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Progress in Active Ingredient Formulations

Towards smart stimuli-responsive formulations

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ABSTRACT

The formulation and delivery of the biologically active ingredients (AIs) (e.g. agrochemicals and pharmaceuticals, active pharmaceutical ingredients (APIs)) is an inherently interdisciplinary area of research and development. In this short review we discuss the evolution of AI/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 B.C.E.; Peseshet the first recorded female physician in ca. 2400 B.C.E.), and important examples of prescriptions for medications (e.g. the Ramesseum medical papyrus in ca. 1800 B.C.E; the Kahun Papyrus in ca. 1800 B.C.E.; the Ebers Papyrus in ca. 1550 B.C.E., and the Edwin Smith Papyrus, 1500 B.C.E.) also from Egypt. Important contributions to medicine have been made by researchers worldwide, with Nobel Prizes in

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Physiology or Medicine awarded to researchers from Africa, Asia, Australasia, Europe, North and South America (see **Table I**).

Insert Table I here.

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 (e.g. Merck, Bayer and BASF in Germany; CIBA-Geigy, Roche and Sandoz in Switzerland; and Beecham, Glaxo, Burroughs and Wellcome in the UK) and the United States (Eli Lilly, 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 1,000 Billion US dollars revenue every year from 2014), and health and societal impacts (improvements in life expectancy, etc.).

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, design and synthesis of variants to screen their therapeutic potential. Whereas the bioactive development process is used to establish the suitability of the bioactive manufacture process (appropriate design of synthetic route [answering such questions as: is it affordable? are the building blocks available from a reliable source?], identification and toxicology of intermediates and impurities, etc.) (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

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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/industrial contractor prior to clinical trials in collaboration with health services (e.g. the National Health Service in the UK) and regulatory bodies depending on the specific market (5). The bioactive molecule industry is constantly evolving to deal with national/international regulations and the scrutiny of healthcare organisations (6). New synthetic strategies and analytical/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 the biologically active ingredients (AIs) in agrochemical and pharmaceutical formulations (also known as active substances, bioactives, bulk actives, active pharmaceutical ingredients (APIs) and drugs), primarily for application to humans (cognizant 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 (e.g. 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/physiology provide many opportunities for API intervention (e.g. specific intracellular functions) when required to affect the desired response (7). APIs have a

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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).

Insert Figure 1 here.

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 2 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 (e.g. prodrugs) (9). Formulations need to be tailored to suit their route of administration (e.g. inhalation, injection, oral, transdermal, etc.), and for humans oral intake is by far the most popular, providing fast release, cost effectiveness and relatively high patient compliance (10). The fast release provided by traditional methods of API delivery (e.g. inhalation, injection, oral, transdermal, etc.) can be beneficial (e.g. 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 (11), which 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/physicochemical properties of the APIs (e.g. solubility, absorption) (12, 13) and patient compliance (of growing importance with ageing populations worldwide) highlight the market need for controllable API delivery

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systems for medical/veterinary applications (similarly for agrochemical applications) (14). Indeed, API delivery systems that reduce the number of administrations required offer potentially significant economic, health and societal impacts (15).

Insert Table II here.

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 1st generation delivery systems developed between 1950-1980, 2nd generation delivery systems developed between 1980-2010, and 3rd generation delivery systems developed from 2010 onwards (16-18). The first case of controlled API release was published by Smith Kline & French when they demonstrated the ability to release dextroamphetamine (**Figure 2**) over a 12 hour period in 1952 (19). 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 dissolution) (20). By understanding these release mechanisms it was possible to begin to control the physiochemical characteristics of API delivery systems and thereby the release profiles of the APIs. While 1st 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), 2nd 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 which 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 (21, 22).

Insert Figure 2 here.

2nd generation API delivery systems also include examples capable of delivering high molecular weight APIs (e.g. peptides, proteins, DNA, etc.) potentially from hydrogel- or nanoparticle-based API delivery systems, that were optionally cell-targeted or stimuli-responsive (20). The 3rd generation API delivery systems are characterised by efforts to: deliver poorly soluble APIs; tightly control release kinetics (e.g. via application of one or more external stimuli); and overcome biological barriers (e.g. the blood-brain barrier) (18, 20).

