

Progress in Active Ingredient Formulations

Towards smart stimuli-responsive formulations

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The formulation and delivery of the biologically active ingredients (AIs) (for example, agrochemicals and active pharmaceutical ingredients (APIs)) is an inherently interdisciplinary area of research and development. In this short review we discuss the evolution of AI and API delivery systems towards smart stimuli-responsive formulations with precisely controlled delivery for specific applications. We also highlight a few examples of such systems using AIs from Johnson Matthey's controlled substance and API portfolio.

Introduction

The study of medicine has a long history, with the first records of physicians in Egypt (Hesy-Ra the first recorded male physician in ca. 2700 BCE; Peseshet the first recorded female physician in ca. 2400 BCE)

and important examples of prescriptions for medications (for example the Ramesseum medical papyrus in ca. 1800 BCE; the Kahun Papyrus in ca. 1800 BCE; the Ebers Papyrus in ca. 1550 BCE and the Edwin Smith Papyrus, 1500 BCE) also from Egypt. Important contributions to medicine have been made by researchers worldwide, with Nobel Prizes in Physiology or Medicine awarded to researchers from Africa, Asia, Australasia, Europe, North America and South America (see **Table I**).

While early medications were all natural products, the industry supporting the production of medications on large scales is inextricably linked to the chemical sciences, with companies in Europe (for instance, Merck & Co, Bayer and BASF in Germany; Ciba-Geigy, Roche and Sandoz in Switzerland; and Beecham Group, GlaxoSmithKline, Burroughs and Wellcome in the UK) and the USA (Eli Lilly and company, Pfizer and Squibb) making important early contributions (1). While the scale of the industry and complex developments in regulations and mergers are outside the scope of this review, it is noteworthy that the industry has a hugely beneficial economic impact (worldwide the pharmaceutical industry employs millions of people and has a revenue that exceeded US\$1000 billion

Table I First Examples of Nobel Laureates in Physiology or Medicine from Specific Geographic Regions

Year	Laureate	Country	Justification	Geographic region
1901	Emil Adolf von Behring	Germany	For work on serum therapy	Europe
1902	Ronald Ross	UK, India	For work on malaria	Europe, Asia
1923	Fredrick Grant Banting, John James Rickard Macleod	Canada, UK	For the discovery of insulin	North America, Europe
1945	Alexander Fleming, Ernst Boris Chain, Howard Walter Florey	UK, Australia	For the discovery of penicillin	Europe, Australasia
1947	Carl Ferdinand Cori, Gery Theresa Cori, Bernardo Alberto Houssay	USA, Argentina	For their discovery of the course of the catalytic conversion of glycogen	North America, South America
1951	Max Theiler	South Africa	For discoveries concerning yellow fever and how to combat it	Africa

every year from 2014) and health and societal impacts (such as improvements in life expectancy).

The success of this industry is contingent on significant investment in research and development (R&D) processes (2). The bioactive molecule discovery process involves identification of lead compounds plus design and synthesis of variants to screen their therapeutic potential. The bioactive development process is used to establish the suitability of the bioactive manufacturing process, including: appropriate design of synthetic route answering such questions as whether it is affordable and if the building blocks are available from a reliable source, identification and toxicology of intermediates and impurities (3). Early stage bioactive discovery (technology readiness levels (TRLs) 1–4) is carried out by researchers in academia and industry; late stage development (particularly to increase the selectivity, bioavailability and therapeutic efficiency of the compounds) (4) is most often carried out by industry, with formulation studies and *in vitro* and *in vivo* validation studies carried out either in house or outsourced to an academic or industrial contractor prior to clinical trials in collaboration with health services (for example, the National Health Service (NHS) in the UK) and regulatory bodies depending on the specific market (5). The bioactive molecule industry is constantly evolving to deal with national and international regulations and the scrutiny of healthcare organisations (6). New synthetic strategies and analytical and computational techniques allow for the exploration of an ever-wider range of bioactives which pose both challenges and opportunities for companies active in this highly competitive market.

The remainder of this review will focus on the formulation of AIs in agrochemical and

pharmaceutical formulations (also known as active substances, bioactives, bulk actives, APIs and drugs), primarily for application to humans (cognisant of the vast market for formulations of bioactives for agrochemical and veterinary applications and different requirements in terms of formulation methodology and regulations).

API Delivery System Development

Organisms are controlled on the cellular level by a multitude of bioactive molecules. It is highly likely that throughout an organism's lifetime one of these systems will falter due to disease or injury and a therapeutic API could be employed to aid in the recovery of normal function (7). The complex nature of an organism's cells and physiology provide many opportunities for API intervention (for instance, specific intracellular functions) when required to affect the desired response (7). APIs have a therapeutic window (as depicted in **Figure 1**). Below the therapeutic window we observe the subtherapeutic region in which an API is ineffective at providing the desired effect, whereas above the therapeutic window unwanted side effects and toxicity may be observed (8).

