives a pH-responsive polymer that will swell in an acidic environment to release insulin entrapped within the matrix, this method being the basis for the early development of these GOD-modified systems [22].

An improvement to these homogenous systems was achieved through the use of linear grafted PAA chains with immobilised GOD as a gating mechanism in a porous membrane for more rapid insulin delivery, whereby the response time to glucose could be reduced to 16 s [23]. At neutral pH in the absence of glucose, the PAA chains are dissociated and the repulsive forces of the negatively charged carboxylate moieties result in the ligands extending and 'closing' the membrane gates. In the presence of glucose, again converted to gluconic acid by means of the immobilised GOD on the ligands, the pH is decreased to form an acidic environment and the carboxylic groups of PAA become protonated, reducing the electrostatic repulsive forces. The PAA ligand contracts to its desired confirmation and the gates are opened [24].

Gated porous systems are limited in their potential application, as the release rate of insulin is governed by concentration-driven diffusion, which limits the maximum release of insulin. Combining the ligand gating system with a negatively pH-responsive DMAEMA hydrogel inside the reservoir, which swells in acidic conditions, can force a drug in the reservoir out through the membrane, effectively acting as a pump [25]. This approach shows a more effective pH-responsive controlled release system when compared with the previous gated and homogenous release systems described above.

3. Light-triggered release

The use of light as a stimulus for triggered release from biomaterials potentially provides a high level of pharmacological control. The ability to manipulate light in terms of its wavelength, intensity, site of application and duration allows for precise control with regard to the location, dose and time at which a therapeutic agent is released, if the liberation of drug is linked to a photochemical event [26]. The level of control extends potentially to the molecular level, giving complete control over drug release profiles. The use of light in implants is restricted to materials that can be addressed effectively, and early applications will exploit medical devices such as urinary catheters and endotracheal tubes, or subcutaneous biomaterial implants, to which light can readily be applied.

Light-induced molecular processes such as photochromism offer potential for light-regulated implantable hydrogels. A photochromic molecule is characterised by its ability to undergo reversible photoinduced transformation between two molecular states, which have different absorption spectra when irradiated with light of appropriate wavelengths [27]. Apart from having differing electronic properties, several classes of photochrome are also associated with different properties, such as steric configurations (e.g., diarylelkenes) or dipole changes (e.g., spiropyrans) between the two forms. Spiropyrans are readily converted to a significantly more polar merocyanine form on irradiation with light. This large change in dipole has been suggested as the basis for a triggered implantable hydrogel-based delivery system, where spiropyran is permanently embedded in a pHEMA matrix, which expands (and hence changes drug porosity and release rate) on irradiation owing to charge repulsion [28].

The use of a photolabile protecting group in the form of a caged compound or a photocleavable linker has many advantages over other protecting groups used in organic synthesis. The use of light as the stimulus for the cleavage of a compound from a parent compound negates the need for strong acids or bases, which may damage the parent and substrate compound in the process. The use of photolabile protecting groups such as the *o*-nitrobenzyl alcohol derivatives [29-32] or benzoin esters has been widely reported [33-35]. These early systems suffer from the release of the potentially toxic protecting group in addition to the caged bioactive compound. To address this, this concept has recently been expanded to demonstrate light-triggered drug delivery through 3,5-dimethoxybenzoin conjugates with model drugs. Several of these have been incorporated successfully into a proposed urinary catheter coating hydrogel, and the materials show a correlation in the amount of drug dosed from the material with the amount and wavelength of light applied, and have achieved light-triggered drug release [36,37].

Laser holography and the use of an azopolymer membrane was an innovative method of accurate light triggered drug delivery developed by Lee *et al.* [38]. An azopolymer membrane on a drug agent attached to a substrate coated with fluorescent dye was exposed to holographic laser interference, which in turn created a surface relief grating pattern on the azopolymer surface, making it permeable to the drug agent and releasing the fluorescent dye [39]. By adjusting the incident angle and irradiation time, the widths and depths of these drug-eluting gates could be altered. This triggered release of a potentially therapeutic agent from an azopolymer has been explored for application in ophthalmic drug delivery. A further strategy for light-triggered ocular delivery is to induce polymer degradation using light. Methylene blue has been used as a photosensitiser in the presence of H_2O_2, which in the presence of visible light undergoes photochemical autooxidation causing the degradation and scission of hyaluronic acid crosslinks within a hydrogel. The resulting increase in water content allows release of previously entrapped lipid microspheres from the hydrogel network into the external environment. [40].