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 2) (23). Different situations require different API release profiles, and application-/patient-specific API delivery profiles are desirable for the medical, veterinary and agrochemical industries (24).

API delivery systems incorporating polymers have been developed for 1st, 2nd and 3rd generation of delivery systems, and polymers of various architectures are key components of both non-synthetic (e.g. aerosols, dispersions, emulsions, foams, suspensions) and synthetic formulations (e.g. as a polymer prodrug). The pioneering research of Robert Langer and co-workers underpins the development of polymer-based drug delivery systems in academic and industrial settings (25-27). Polymer

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chemistry/engineering to tailor the structures of polymers for specific applications is an area of intense ongoing research interest (28), particularly with a view to developing API delivery systems that provide control over the quantity/location/time of API delivery (29).

Polymer-based API delivery systems can enhance the duration of activity for APIs with short half-lives (23). 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/tissues (30). Poly(ethylene glycol) (PEG, **Figure 2**) is a polymer often conjugated to macromolecular APIs (commonly known as PEGylation) (31) to enhance their half-lives by reducing their rate of clearance via the renal system and eliciting minimal inflammatory response (32).

The utilisation of biodegradable/bioerodible polymers such as poly(caprolactone) (PCL, **Figure 2**), of poly(D,L-lactic-co-glycolic acid) (PLGA, **Figure 2**) and poly(ethylene glycol) (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 (33-34). Cisplatin (**Figure 2**) (35) 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 (36). A recent study into the construction of Platinum(IV)-encapsulated prostate-targeted nanoparticles of poly(D,L-lactic-co-glycolic acid)-poly(ethylene glycol)-functionalized with prostate-specific membrane antigen (PSMA) targeting aptamers was found to help optimize the delivery of a lethal dose of cisplatin to prostate cancer cells (36).

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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 targeted specific targeting the cancer cells.

Other physicochemical triggers (e.g. 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 minimized (37). Likewise, the acidic milieu within dental caries-producing biofilms are another situation in which pH can be a useful trigger for oral drug delivery (38).

API Delivery Systems For Specific Contexts

Oral API Delivery Systems

Oral administration of APIs necessitates the stability of the API in the digestive tract (and its respective acidic and basic components), and effective permeation of cell membranes (39). 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 (15). However, human physiology makes API delivery via gastrointestinal (GI) tract challenging (40). The short GI transit time (ca. 12 hours) makes the delivery of macromolecular therapeutics such as proteins and nucleic acids difficult (40). The limitations of API delivery in the GI tract (39) have helped to shape the development of polymer-based API delivery systems to deliver macromolecules such as insulin orally or via inhalation (41, 42).

An ideal API delivery system would allow a patient to monitor and administer drugs (e.g. insulin) on demand with control over the dose and no need for invasive

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injections, and variations of these are currently being developed for the self-regulated treatment of diabetes (43).

Transdermal API Delivery Systems

Transdermal patches were amongst the 1st 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 (44). 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 (45). Nowadays, many APIs are administered via transdermal patches (e.g. daytrana, emsam, exelon and fentanyl, **Figure 2**) covering a wide range of medical conditions from Alzheimer's to attention deficit hyperactivity disorder (ADHD) (46).

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 (44). One solution to this problem is the utilisation of chemical enhancers (44) to alter the permeability of an API, for example, the skin permeability of estradiol (**Figure 2**) can be increased 20-fold via formulation with ethanol (47). 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 (48); and the use of arrays of microneedles for transdermal delivery is increasingly popular because of their broad applicability and minimal pain (49).