The formulation of APIs to deliver quantities of the API within the therapeutic regime is of key importance to their clinical translation and success. Formulations can be divided into two broad categories: non-synthetic formulations (the most common) where the API is used unmodified in combination with other ingredients in order to achieve the desired effect (see **Table II** for examples); or synthetic formulations, where the API is synthetically modified to impart the desired properties, for example, prodrugs (14). Formulations need to be tailored to suit their route of administration such as inhalation, injection,

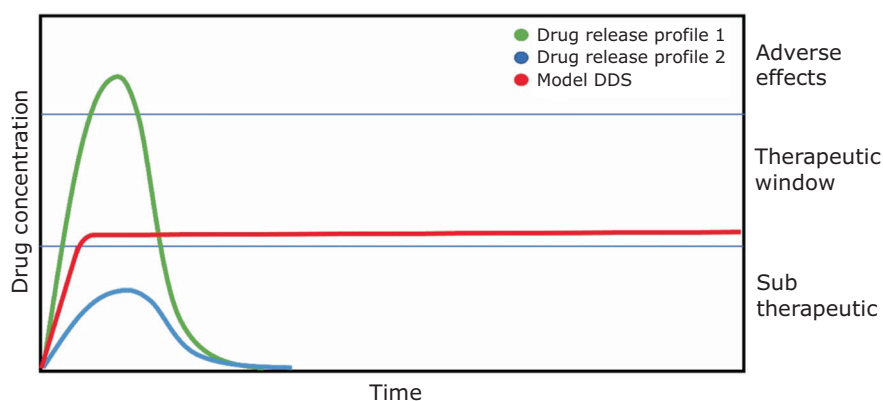


Fig. 1. Examples of release profiles

Table II Examples of Clinically Translated Stimuli-Responsive Formulation Systems

Stimulus	Treatment	Reference
Radiation	Radiotherapy	(9)
Light	Photodynamic therapy	(10)
Electricity	Electroconvulsive therapy	(11)
Ultrasound	Sonograms	(12)
Infrared	Thermography	(13)

oral or transdermal. For humans, oral intake is by far the most popular, providing fast release, cost effectiveness and relatively high patient compliance (15). The fast release provided by traditional methods of API delivery such as inhalation, injection, oral and transdermal can be beneficial for pain relief, however they often require the patient to take a relatively high dose of an API to ensure a small amount of the API reaches the desired location to elicit the desired therapeutic response (16). This may also result in issues related to API clearance from the body (metabolised or excreted *via* the renal system) which can limit the duration the API is within the therapeutic window. Other factors including the biological and physicochemical properties of the APIs (such as

solubility and absorption) (17, 18) and patient compliance (of growing importance with ageing populations worldwide) highlight the market need for controllable API delivery systems for medical or veterinary applications, similarly for agrochemical applications (19). Indeed, API delivery systems that reduce the number of administrations required offer potentially significant economic, health and societal impacts (20).

Researchers based in industry and academia have therefore invested significant effort in the development of API delivery systems to address these issues, which are often classified generationally, with first generation delivery systems developed between 1950–1980, second generation delivery systems developed between 1980–2010 and third generation delivery systems developed from 2010 onwards (21–23). The first case of controlled API release was published by Smith, Kline & French, USA, when they demonstrated the ability to release dextroamphetamine (**Figure 2**) over a 12 h period in 1952 (24). The success of this breakthrough prompted an investigation of new controlled API delivery systems designed to reduce intake to once or twice a day and mechanisms of API release (osmosis, ion-exchange, diffusion and