Coumarin derivatives show photochemical behaviour that is attractive for drug-releasing biomaterials applications as they readily undergo two-photon photochemical rearrangements [41]. Kim *et al.* [42] extended this idea using a Coumarin derivative that releases a model drug from an intraocular lens biomaterial using wavelengths not present in normal incident light to the eye.

Light has been used to activate photsensitisers clinically in photodynamic therapy (PDT) since the 1980s. Although PDT is outside the scope of this review, the photodynamic effect has been demonstrated to be localised from the surface of proposed intraocular lens biomaterials that incorporate a thin layer of sensitiser at their surface. Excitation using visible light leads to a high surface concentration of singlet oxygen, which acts effectively against adhering bacteria, which can cause infectious endophthalmitis [43,44].

4. Heat-triggered drug release

Heat-triggered drug release has been widely documented and discussed within the literature. It has been the topic of previous reviews by, among others, Chilkoti *et al.*, Schmaljohann and, recently, Klouda and Mikos [45-47]. This section focuses on applications exploiting drug release changes arising from the ability of these polymers to swell and deswell, depending on temperature. There are two basic types of thermosensitive material. These are:

(1) Positive temperature-sensitive hydrogels that are swollen and hydrated at higher temperatures and contract on cooling below the upper critical solution temperature (UCST).

(2) Negative temperature-sensitive hydrogels that are swollen at lower temperatures and contract on heating above the lower critical solution temperature (LCST). Water solubility of the system decreases as temperature increases. This type of system dominates the literature on drug release applications.

Most reports involve the use of poly(*N*-isopropylacrylamide (pNIPAAm) [48] because it shows phase change behaviour close to mammalian physiological temperatures. It is hydrated with an expanded structure and large mesh size at lower temperatures but, above a certain temperature, the LCST, it 'shrinks' or contracts and expels water as the hydrogel water solubility is decreased, which will subsequently lead to the expulsion of any drug dissolved within the system. Below the LCST drug release is controlled by means of diffusion. PNIPAAm has an LCST ~ 32°C, which may be modified to a physiologically relevant/desired temperature by means of copolymerisation. Below the LCST, hydrogen bonding predominates between the hydrophilic segments of pNIPAAm (specifically the amine group) and water. This corresponds to swelling and dissolution of the polymer. Above the LCST, hydrophobic forces expel water, which will force drug expulsion from the system. Hydrogen bonds weaken and the hydrogel contracts. As hydrophobic content of the polymer is increased, the LCST is decreased. Conversely, when hydrophilic content of the material is increased, the LCST is also increased. An abrupt temperature increase above the LCST of pure pNIPAAm leads to the formation of a dense, shrunken 'skin' layer on the hydrogel surface, which impedes water permeation. This may provide an element of control to drug release and allow 'on-off' drug release [49]. The thermoresponsive polymer can also act as an actuator within a restricted geometry, where deswelling opens release holes for drug to diffuse through (**Figure 3**) [50]. Biocompatibility of early pNIPAAm systems was considered relatively poor; however, this does not preclude their potential for use in non-blood contact applications such as coatings for the interior lumen of urinary catheters, and improved biocompatibility and low cytotoxicity on polymer breakdown in, for example, infracted myocardial tissue, has been reported [51].

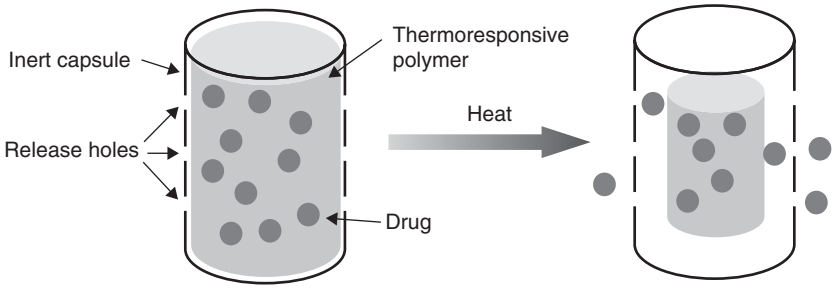

Figure 3. Schematic representation of triggered release from a thermosensitive polymer that shrinks above a critical temperature. The change in morphology allows passage of drug through the release holes of an inert capsule.