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The use of microneedles in drug delivery began in the 1990's as a result of the emergence of microfabrication techniques that enables their manufacture (50). Microneedles are used in a variety of medical systems including; skin pre-treatment for increased permeability, drug coated needles and drug encapsulated needles (50). 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 (50). The delivery of the influenza vaccine using a microneedle is common in modern medicine (51). Microneedle delivery depends on a variety of factors including, skin permeation, drug stability, drug storage and patient response (50). 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 (e.g. 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**) (52).

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 FDA approval for use for the treatment of alcohol dependence (2006) and opioid dependence (2010) (53).

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 (54); implantation of pilocarpine encapsulated between two polymer membranes controlled the release at a rate of 20 mg/hour for up to a week (54). 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 (55).

Biodegradable polymers (such as poly(anhydrides), polyesters, etc.) used for polymer-based API delivery systems can slowly degrade and release APIs (e.g. 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 (56).

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 (57). 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 (57). The use of PGLA prevents the burst release of Apomorphine and increases longevity of the API within the target

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tissues (57) This system demonstrated controlled release of the API over 10 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) (58), UV-visible light (59, 60) magnetism (61), temperature (62), ultrasound (63), electric fields (64) and radiation (65). 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/prevents the onset of side effects, and there are API delivery systems that respond to multiple stimuli to further improve selectivity for specific functions (66), see below for a fuller discussion.

Another emerging aspect of formulation science involves the use of shape memory materials (SMM's). SMM's demonstrate plastic deformation when stimulated by an external stimulus and return to their original shape upon removal of the stimuli (67). Shape memory polymers (SMP's) are stimuli responsive compounds which are able to demonstrate mechanical action in response to a range of stimuli depending

on the material make up. SMP's offer a range of advantages including; wide glass transition states, tailored stiffness, high shape recovery, high elastic deformation, biodegradability, biocompatibility and low thermal conductivity (67). 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 SMP's as they have distinctive glass transition states and are inherently biodegradability and biocompatibility (68). The use of these polymers in SMP's can assist in drug delivery via two mechanisms, either; the shape recovery of the polymer enhances induces drug release or the polymer facilitates delivery of the drug delivery device to the body in a minimally invasive manner (68). 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 SMP's in urethral stents has been demonstrated using the SMP as a method of controlled release of anti-inflammatory drugs (69). This method demonstrated the ability of SMP's to show controlled release of a drug and upon completion degradation into non-toxic products (69). This example highlights the potential use of SMP's in drug delivery and wider medicinal applications (70).

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, photoisomerization and photothermal (71). 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 (72). 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 (58).

Photochemical API delivery systems release a therapeutic payload upon covalent bond cleavage in response to light irradiation (71), an example of such chemistry is the cleavage of an *o*-nitrobenzyl ester derivative releasing a carboxylic acid (**Figure 3**), which release the carboxylic acid-displaying molecule over several hours at surface power of 1.3 mW/cm^2, however when increasing the power to 20mW/cm^2 release was only observed over 5 minutes (73). This system demonstrates a high degree of control that shows promise in being utilised in API delivery studies.

Insert Figure 3 here.

A library of photo-responsive units have been explored for API delivery studies including coumarin, pyridylmethyl esters and porphyrins, all of which contain readily cleavable covalent bonds (74). 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(75), making UV (76) and visible light (74) 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 (77). NIR is only fractionally adsorbed by biological tissues thus allowing it to trigger API release in deeper areas of the body (77). 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 10 weeks (78). The

nanoparticles were shown to be biocompatible with no adverse effects observed despite the extended period of implantation (78).

Photo-responsive hydrogel-based API delivery systems (79) offer the opportunity to deliver sensitive bioactive macromolecules (79) 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 reduced risk associated with these triggers (80).

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 etc. (58). 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 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 a API upon

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triggering with an electrical stimulus. 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 Polypyrrole (PPy, **Figure 4**) films (81). The cationic PPy is doped with anionic/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 (82).

Insert Figure 4 here.