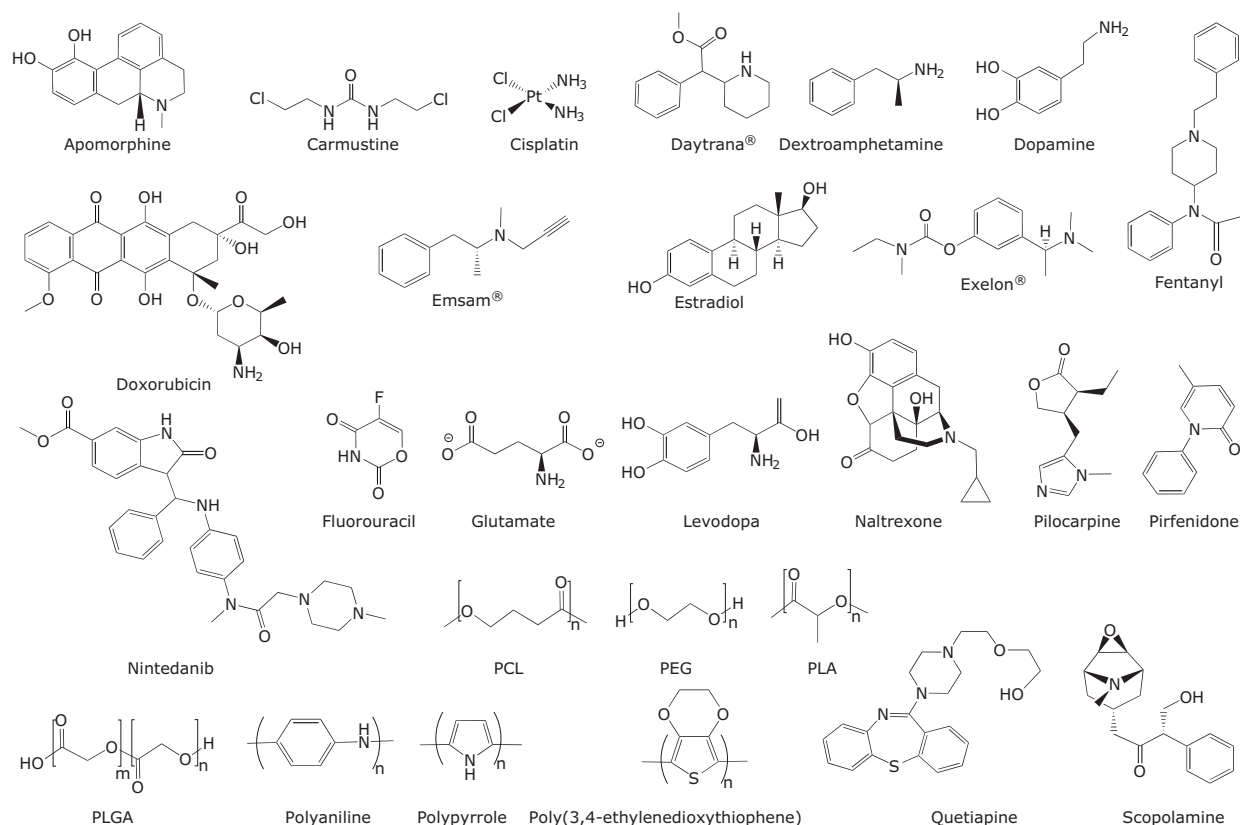


Fig. 2. Examples of chemical structures

dissolution) (25). By understanding these release mechanisms it was possible to begin to control the physicochemical characteristics of API delivery systems and thereby the release profiles of the APIs. While first generation API delivery systems delivered their payloads at a predetermined rate that was often short and did not account for patient needs or varying physiological conditions (8), second generation API delivery systems are characterised by attempts to control the level of API within target tissues above the minimum effective level for prolonged periods. The maintenance of the minimum effective level is important not only to ensure the benefit of the API to the patient over an extended period of time, but also to prevent the onset of side effects and immune responses. An interesting example of this is a formulation capable of sustained release of quetiapine (**Figure 2**, which is used in the treatment of schizophrenia) that has reduced the administration regime to a single dose per day, diminishing problems with patient compliance (26, 27).

Second generation API delivery systems also include examples capable of delivering high molecular weight APIs (peptides, proteins and DNA) potentially from hydrogel- or nanoparticle-based API delivery systems, that were optionally cell-targeted or stimuli-responsive (25). The third generation API delivery systems are characterised by efforts to: deliver poorly soluble APIs; tightly control release kinetics (for example *via* application of one or more external stimuli); and overcome biological barriers (such as the blood-brain barrier) (23, 25).

An ideal API delivery system would be a source of a specific amount of API to a precise location with temporal control, thereby allowing maintenance of a minimum effective level of the API for the duration required to have its therapeutic effect (illustrated in **Figure 1**) (28). Different situations require different API release profiles and application- or patient-specific API delivery profiles are desirable for the medical, veterinary and agrochemical industries (29).

API delivery systems incorporating polymers have been developed for first, second and third generation of delivery systems and polymers of various architectures are key components of both non-synthetic (such as aerosols, dispersions, emulsions, foams and suspensions) and synthetic formulations (for instance, as a polymer prodrug). The pioneering research of Robert Langer and coworkers underpins the

development of polymer-based drug delivery systems (DDS) in academic and industrial settings (30–32). Polymer chemistry and engineering to tailor the structures of polymers for specific applications is an area of intense ongoing research interest (33), particularly with a view to developing API delivery systems that provide control over the quantity, location and time of API delivery (34).

Polymer-based API delivery systems can enhance the duration of activity for APIs with short half-lives (28). API delivery systems that encapsulate a payload of API and break down at a predictable rate can be utilised for a variety of therapeutic agents, particularly when displaying a moiety that targets the API to specific cells or tissues (35). Poly(ethylene glycol) (PEG, **Figure 2**) is a polymer often conjugated to macromolecular APIs (commonly known as PEGylation) (36) to enhance their half-lives by reducing their rate of clearance *via* the renal system and eliciting minimal inflammatory response (37).

The utilisation of biodegradable and bioerodible polymers such as poly(caprolactone) (PCL, **Figure 2**), poly(D,L-lactic-co-glycolic acid) (PLGA, **Figure 2**) and PEG that respond to enzymes such as esterases and lipases are now very popular as a result of their biocompatibility *in vivo* reducing the immune response and averting systemic toxicity (38, 39). Cisplatin (**Figure 2**) (40) is a common anticancer API that has proved effective in the treatment of a variety of tumours however its inherent toxicity and resistance limitations have prevented the full potential of this API being reached (41). A recent study into the construction of platinum(IV)-encapsulated prostate-targeted nanoparticles of PLGA-PEG functionalised with prostate-specific membrane antigen (PSMA) targeting aptamers was found to help optimise the delivery of a lethal dose of cisplatin to prostate cancer cells (41). The use of these polymeric agents in this manner not only provides controlled breakdown of the DDS giving slow release of the API but also provides specific targeting of cancer cells.

Other physicochemical triggers (for instance, pH) are also of interest for API delivery systems. Cancer cells are associated with a lower pH (normally *ca.* 5/6) than normal cells thus making pH sensitive API delivery systems desirable as damage to healthy cells can be minimised (42). Likewise, the acidic milieu within dental caries-producing biofilms are another situation in which pH can be a useful trigger for oral drug delivery (43).

API Delivery Systems for Specific Contexts

Oral API Delivery Systems

Oral administration of APIs necessitates the stability of the API and its respective acidic and basic components in the digestive tract and effective permeation of cell membranes (44). Ion-exchange systems have been investigated for their ability to act as API delivery systems, wherein once the API reaches the gastrointestinal tract the body's salts displace the API allowing it to pass through the cell membrane in a controlled manner (20). However, human physiology makes API delivery *via* gastrointestinal (GI) tract challenging (45). The short GI transit time (*ca.* 12 h) makes the delivery of macromolecular therapeutics such as proteins and nucleic acids difficult (45). The limitations of API delivery in the GI tract (44) have helped to shape the development of polymer-based API delivery systems to deliver macromolecules such as insulin orally or *via* inhalation (46, 47).

An ideal API delivery system would allow a patient to monitor and administer drugs (such as insulin) on demand with control over the dose and no need for invasive injections. Variations of these are currently being developed for the self-regulated treatment of diabetes (48).

