Review

Stimuli sensitive polymers and self regulated drug delivery systems: A very partial review

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ABSTRACT

Since the early days of the Journal of Controlled Release, there has been considerable interest in materials that can release drug on an "on-demand" basis. So called "stimuli-responsive" and "intelligent" systems have been designed to deliver drug at various times or at various sites in the body, according to a stimulus that is either endogenous or externally applied. In the past three decades, research along these lines has taken numerous directions, and each new generation of investigators has discovered new physicochemical principles and chemical schemes by which the release properties of materials can be altered. No single review could possibly do justice to all of these approaches. In this article, some general observations are made, and a partial history of the field is presented. Both open loop and closed loop systems are discussed. Special emphasis is placed on stimuli-responsive hydrogels, and on systems that can respond repeatedly. It is argued that the most success at present and in the foreseeable future is with systems in which biosensing and actuation (i.e. drug delivery) are separated, with a human and/or cybernetic operator linking the two.

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1. Introduction

"Stimuli responsive" and "self regulating" drug delivery systems have captured the imagination of researchers, in large part because they suggest a means to mimic the physiological homeostatic feedback mechanisms that are essential for health. As dysregulation of homeostasis is a feature of many diseases such as diabetes and cancer, the design of systems that target drugs in space and time to re-establish homeostasis has been pursued by numerous groups.
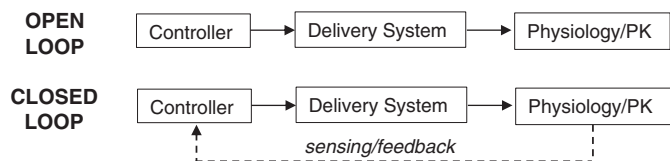
Self regulating systems also permit those with an engineering bent to think of drug delivery in terms of closed loop (feeback) control versus open loop control. These two control philosophies are illustrated in Fig. 1. In open loop control, the control and delivery scheme are predetermined by a control program that governs drug release. In closed loop control, physiological information is gathered and fed back to the controller, which alters the rate of drug release. Although the controller and delivery device are pictured as being separate, their realization may be in a device whose release characteristics are either programmed (open loop) or responsive to physiological signals (closed loop). Discovering means to build sensitivity to endogenous and external physical and chemical stimuli into drug delivery systems has provided a problem that can be attacked using physical, chemical, and engineering ingenuity, particularly in the area of polymers.

A large fraction of delivery drug systems are stimuli responsive, at least in a trivial sense. For example, one would not wish a tablet to release its contents until it is ingested and exposed to the aqueous environment of the GI tract, which is a kind of stimulus but not very interesting. On the other hand, oral delivery systems in which release is triggered by exposure to a particular pH range characteristic of a locale in the GI tract are more interesting [1–3]. It should also be recognized that during the course of drug release, the device might create a "stimulus" that modulates its own release properties. For example, autoacceleration of degradation of poly(lactic-co-glycolic acid) and poly(ortho ester) polymers, mediated by accumulation of acid products, is a mechanism underlying the delayed bursting of drug release from these systems [4]. As this phenomenon is a result of the material's intrinsic kinetic properties, it would not ordinarily be considered to be the result of an external stimulus.

It has been fashionable to call responsive drug release systems "intelligent" or "smart," reflecting nomenclature that has arisen in the materials literature. Although these terms may have a certain sex appeal, they do not seem appropriate, insofar as their definition might imply some cognitive capabilities. No material has passed the Turing test [5]. We avoid such anthropomorphic terminology, as it places too high expectation on the materials and seems demeaning to sentient beings.

In order to narrow the scope of this review, we focus on systems that respond repetitively to a stimulus, releasing drug in a programmed manner each time. Thus we will ignore the very extensive literature on systems that release drug only once in response to a stimulus, depleting their contents. The pH-regiospecific oral drug delivery systems

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OPEN
LOOP

Controller → Delivery System → Physiology/PK

CLOSED
LOOP

Controller → Delivery System → Physiology/PK
↑----------- sensing/feedback -----------┘

Fig. 1. Contrast between open and closed loop drug delivery. In open loop delivery, the system releases drug in a programmed fashion determined by the control. Delivery impinges on the physiological response, which also depends on the drug's pharmacokinetic (PK) properties. In closed loop delivery, physiological and PK information is fed back to the controller, which alters its "commands" to the delivery system. While the controller and delivery system are represented as separate components, the control aspects may be intrinsic to the delivery device.

already mentioned fall into this category, as do most reported responsive systems, and it might be argued that we are being too restrictive. After all, many circulating nanoengineered drug delivery systems have been designed to release their cargo only when receiving a localized stimulus such as heat or light, and repetitive application of the stimulus can lead to multiple release events as the depleted material is replaced by fresh material at the point of stimulation. Furthermore, useful systems may lie dormant for long periods until a critical event, such as inflammation, occurs, which triggers release.

This review is structured as follows. In Section 2 we briefly review some nonpolymeric systems used for automatic feedback controlled drug delivery. These may be regarded as "competitors" to the polymeric systems that are normally studied in the controlled release field. In Section 3, biodegradable systems and monolithic systems with repetitive "on-off" capability are discussed. Section 4 reviews stimuli responsive hydrogels, which have a long history of theoretical and experimental development. Sensing and release actuation modalities involving swelling and shrinking of hydrogels are discussed in Section 5. Systems proposed to utilize such hydrogels in closed and open loop repetitive release systems are reviewed in Section 6. Finally, Section 7 will suggest directions that should be pursued if stimuli sensitive hydrogels are to be useful in feedback controlled drug delivery. We will argue that in the foreseeable future, human decision making is likely to be present in the feedback loop.