The sensitivity of electroactive species can be manipulated to create a range of API release 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 (83). PPy is also non-biodegradable and therefore can be difficult to remove from the patients system once all the loaded API has been used (84). The success of utilising PPy films as API delivery agents prompted an investigation into other polymers such a polyaniline (PANi, **Figure 2**) (85) and poly(3,4-ethylenedioxythiophene) (PEDOT, **Figure 2**) (86) 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 (87, 88), as is the generation of biodegradable versions (89, 90).

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 drug delivery systems. Multi-stimuli responsive drug delivery systems are being explored for their ability to create more varied release profiles, providing an improvement in tuneability and selectivity versus single responsive systems (91). 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 (91).

When constructing multi-responsive DDS separate units, each of which are responsive to a specific stimuli, are blended together without affecting each units responsiveness. Several systems are currently in development based on the ability of one stimuli to act as a targeting moiety whilst the other stimuli are responsible for affecting 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 towards cancer cell based on the targeting of the lower pH cancer cells makes them desirable in modern cancer treatments (92-95). pH is often combined with a variety of other stimuli including light, electricity and magnetism to affect a desired response in cancerous tissues. pH/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 (96). 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 (96).

Dual responsive DDS which incorporate multiple stimuli capable of affecting 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/magnetic drug release system (97). 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 (98). It has been combined with chitosan, pectin and gelatin for use in drug delivery with all systems displaying a high degree of biocompatibility (98). The resulting material has demonstrated the ability to show controlled release of the anti-cancer drug 5-Fluorouracil (**Figure 2**) over extended periods of time (97). 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 electrospraying, generating compartmentalised storage of multiple drugs (99). The use of this method provides a PCL fibre structure with a hyaluronic acid core, allowing drugs to be loaded in the polymer film (99). 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 (99). A minimal immune response when using Pirfenidone (**Figure 2**), an anti-fibrotic drug, in one of the release compartments (99).

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 of which for APIs displayed in **Figure 5** and **Figure 6** are highlighted in **Table 3**).

Future Outlook & 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 (37). New materials are being developed aimed at improving biocompatibility, generating new release profiles and improving patient care (100). 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 (some examples of which for APIs displayed in **Figure 5** and **Figure 6** are highlighted in **Table 3**).

Advancements of the field of API delivery and controlled release have had a direct impact on other fields of chemistry such as synthetic/polymer chemistry, chemical engineering, materials science, chemical biology and bioengineering (28). 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 prompting further investigations in this field. 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

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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.
The field of controlled delivery of API's is broadening with new emerging concepts such as systems based on 3D printed technologies and gene delivery systems becoming useable alternatives (101).

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 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 (some examples of which for APIs displayed in **Figure 5** and **Figure 6** are highlighted in **Table 3**).

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	**Mark David Ashton:** I received my MChem in Chemistry from the University of Hull and am currently studying for my PhD under the supervision of Dr John G. Hardy at Lancaster University. From 2015-2016 I spent time working at Proctor & Gamble, in the fabric care department and obtained my master's degree (2017) after working with Prof Ross W. Boyle on the synthesis and development of porphyrin radiosensitiers for use in cancer treatments. My current PhD project focuses on the synthesis of drug delivery systems with a specific interest in the use of non-invasive methods of controlling drug release.
	**John George Hardy:** I received my MSci and PhD in Chemistry from the Universities of Bristol and York, respectively. Thereafter I undertook postdoctoral research in Biochemistry, Biomedical Engineering, Materials Science and Pharmacy (in France, Germany, Northern Ireland and the USA) before returning to the UK to lead a research group developing stimuli-responsive materials for technical and medical applications.