Transdermal API Delivery Systems

Transdermal patches were amongst the first systems to be available to patients with APIs being attached to an adhesive patch before delivering a specific dose through the patient's skin and into the bloodstream (49). Transdermal patches enable controlled release *via* a porous membrane slowly releasing an API from a reservoir within the patch. The first transdermal patch was FDA approved in 1979 for the delivery of prescription API scopolamine (**Figure 2**) for the treatment of motion sickness (50). Nowadays, many APIs are administered *via* transdermal patches (for example, Daytrana[®], EMSAM[®], Exelon[®] and fentanyl, **Figure 2**) covering a wide range of medical conditions from Alzheimer's to attention deficit hyperactivity disorder (ADHD) (51).

Whilst API delivery from transdermal patches is effective, the skin is a barrier to entry from external bodies which results in a high proportion of the API being prevented from entering the body and a reduced therapeutic efficiency (49). One solution to this problem is the utilisation of chemical enhancers (49) to alter the permeability

of an API, for example, the skin permeability of oestradiol (**Figure 2**) can be increased twenty-fold *via* formulation with ethanol (52). A common side effect of the use of chemical enhancers is skin irritation at the site of the patch which may make the use of the enhancer non-viable. Another method is to chemically modify the structure of the API to improve its permeability; however, this can be difficult, expensive and time consuming (53). The use of arrays of microneedles for transdermal delivery is increasingly popular because of their broad applicability and minimal pain (54).

The use of microneedles in drug delivery began in the 1990s as a result of the emergence of microfabrication techniques that enable their manufacture (55). Microneedles are used in a variety of medical systems including skin pre-treatment for increased permeability, drug coated needles and drug encapsulated needles (55). Microneedles are now widespread in drug delivery having shown the ability to give controlled release of a wide range of low molecular weight drugs and vaccines (55). The delivery of the influenza vaccine using a microneedle is common in modern medicine (56). Microneedle delivery depends on a variety of factors including skin permeation, drug stability, drug storage and patient response (55). This emerging field of medicinal chemistry shows great promise in forwarding the field of drug delivery.

Injectable and Implantable API Delivery Systems

Injectable and implantable API delivery systems are particularly useful for conditions requiring the delivery of APIs to specific sites within the organism. Many APIs suffer from an inability to reach the required site of action due to a biological barrier (for example, the blood-brain barrier). Parkinson's disease caused by dopamine deficiency cannot be treated by administration of dopamine because it does not cross the blood-brain barrier, however, the prodrug levodopa (**Figure 2**) is capable of crossing the blood-brain barrier after which it is metabolised to dopamine (**Figure 2**) (57).

Likewise, <2% of the administered dosage of naltrexone (**Figure 2**), an API used in the treatment of opioid dependence reaches the brain and naltrexone-polymer conjugates can increase the amount of API working at the site of action resulting in US Food and Drug Administration (FDA) approval for use for the treatment of alcohol dependence (2006) and opioid dependence (2010) (58).

Implanting API delivery systems at or near the desired site helps to maximise local delivery and minimise undesirable side effects. A polymer-based API delivery system known as Ocusert which controls the release of pilocarpine (**Figure 2**) and reduces pressure in the eyes (59); implantation of pilocarpine encapsulated between two polymer membranes controlled the release at a rate of 20 mg h⁻¹ for up to a week (59). Several polymeric versions of the Ocusert delivery system exist, all capable of delivering pilocarpine in a controlled manner with differing release profiles. Early uses of this system were limited by poor biodegradability, however, new formulations of biodegradable polymers have helped to improve degradation profiles (60).

Biodegradable polymers (such as poly(anhydrides) and polyesters) used for polymer-based API delivery systems can slowly degrade and release APIs (for example, carmustine (**Figure 2**) a chemotherapeutic treatment for brain cancer) and carmustine-loaded polyanhydride films directly at the tumour site were shown to significantly improve patient survival rates when treating glioblastoma multiforme (61).

PGLA has also been used in the controlled delivery of the API apomorphine (**Figure 2**) which is used in the treatment of Parkinson's disease (62). Apomorphine has poor oral availability and a short half-life, resulting in multiple administrations being required which limits its widespread usage, therefore controlled release methods are used to overcome this shortcoming (62). The use of PGLA prevents the burst release of apomorphine and increases longevity of the API within the target tissues (62). This system demonstrated controlled release of the API over ten days, releasing 90% of the payload.

Stimuli-Responsive API Delivery Systems

The investigation of smart devices in medicine has probed the use of API delivery systems that can control API release using an external stimulus or by interactions between the API delivery systems and changes in their environment. By implanting a biocompatible device within the patient and then triggering API release externally, the patient would be provided with the therapeutic benefit over an extended period of time. An ideal API delivery system would allow control of the dosage, timing, duration and site of API release, resulting in delivery of the therapeutic agent in a remote and non-invasive manner. A range of stimuli can be used to

trigger API release including pH, infrared (IR) (63), ultraviolet (UV)-visible light (64, 65) magnetism (66), temperature (67), ultrasound (68), electric fields (69) and radiation (70). Many of these stimuli are already utilised in clinically translated API delivery systems (**Table II**). The development of API delivery systems that respond to these stimuli and provide the controlled release of loaded APIs potentially improves treatment efficiency and diminishes or prevents the onset of side effects. There are API delivery systems that respond to multiple stimuli to further improve selectivity for specific functions (71), see below for a fuller discussion.