PNIPAAm has been studied as a carrier for the delivery of many drugs and active agents. These include proteins such as insulin and bovine serum albumin [52]. Being a smaller molecule, insulin was released at a higher rate than albumin. Pulsatile release of theophylline, salicylic acid, doxorubicin and naltrexone has also been demonstrated [53-55]. All of these systems (based on pNIPAAm) show potential for use as biomedical polymers and may subsequently be used to release active agent from the polymer.

Physical entrapment of active agents is the simplest method for their incorporation into the hydrogel. This is where a drug is loaded into the hydrogel during the polymerisation process and may be retained owing to the crosslinking and entanglement of the structure, which inhibits diffusion [56].

It has been reported that the physicochemical properties of the incorporated drug may have a significant impact on the release kinetics from a thermally sensitive pNIPAAm system [57] as well as the swelling of the system. It was shown that the presence of hydrophobic drugs reduced the hydrogel swelling rate while the inclusion of hydrophilic drugs increased hydrogel swelling. Subsequent drug release from the system above the LCST was influenced by the extent of swelling. Also, hydrophobic drug release is influenced by its solubility in the system medium. One significant study of note assessed the *in vivo* release of heparin from thermosensitive polymer coatings composed of pNIPAAm blends as a method to prevent surface-induced thrombosis on biomaterials [58]. At room temperature, the polymers were in a swollen state, which allowed fast loading of heparin into the coating. At physiological temperature, the coatings are in an unswollen state and the heparin may be released by means of a diffusion-controlled mechanism. This was evaluated *in vivo* in a canine model and was found to cause a significant reduction in thrombus formation.

The antiglaucoma drug epinephrine was studied and released from a thermosensitive vehicle, as reported by Hsiue *et al.* [59]. A polymeric eye drop was produced by copolymerising pHEMA (p(2-hydroxyethyl methacrylate) with pNIPAAm and mixing epinephrine. This solution forms a soft film on contact with the cornea, which allows progressive drug release and an *in vivo* activity of 26 h. This is a greater duration of action than that of conventional eye drops and may therefore be advantageous in this area.

Recently, Ankareddi and Brazel [53] studied the release of theophylline and insulin from pNIPAAm hydrogels grafted with HEMA. This grafting inhibited the diffusion of the active drug at low temperatures and on heating above the LCST the collapsed oligomers widened the mesh space to allow diffusion of the active agent into the environment.

Potential applications of thermally responsive polymers include the treatment of tumours. These may be injected into the bloodstream where they accumulate in tumour cells that have been heated to above the polymer LCST using externally applied stimuli, which may then lead to the local delivery of drugs to the tumour [60]. In such instances, the LCST of the polymer must be modified to be above physiological temperature. Meyer *et al.* copolymerised NIPAAm with acrylamide to achieve this [60]. They also used a genetically engineered thermally responsive elastin-like polypeptide (ELP), which showed preferential accumulation characteristics in locally heated tumour cells.

Chitosan-based hydrogel films have also been studied as potential biomaterial drug delivery systems. A study by Sun *et al.* [61] reported the production of hydrogel films possessing both thermal and pH sensitivity. These films were made by copolymerisation of chitosan with pNIPAAm and the study showed that the film was more porous at 37°C than at room temperature owing to the crystallinity of the chitosan component, which may have potential applications for physiological drug delivery. Dual temperature and pH sensitivity was also demonstrated by Wang *et al.* [62], who copolymerised pNIPAAm with DMAEMA [N-(2-(diethylamino)ethyl)-methacrylate], which did not impact on the thermosensitivity.