<Tables>

Table I

First Examples of Nobel Laureates in Physiology or Medicine From Specific Geographic Regions

Year	Laureate	Country	Justification	Geographic Region

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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 Waiter Florey	UK & Australia	For the discovery of penicillin.	Europe & Australasia
1947	Carl Ferdinand Cori, Gery Theresa Cori & Bernardo Alberto Houssay	United States & 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

Table II

Examples of clinically translated stimuli-responsive formulation systems

Stimulus	Treatment	Review Articles

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Radiation	Radiotherapy	(102)
Light	Photodynamic therapy	(103)
Electricity	Electroconvulsive therapy	(104)
Ultrasound	Sonograms	(105)
Infrared	Thermography	(106)

[a] Add table footnotes if desired

Table III

Examples of API Formulations

API	CAS number	Shown in Figure Number	Examples	Reference
Afatinib Dimaleate	850140-72-6	5	Injection	(107)
Alprostadil	745-65-3	5	N/A	
Apomorphine HCl	41372-20-7	2	Various	(108, 109)
Atropine Sulfate	51-55-8	5	Inhaler	(110)
Auranofin	34031-32-8	5	Oral	(111)
Bimatoprost	155206-00-1	5	Implant	(112)
Bromfenac Sodium	120638-55-3	5	N/A	
Carboplatin	41575-94-4	5	Oral	(113)
Carmustine	154-93-8	2	Implant	(114)
Cisplatin	15663-27-1	2	Various	(115, 116)
Crisaborole	906673-24-3	5	N/A	
Decitabine	2353-33-5	5	Various	(117)
Diprenorphine	14357-78-9	5	N/A	
Dofetilide	115256-11-6	5	Oral	(118)
Edrophonium Chloride	312-48-1	5	Various	(119, 120)
Ethacrynic Acid	58-54-8	5	Various	(121)
Ethacrynate Sodium	58-54-8	5	Various	(98)
Fluvoxamine Maleate	54739-20-7	5	Oral	(122)

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Isoproterenol HCl	51-30-9	6	Oral	(123)
Ivabradine HCl	148849-67-6	6	Implant	(124)
Lenalidomide	191732-72-6	6	Oral	(125)
Lurasidone HCl	367514-87-2	6	Oral	(126)
Miglustat	72599-27-0	6	Inhaler	(127)
Naloxone HCl	465-65-6	6	Hydrogel	(128)
Naltrexone HCl	16590-41-3	2	Various	(129)
Nilotinib	641571-10-0	6	N/A	
Nintedanib	656247-17-5	6	Various	(130) (78)
Nitisinone	104206-65-7	6	Various	(131, 132)
Phytonadione	Phytonadione	6	Various	(133)
Pirfenidone	53179-13-8	2	Various	(134, 135)
Pomalidomide	19171-19-8	6	Various	(136)
Roflumilast	162401-32-3	6	Various	(137, 138)
Silodosin	160970-54-7	6	N/A	
Sorafenib	284461-73-0	6	Various	(139-141)
Travoprost	157283-68-6	6	Implant	(112, 142, 143)
Trientine HCl	38260-01-4	6	Oral	(144)
Venetoclax	1257044-40-8	6	N/A	