2. Nonpolymeric systems

Self regulation occurs whenever monitoring of the effects of a dosing history causes a change, or feedback, to the subsequent dosing pattern. This process of "dose titration" is common in both inpatient and outpatient clinical practice, and there need not be any advanced technology except for reliable record keeping and some pharmacokinetic calculations. This practice is typically "low frequency" since observations and corrections may occur on the time scales of days, weeks, or months. Cancer chemotherapy may be one area in which relatively sophisticated models of dosing and monitoring are of importance, due to the severity of side effects [6].

There has been considerable research, however, into automatic control algorithms and instrumentation in the domains of anesthesia and critical care [6–10]. In this case, a patient's vital signs, including blood pressure, tidal volume, heart rate, cardiac output, EKG, EEG, and blood chemistry (including pH, pO_2, and pCO_2) can be monitored nearly continuously, and the critical state of the patient is such that sudden changes in these signs require rapid attention and compensation. In most cases, a system of alarms can alert attending staff when these variables exceed tolerable limits, but there has been interest in automating the infusion of drugs that maintain blood pressure and heart rate close to a chosen set point. Such controllers can operate by simple PID (proportional, integral, derivative) control algorithms, in which the present levels, recent time averages, and slopes of physiological variables are combined in calculating infusion rates. More sophisticated systems can update, or adapt their control dynamics by probing the patient's

dynamic response. Neural net and fuzzy logic based controllers have also been considered. Neural nets are nonlinear, multilayered learning schemes, while fuzzy logic algorithms combine several kinds of data that are classified into intervals. The latter approaches may emulate what anesthesiologists do without necessarily giving it a name.

Type I diabetes probably represents the best known disease in which tight closed loop regulation is needed [11]. Following ingestion of carbohydrate, blood sugar levels start to increase drastically. While this increase is not in itself life threatening, glucose should be quickly converted to glycogen for storage. Conversion is mediated by insulin, which is normally secreted from the beta cells of the pancreas when the body senses or anticipates an increase in blood glucose level. Insulin also officiates in the delivery of glucose to tissues for utilization. However, too much insulin leads to hypoglycemia, with acute effects such as coma and death. In normal glucose regulation, insulin secretion is reduced to a low basal rate when glucose levels fall into the normal range. By this means average glucose levels remain within the normal range, but with a safety margin that prevents hypoglycemia.

Type I diabetics do not secrete adequate insulin, causing a persistent average state of hyperglycemia, accompanied by a variety of degenerative sequelae over time, including blindness, neuropathy, and loss of extremities. Thus exogenous insulin must be provided, and traditional delivery systems involve injections around meal times. In recent decades the situation has improved tremendously, with advances in glucose sensor technologies, accurate pumps, chemical modifications to insulin that improve its performance, better catheters, and improved understanding of glucose/insulin dynamics [12]. The ultimate goal is to mimic the closed loop control that is effected by a healthy functioning pancreas. (We note in passing that a whole parallel endeavor using transplanted pancreatic islets is under way. Unfortunately, issues of adequate supply of donor islets and challenges associated with immunoisolation have limited this approach [13–19].)

Early studies of an "artificial beta cell" involved a (volunteer) patient lying on a hospital bed [20–23]. The patient's blood glucose was sampled frequently and analyzed off line, with results fed into a computer. Using a "minimal model" of the patient's glucose/insulin dynamics [24], infusion schedules were calculated, and these were administered through an i.v. line. While of little practical use for ambulatory patients, this system was useful in validating algorithms. It can also be regarded as a precursor for critical care monitoring of blood glucose.

All aspects of closed loop insulin therapy have been the object of intensive research. A wide variety of increasingly noninvasive electrochemical and optical approaches to glucose sensing have been proposed [25–30]. On the actuation side, precision pumping, the synthesis of insulins that do not clog catheter lines, and the ability to store, retrieve and analyze blood glucose time series, have improved therapy substantially. Presently, the most advanced systems consist of a small electrode tipped with glucose oxidase, which pierces the skin and transmits, by radio, the sensed glucose concentration to the pump controller (e.g. Medtronic Guardian® REAL-Time CGM, Dexcom G4™ PLATINUM). Fig. 2 presents a cartoon of these systems. The pump controller reports the present glucose level, and can store and report preceding glucose time series. With this information, the patient can make informed decisions regarding rate and amount of insulin to be delivered. Data can be downloaded or transmitted over the internet, permitting *post hoc* analysis by a physician or by a cadre of experts. Perhaps the most important benefit of the sensor-pump system is that the patient and physician can track, over time, the efficacy of dosing decisions, along with the effects of aging, exercise, diet, and other behavioral variables. This benefit may also extend to Type II diabetes therapy, in which behavior is a strong determinant of disease.

Present glucose sensing electrodes must be changed every three days due to fouling and loss of function. Thus, skin must be breached at a new site, and not all patients are satisfied with this inconvenience. Recently, a fully implantable bioelectrochemical sensor system with