Another emerging aspect of formulation science involves the use of shape memory materials (SMMs). SMMs demonstrate plastic deformation when stimulated by an external stimulus and return to their original shape upon removal of the stimuli (72). Shape memory polymers (SMPs) are stimuli responsive compounds which are able to demonstrate mechanical action in response to a range of stimuli depending on the material make up. SMPs offer a range of advantages including; wide glass transition states, tailored stiffness, high shape recovery, high elastic deformation, biodegradability, biocompatibility and low thermal conductivity (72). The ability of these materials to assume a specific shape upon triggering can be utilised for drug delivery. PCL and poly(lactide) (**Figure 2**) are often utilised in medical SMPs as they have distinctive glass transition states and are inherently biodegradable and biocompatible (73). The use of these polymers in SMPs can assist in drug delivery *via* two mechanisms: either the shape recovery of the polymer enhances drug release or the polymer facilitates delivery of the drug delivery device to the body in a minimally invasive manner (73). The incorporation of a drug into a SMP delivery system has been demonstrated to affect performance of the DDS however controlled release is still possible. The use of SMPs in urethral stents has been demonstrated using the SMP as a method of controlled release of anti-inflammatory drugs (74). This method demonstrated the ability of SMPs to show controlled release of a drug and upon completion degradation into non-toxic products (74). This example highlights the potential use of SMPs in drug delivery and wider medicinal applications (75).

Light-Responsive API Delivery Systems

Light triggered API delivery systems are very popular in the literature due to their ability to

provide temporal and spatial control, functioning *via* various mechanisms including photochemical, photoisomerisation and photothermal (76). Photodynamic therapy (PDT) is one of the most well-established techniques and uses light in the UV-visible spectrum to treat skin and throat cancers (77). PDT is less effective when attempting to affect deeper set tumours such as prostate and liver cancers for which light in the IR spectrum is preferable as a result of its relatively low absorption by mammalian tissues (63).

Photochemical API delivery systems release a therapeutic payload upon covalent bond cleavage in response to light irradiation (76). An example of such chemistry is the cleavage of an *o*-nitrobenzyl ester derivative releasing a carboxylic acid (Figure 3). The carboxylic acid-displaying molecule was released over several hours at surface power of 1.3 mW cm^{-2} , however when increasing the power to 20 mW cm^{-2} release was only observed over 5 min (78). This system demonstrates a high degree of control that shows promise in being utilised in API delivery studies.

A library of photo-responsive units have been explored for API delivery including coumarin, pyridylmethyl esters and porphyrins, all of which contain readily cleavable covalent bonds (79). Photo-responsive API delivery systems function on the requirement of light with a wavelength that possess sufficient energy per photon to affect the breakage of covalent bonds (80), making UV (81) and visible light (79) popular triggers. One of the most prevalent problems with light triggered API delivery systems is the relatively poor tissue penetration of UV and visible light, this has been addressed by the development of near-infrared (NIR) API delivery systems (82). NIR is only fractionally adsorbed by biological tissues thus allowing it to trigger API release in deeper areas of the body (82). Almutairi *et al.* report the use of a UV responsive nanoparticle DDS in which nintedanib (Figure 2), a drug used in the treatment of idiopathic pulmonary fibrosis, is released over ten weeks (83). The nanoparticles were shown to

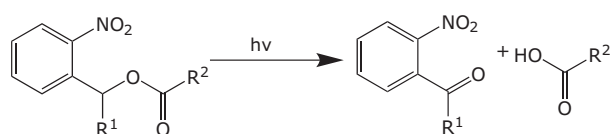


Fig. 3. Photochemical cleavage of an *o*-nitrobenzyl ester yielding an *o*-nitrosobenzaldehyde derivative and an API displaying a carboxylic acid

be biocompatible with no adverse effects observed despite the extended period of implantation (83).

Photo-responsive hydrogel-based API delivery systems (84) offer the opportunity to deliver sensitive bioactive macromolecules (84) and minimise the body's immune response. A recent trend in the literature points towards the development of systems that do not require the use of UV as a result of the risk it poses to the skin and eyes. The use of NIR and visible light triggered systems are increasingly popular in photochemical API delivery due to reduced risk associated with these triggers (85).

Whilst a great deal of progress has been made in the field of photochemical API delivery many problems still persist and must be overcome before these systems are fully utilised in modern medicine. Early attempts at photochemical triggering often resulted in one effective dosage of the API before the system is empty, however new innovative systems have demonstrated pulsatile delivery with few adverse effects. Tissue penetration is still a problem in this field with visible light-based systems limited to the skin, throat and nose (63). As with all new systems being introduced to the body, biocompatibility is a huge stumbling block. Even the most biocompatible systems generate some form of immune response, sometimes in the form of inflammation but others can be more serious and so systems must be vetted fully before use. Despite these problems, photochemical API delivery remains a very popular research area with huge progress being made throughout this field.

Electro-Responsive API Delivery Systems

Early attempts to develop stimuli responsive systems included the development of conducting polymers which were theorised to be able to release an API upon triggering with an electrical stimulus. Polypyrrole (PPy) in its conducting (oxidised) form allows oppositely charged ions to be doped into the polymer backbone which was pioneered by the Miller Group in 1984, who demonstrated their ability to release glutamate ions (Figure 2) *via* the reduction of PPy (Figure 4) films (86). The cationic PPy is doped with anionic or neutral API molecules. When an electric current is applied to the system the polymer changes redox state and the API is released in order to charge balance the system (87).