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<Figure captions>

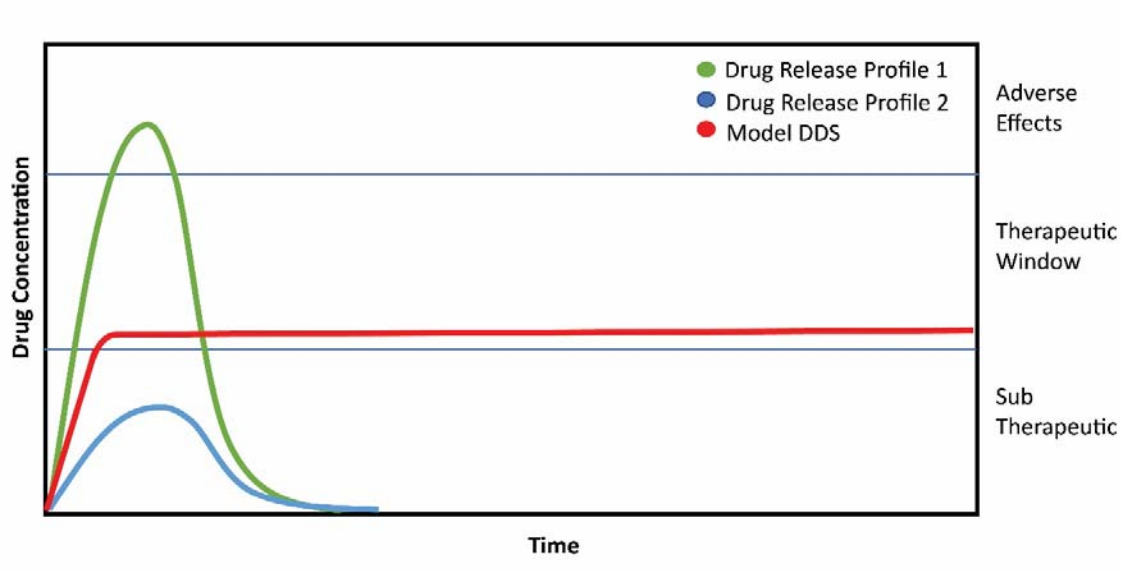

Fig. 1. Examples of release profiles.

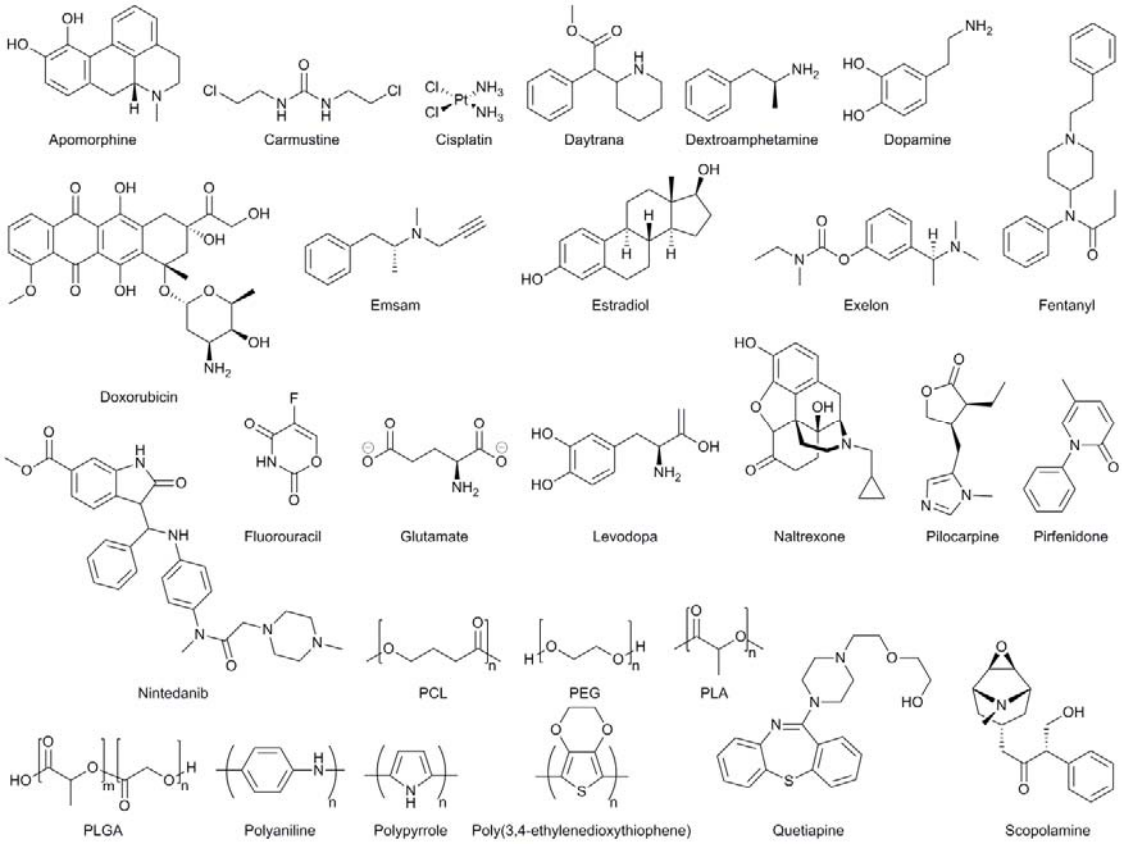

Fig. 2. Examples of chemical structures.