A recently published study reported the use of terpolymers of NIPAAm-AAm and vinyl pyrrolidone as release carriers for naltrexone [63]. These polymers showed pH sensitivity as well as temperature sensitivity, which allowed modification of the LCST of the copolymer in response to a variance in pH. The study reported up to 70% of drug release occurred within 30 days at a physiological temperature.

Recent advances have shown faster shrinking and reswelling rates, which may be obtained by copolymerising pNIPAAm

with PVA to form a semi-IPN [64]. This type of system has improved temperature sensitivity and swelling properties and may allow tighter control of drug release from the material. The introduction of graft chains independent from the hydrogel main chains is well documented as a method for accelerating the deswelling rate of the hydrogel and may thus improve the drug release profile.

5. Magnetically triggered drug release

The use of magnetic fields was one of the first methods investigated as a means of exerting an external influence over drug delivery [65]. These systems consist of magnetic-responsive particles suspended in a drug-loaded polymer [66]. Application of an oscillating magnetic field modulates drug release, producing movement of the embedded magnets, resulting in alternating expansion and compression of the matrix and acting to pump increased amounts of drug out of the matrix [66]. An early example of magnetic triggering involved the release of bovine serum albumin (BSA) from an ethylene-vinyl acetate (EVAc) copolymer embedded with magnetic steel beads [65]. The release rate of BSA was increased by up to 100% on each exposure to an oscillating magnetic field over a 5-day period.

There have been several reports investigating the potential use of magnetic triggering to produce on-demand, pulsatile release of insulin. Successful experiments have been performed *in vitro* and the potential for use *in vivo* has been demonstrated with enhanced blood glucose control in diabetic rats [67,68].

The influence of both magnetic field characteristics and mechanical properties of the polymer on release rate in response to oscillating magnetic fields has been established [69,70]. Increasing both the frequency and the amplitude of the magnetic fields results in an increase in drug release rates. Polymers with higher elastic moduli show reduced release rates owing to resistance to the motion of the magnetic particles. The positioning, orientation and magnetic strength of the embedded magnetic materials have also been found to be important in tailoring drug release in these systems [71].

It has been postulated that increases in temperature during exposure to oscillating magnetic fields may influence drug release rates from magnetically triggered systems, and this effect can be exploited as a means of externally controlling release from negative temperature-sensitive hydrogels [72]. In such systems, application of oscillating magnetic fields produces local temperature increases in excess of the LCST of the polymer, resulting in collapse of the hydrogel and expulsion of water and drug. Temperature response, hydrogel collapse and subsequent increase in release rates were rapid and systems demonstrated a less rapid recovery to normal levels as a result of slower heat dissipation and ingress of water [73,74].

6. Ultrasonically triggered systems

Ultrasound has been used extensively in medicine for a variety of diagnostic and therapeutic purposes, including medical imaging, physiotherapy and ultrasonic surgery, and was proposed as a method for triggering drug delivery by Langer and co-workers in 1989 [75]. Recently ultrasound has been explored as a means of exerting external control in drug delivery from biomaterials for pulsatile release. The advantage of ultrasound is that it is non-invasive and may be focused at depth in soft tissue throughout the body [76].

Early attempts by Miyazaki *et al.* to control drug release using ultrasound irradiation involved ethylene-vinyl alcohol copolymers containing the chemotherapeutic 5-fluorouracil (5-FU) [77]. Under normal conditions, the drug was released slowly by passive diffusion. However, when exposed to ultrasound, 5-FU was released at a much higher rate, up to 27 times greater than that achieved in the absence of ultrasound. This work also demonstrated direct proportionality between ultrasonic strength and drug release. Later work focusing on the delivery of bovine insulin demonstrated similar effects, which were reproduced *in vivo*, resulting in sharp decreases in the blood glucose levels of diabetic rats [78]. Ultrasound is an attractive mechanism for delivery of proteins, especially insulin, as it offers a reproducible, rapid and reversible method of controlling release, with no degradation of proteins.

Ultrasonically triggered drug release from both bio-erodible (e.g., poly(glycolic acid) and poly(lactic acid)) and non-erodible polymers (e.g., ethylene-vinyl acetate) has been studied [75]. Bio-erodible polymers show enhanced sensitivity to the effects of ultrasonic energy, owing to enhanced degradation rates, resulting in much greater increases in drug release rate compared with non-erodible polymers. Experiments in degassed solutions demonstrated the importance of cavitation and acoustic streaming in this process.