The sensitivity of electroactive species can be manipulated to create a range of API release

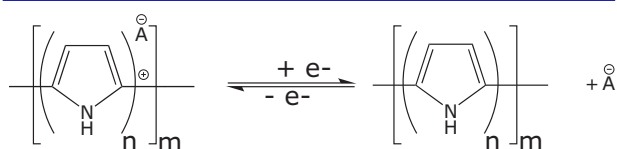


Fig. 4. Redox switching of PPy releasing API dopants

profiles through redox switching. Despite the widespread usage of PPy as an API delivery agent it is difficult to process due to its poor solubility in most solvents. Many attempts have been made to improve the solubility of PPy with limited success (88). PPy is also non-biodegradable and therefore can be difficult to remove from the patient's system once all the loaded API has been used (89). The success of utilising PPy films as API delivery agents prompted an investigation into other polymers such as polyaniline (PANI, **Figure 2**) (90) and poly(3,4-ethylenedioxythiophene) (PEDOT, **Figure 2**) (91) with varying degrees of success. The biocompatibility of the polymers and the amount and molecular weight of API that can be loaded onto these films are areas of current research (92, 93), as is the generation of biodegradable versions (94, 95).

Multi-Responsive API Delivery Systems

Whilst single stimuli responsive systems are very useful, they are restricted to certain release profiles based on the stimuli in question. The complex nature of the human body and the conditions which affect it often require additional more complex solutions than single stimuli-responsive DDS. Multi-stimuli responsive DDS are being explored for their ability to create more varied release profiles, providing an improvement in tuneability and selectivity *versus* single responsive systems (96). In theory multi-responsive DDS allow for the treatment of a wider range of complex conditions by regulating release by one or more stimuli based on patient needs (96).

When constructing multi-responsive DDS separate units, each of which is responsive to a specific stimulus, are blended together without affecting each unit's responsiveness. Several systems are currently in development based on the ability of one stimulus to act as a targeting moiety whilst the other stimuli are responsible for producing a response in the desired tissue.

pH is one of the most commonly used stimuli in dual responsive DDS. The ability of these systems to be

selective based on the targeting of the lower pH of cancer cells makes them desirable in modern cancer treatments (97–100). pH is often combined with a variety of other stimuli including light, electricity and magnetism to create a desired response in cancerous tissues. pH and light responsive materials are popular dual responsive DDS. Nie *et al.* have demonstrated the ability of these systems to show controlled release of the chemotherapy agent doxorubicin hydrochloride (**Figure 2**) *via* photothermal drug release (101). The use of a pH responsive group ensured selectivity towards cancer cells over healthy cells with an NIR responsive group providing photothermal release of doxorubicin hydrochloride in a controlled manner (101).

Dual responsive DDS which incorporate multiple stimuli capable of creating the desired drug release response are less common, however several examples exist in the literature. Argouz *et al.* have developed such a system with the use of sodium alginate gel beads in a pH or magnetic drug release system (102). In this system pH sensitive sodium alginate is combined with methyl cellulose which has shown to be responsive to magnetic fields. Sodium alginate is a biodegradable, biocompatible, non-toxic polysaccharide and can be readily modified making it a useful tool in drug delivery (103). It has been combined with chitosan, pectin and gelatin for use in drug delivery with all systems displaying a high degree of biocompatibility (103). The resulting material has demonstrated the ability to show controlled release of the anticancer drug 5-fluorouracil (**Figure 2**) over extended periods of time (102). This system is comprised of both a targeting stimulus and two active delivery stimuli providing a high degree of impact when attempting to affect cancer tissues.

Kyriakides *et al.* took a different approach to multi-responsive DDS being able to generate constructs *via* simultaneous electrospinning and electrospaying, generating compartmentalised storage of multiple drugs (104). The use of this method provides a PCL fibre structure with a hyaluronic acid core, allowing drugs to be loaded in the polymer film (104). Further studies have shown the ability to trap other spheres of drug within an electrospun mat, allowed for delivery of multiple drugs with differing solubilities demonstrating various release profiles (104). A minimal immune response was found when using pirfenidone (**Figure 2**), an anti-fibrotic drug, in one of the release compartments (104).

Multi-responsive systems are becoming more prevalent in the literature with many systems

demonstrating effectiveness in drug delivery, particularly when attempting to affect cancerous tissues. This field will continue to grow as scientists find more ways to incorporate more stimuli into existing systems, providing ample opportunity to treat a variety of conditions and improve patient care. Some examples for APIs displayed in **Figure 5** and **Figure 6** are highlighted in **Table III**.

Future Outlook and Conclusions

Significant progress has been made in the field of API delivery over the past sixty years and the scope of controlled API delivery systems has greatly increased. Many challenges still remain in this field, such as delivering APIs to specific cells, targeting genes and designing systems to cross complex barriers such as the blood-brain barrier (42). New materials are being developed aimed at improving biocompatibility, generating new release profiles and improving patient care (142). Continued investment and effort in this field will lead to the development of API delivery systems capable of the delivery of APIs to specific tissues to the benefit of patients and the healthcare industry.

Advancements in the field of API delivery and controlled release have had a direct impact on other fields of chemistry such as synthetic and polymer chemistry, chemical engineering, materials science, chemical biology and bioengineering (33). Many API delivery systems exist generating a variety of release profiles and targeting different conditions. Conditions can now be treated at the required site of action leading to more effective treatments and broadening our understanding of biological mechanisms that affect diseases. Despite the increase of treatments and the deepening of our understanding of API release, clinical needs are still unmet and many challenges still remain. Administrative demand has forced new methods of API delivery to be formulated that protect sensitive molecules as well as targeting deep set regions of the body which are often unreachable by oral delivery systems. Advances in synthetic chemistry have allowed for the development of new classes of therapeutic agents that aim to address administrative demands and in tandem with materials science, have allowed release of APIs to occur over extended periods to treat chronic conditions.