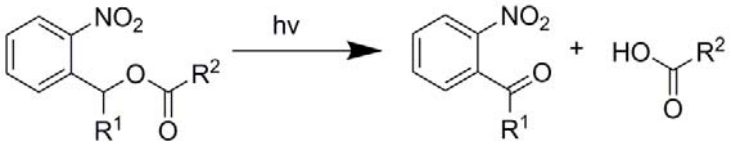

Fig. 3. Photochemical cleavage of an *o*-nitrobenzyl ester yielding an *o*-nitrosobenzaldehyde derivative and an API displaying a carboxylic acid.

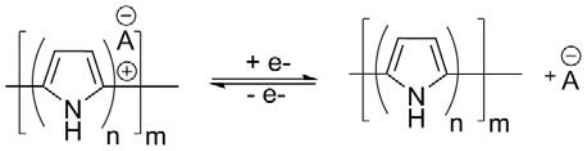

Fig. 4. Redox switching of PPy releasing API dopants.

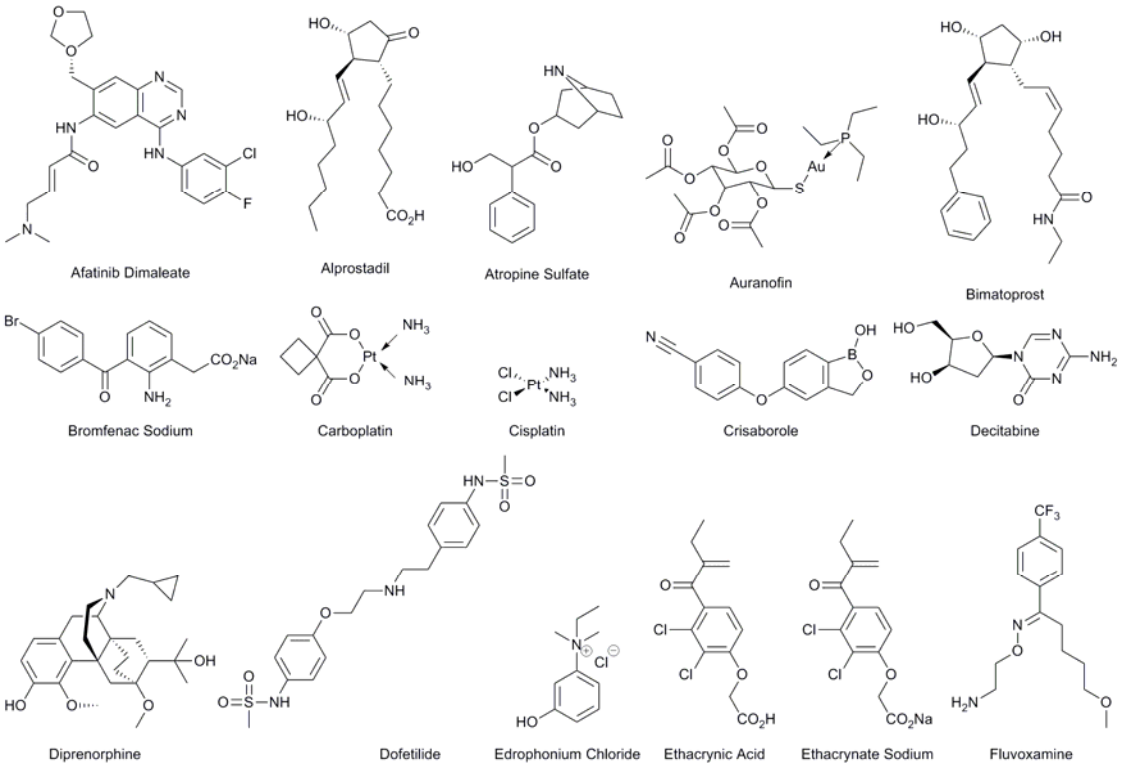

Fig. 5. Examples of APIs formulated in controlled delivery systems highlighted in Table 3.