Later work with non-erodible ethylene-vinyl acetate showed that utilising lower ultrasound frequencies enhanced drug release rates [79]. This is the result of two separate effects. First, as ultrasound frequency is reduced, the absorption coefficient is also reduced, enabling greater depth of penetration of the ultrasound energy. Second, reduced ultrasound frequencies are responsible for higher levels of cavitation and acoustic streaming.

One issue with ultrasonically triggered systems, and polymer-based drug delivery systems in general, is the initial burst release on implantation and subsequent leaching of drug at subtherapeutic levels from the polymer matrix. Recent work has proposed the use of an ultrasound-responsive coating consisting of ordered methylene chains [80]. Intact, such coatings form highly effective barriers to drug release; however, on exposure to ultrasonic waves this layer is disrupted, permitting instant drug release. Insulin release from this system, without the undesirable initial burst, has been demonstrated [80]. This method has also been considered to prevent the development of bacterial resistance in response to antibiotic release from medical prostheses to prevent device-related infection [81]. Similar results have been observed using poly(dimethylsiloxane)-mesoporous silica composites [82].

7. Mechanically triggered systems

Drug release systems responsive to mechanical stimuli have received much less attention than other triggered release systems. One method investigated involves forming a depot of drug-loaded liposomes by subcutaneous injection into the interstitial space [83]. Typically, small molecules would diffuse into the lymphatic system through interendothelial gaps and pass into the bloodstream, while larger molecules, such as liposomes, remain trapped in the interstitium. However, under hydraulic pressure, such as that experienced during massage or muscular activity, the gaps between endothelial cells are opened further allowing passage of the liposomes into the lymph and increased drug blood levels. A related system involves the use of drugs reversibly bound to hydrogels [84]. When subjected to mechanical stress, increased pressure causes the release of free drug. On relaxation, free drug is replenished by dissociation of polymer-bound drug. This mechanism has been used for controlled release of vascular endothelial growth factor in response to muscular activity, resulting in increased granulation and vascularisation surrounding the implant [85].

Thermosensitive polymers (as discussed in Section 4) have properties that may make them useful for mechanical triggering [86]. Increases in pressure cause an increase in the LCST of the polymer. When pressure is applied at temperatures close to the LCST, large increases in polymer swelling occur. Mechanical stimuli, such as massage, could produce cyclical swelling and deswelling, acting as a pump to release drug loaded into the polymer network.

8. Electrically triggered systems

Electrical fields may be used to modulate drug delivery by several different mechanisms. Electrically erodible polymers have been studied as a means of controlled drug release [87]. This approach has been used to control release of insulin from mixtures of poly(ethyloxazoline) and either poly(methacrylic acid) or poly(acrylic acid). Hydrogen bonding between both polymers results in the formation of a solid polymer complex. On application of an electrical field, local pH changes at the cathode cause hydrogen bonding in areas of the polymer adjacent to the cathode to begin to break down and consequently begin to dissolve, resulting in a burst release of insulin. Removal of the electrical field arrests the dissolution of the polymer and the release rate of insulin returns to the previously observed rate.

Electrically controlled permeation of ionic drugs through a rate-limiting membrane has been demonstrated [88,89]. Electrodes placed across the membrane modulate drug release. On application of an electric current, drug migrates across the membrane to the oppositely charged electrode and once the current is removed the release rate returns to normal. Numerous other electrically triggered release systems have been described, including devices using biodegradable polymer microchips and drug-loaded conductive polymer nanotubes [90,91].

9. Conclusion

This article has detailed and categorised the diverse triggers, or stimuli, which can be used to control drug delivery rates from biomaterials. Each of the stimuli can either be easily and accurately controlled externally, or is provided internally as the stimulus for drug release. To be classified as a triggered delivery biomaterial, the material must demonstrate a useful modulation in the rate at which drug is released when the trigger is present, in comparison with when the trigger is absent.