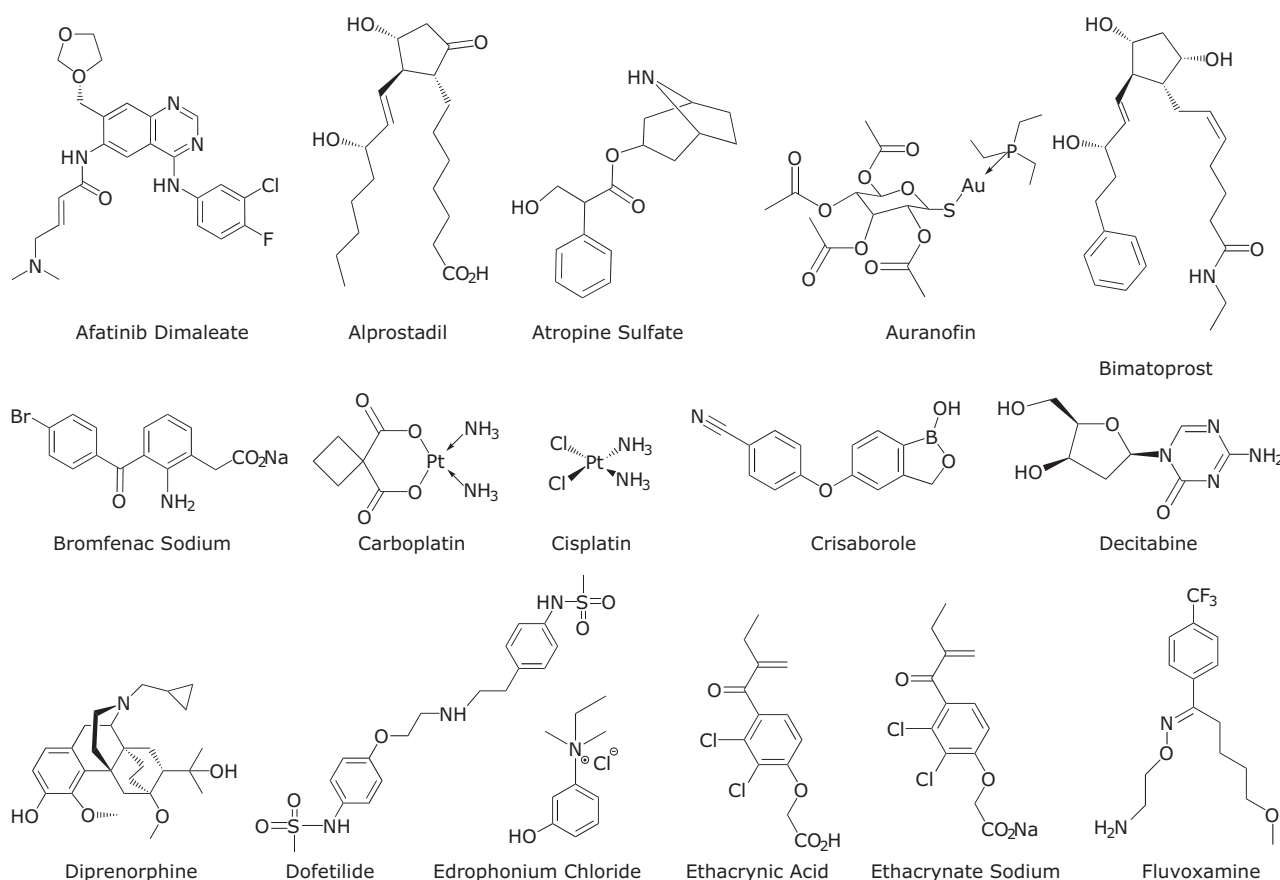


Fig. 5. Examples of APIs formulated in controlled delivery systems highlighted in Table III