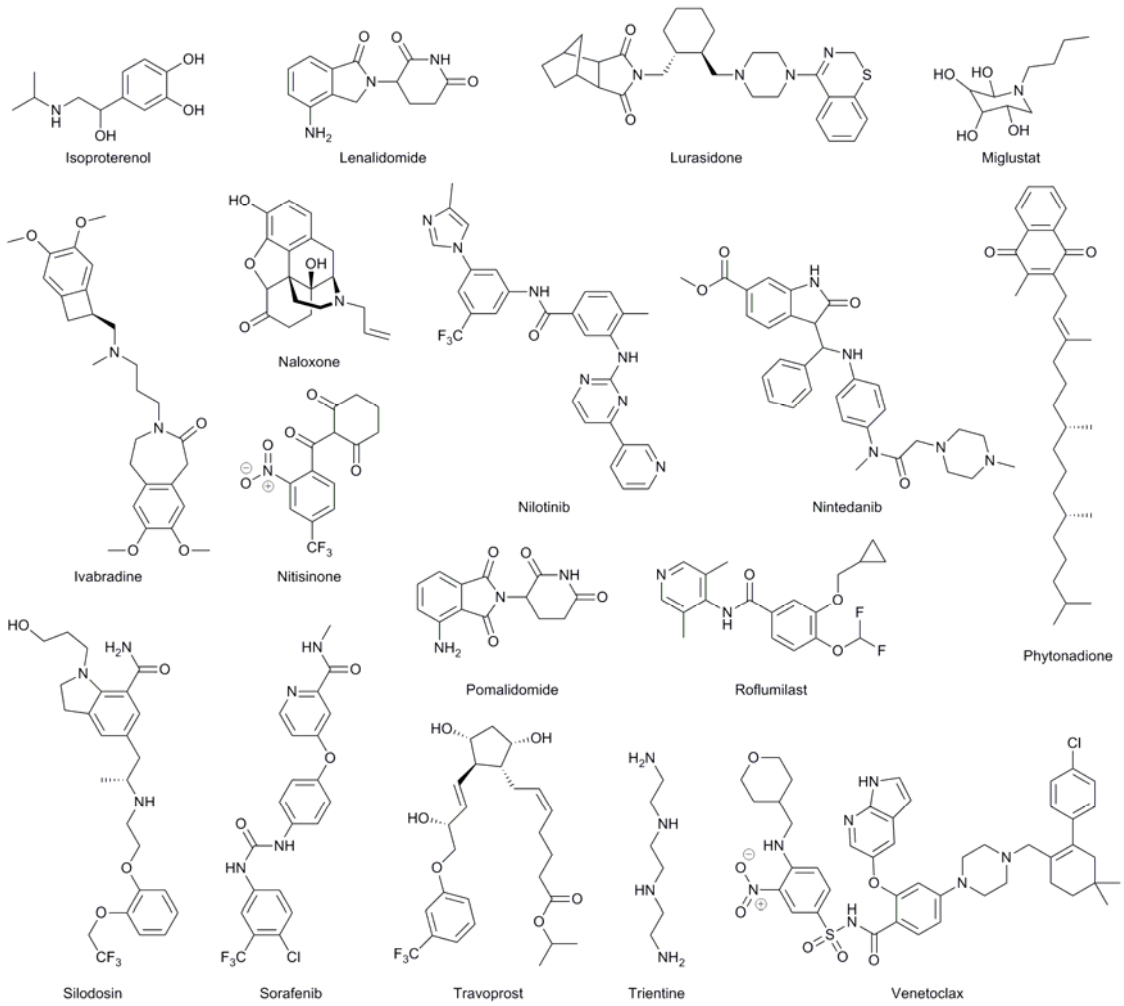

Fig. 6. Examples of APIs formulated in controlled delivery systems highlighted in Table 3.