Each trigger may be summarised as operating in one of two ways. First, the trigger may operate so as to induce a macroscopic change in the physical topography of the biomaterial, which alters its porosity and hence the rate at which drug elutes from it. Examples of this mode of operation are given for each of the triggers described. Second, the trigger may serve to induce directly a molecular rearrangement, such that drug which is maintained as an integral part of the biomaterial in the absence of the trigger is liberated in proportion to the applied trigger. Such systems are particularly suited to light-triggered or chemically triggered materials, where the control of light-driven or chemically-driven reactions is exploited to trigger drug delivery.

10. Expert opinion

Despite the large number of reports in the literature of systems that can be classified as triggered materials, there are relatively few examples of attempts at formal organisation and classification of systems. For example, the major difference in triggered systems reported so far is the fact that one class involves the use of the trigger to modulate the physical dimensions of the polymeric material in which drug has been incorporated, whereas the other class involves the use of the trigger directly to cause cleavage and subsequently elution of drugs from polymeric media. Heat-triggered systems are almost exclusively in the former class, whereas light-triggered and chemically triggered systems are moving increasingly towards systems in the latter classification. Although there have been attempts to describe these classes as 'open' or 'closed' loop systems, or internally or externally regulated, a formal recognition of the underlying physical phenomena would serve to unify the variable – and sometimes confusing – methods of classification in current use.

To be truly clinically useful, there is a need for triggered systems to deliver a high degree of modulation in their release rate, which would move towards true 'on-off' materials. Although some of the systems that modulate the physical dimensions of materials can achieve this (e.g., by using materials as actuators within restricted geometries [50]), the degree of modulation that systems of this class afford is generally much lower than that of systems that directly correlate the degree of application, in terms of duration or intensity, of the trigger to the cleavage of drug, which often achieve a true

'on-off' action. To this end, it is likely that both chemically and light-triggered systems will become increasingly important in the medium term. Systems in each of these classes have been shown to be able to respond in proportion to the applied stimulus, which is highly significant. For example, if a system can deliver a quantity of drug in direct proportion to a specific chemical marker of infection, it gives a more patient-tailored response than a material that allows passive diffusion of drug only. Even though diffusion-controlled systems can be engineered to give zero-order release, this is not necessarily the optimum method of controlling the clinical requirement. The development of a range of systems that respond in a highly selective manner to various chemical species is therefore likely in the future. In particular, the specificity of enzyme–substrate interactions could be exploited for tailored, chemically responsive drug-polymer conjugates capable of delivering a wide range of therapeutics in a close-to-ideal manner. Similarly, the level of control available over light sources offers much promise for light-triggered materials. Light-triggered delivery of singlet oxygen is now clinically routine in PDT, but correlating the location and dose of drug liberation to the wavelength and intensity of applied light allows potentially molecule-scale dosing to be regulated from any material that can be addressed by light. Examples of such biomaterials that are being investigated for clinical applications are urinary catheters, endotracheal tubes and ophthalmic biomaterials such as contact lenses and intraocular lenses. Indeed, the single largest application of these technologies is likely to be in the establishment of infection-resistant biomaterials. Also, there is potential for implanted biomaterials for drug delivery that can be externally triggered in this way, though there are issues in the medium term to address, such as the quantities of drug that can be loaded, issues of long-term biocompatibility and potential regulatory hurdles. The regulatory position may be more straightforward, however, for devices where solely drug elutes from the responsive polymer. Responsive systems therefore show great promise in delivering patient-specific responses, in direct line with their actual clinical need in terms of dose, timing and location. Chemically triggered erodible systems, which can rapidly degrade above a given pH, also offer promise as materials that, rather than changing physical dimensions, break into soluble, low-molecular-mass fragments, with a concomitant release of drug in a highly modulated manner.

The establishment of many of the classes of system described in this article in clinical practice will inevitably require regulatory hurdles to be overcome, but nonetheless there is significant potential for this field to deliver both a range of infection-resistant medical devices and patient-tailored therapy, where an individual's own clinical requirement feeds back to the dose delivered.

Declaration of interest

The authors state no conflicts of interest and have received no payment in the preparation of this manuscript.

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