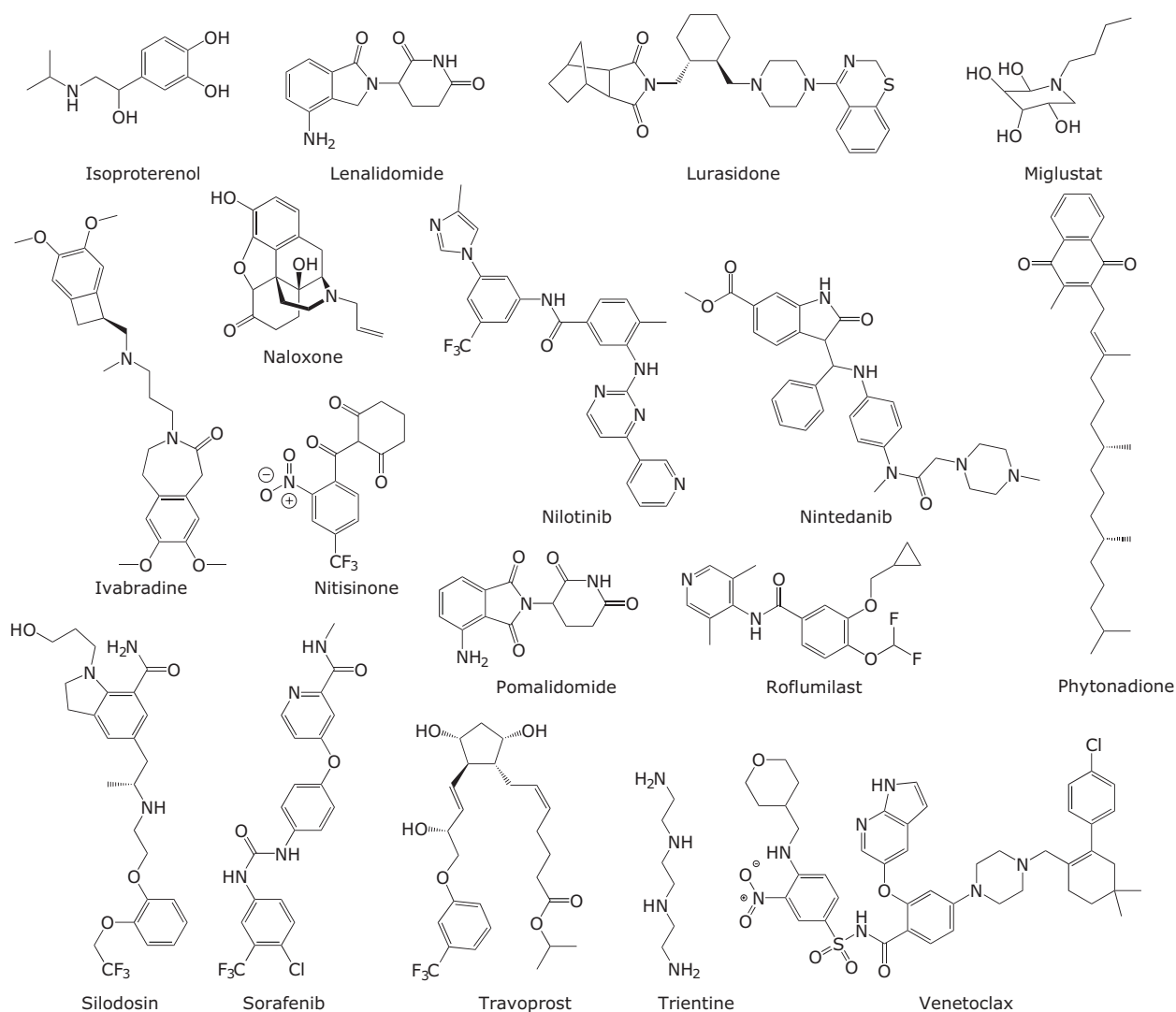


Fig. 6. Examples of APIs formulated in controlled delivery systems highlighted in Table III

Table III Examples of API Formulations

API	CAS number	Shown in figure number	Examples	Reference
Afatinib dimaleate	850140-72-6	Figure 5	Injection	(105)
Alprostadil	745-65-3	Figure 5	N/A	-
Apomorphine hydrochloride	41372-20-7	Figure 2	Various	(106, 107)
Atropine sulfate	5908-99-6	Figure 5	Inhaler	(108)
Auranofin	34031-32-8	Figure 5	Oral	(109)
Bimatoprost	155206-00-1	Figure 5	Implant	(110)
Bromfenac sodium	120638-55-3	Figure 5	N/A	-
Carboplatin	41575-94-4	Figure 5	Oral	(111)
Carmustine	154-93-8	Figure 2	Implant	(112)
Cisplatin	15663-27-1	Figure 2	Various	(113, 114)
Crisaborole	906673-24-3	Figure 5	N/A	-
Decitabine	2353-33-5	Figure 5	Various	(115)
Diprenorphine	14357-78-9	Figure 5	N/A	-
Dofetilide	115256-11-6	Figure 5	Oral	(116)
Edrophonium chloride	116-38-1	Figure 5	Various	(117, 118)

(Continued)

Table III Continued

API	CAS number	Shown in figure number	Examples	Reference
Ethacrynic acid	58-54-8	Figure 5	Various	(119)
Ethacrynate sodium	6500-81-8	Figure 5	Various	(103)
Fluvoxamine maleate	54739-20-7	Figure 5	Oral	(120)
Isoproterenol hydrochloride	51-30-9	Figure 6	Oral	(121)
Ivabradine hydrochloride	148849-67-6	Figure 6	Implant	(122)
Lenalidomide	191732-72-6	Figure 6	Oral	(123)
Lurasidone hydrochloride	367514-88-3	Figure 6	Oral	(124)
Miglustat	72599-27-0	Figure 6	Inhaler	(125)
Naloxone hydrochloride dihydrate	51481-60-8	Figure 6	Hydrogel	(126)
Naltrexone hydrochloride	16676-29-2	Figure 2	Various	(127)
Nilotinib	641571-10-0	Figure 6	N/A	–
Nintedanib	656247-17-5	Figure 6	Various	(128, 83)
Nitisinone	104206-65-7	Figure 6	Various	(129, 130)
Phytonadione	84-80-0	Figure 6	Various	(131)
Pirfenidone	53179-13-8	Figure 2	Various	(132, 133)
Pomalidomide	19171-19-8	Figure 6	Various	(134)
Roflumilast	162401-32-3	Figure 6	Various	(135, 136)
Silodosin	160970-54-7	Figure 6	N/A	–
Sorafenib	284461-73-0	Figure 6	Various	(137–139)
Travoprost	157283-68-6	Figure 6	Implant	(110, 140)
Trientine hydrochloride	38260-01-4	Figure 6	Oral	(141)
Venetoclax	1257044-40-8	Figure 6	N/A	–

The field of controlled delivery of APIs is broadening with new emerging concepts such as systems based on three-dimensional (3D) printed technologies and gene delivery systems becoming useable alternatives (143).

It is important that we continue to strive for a greater understanding of the human body and the DDS we are trying to input. We can begin to exploit expressions exhibited by specific diseases to improve targeting and tailor our systems to maximise therapeutic efficiency. The field of API delivery forms the intersection of chemistry, materials science, medicine and bioengineering. This has proved to be an extremely fruitful area with wide scope for exciting future work.

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