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Cover Story

Rhythmomimetic Drug Delivery

Controlled drug delivery technology has been evolving for more than six decades. During this short period, thousands of innovative controlled release formulations, particularly in oral and transdermal delivery, have been developed to improve patient compliance. Most of these formulations are designed to deliver drugs in a sustained manner over extended time intervals. Such drug delivery technologies are useful for drugs that need to be delivered at a prescribed rate for days, weeks, and months. There are many diseases, however, that require more complex release patterns.

In the body, numerous cellular and physiological systems operate with intrinsic rhythms, whose periods span several orders of magnitude. Among these are ultradian rhythms, whose periods are of the order of hours. Numerous hormones governing a variety of physiological processes are secreted in pulses with varying ultradian periodicities. In some cases the time pattern of pulses of hormone release is at least as important as the amount released. At present, rhythmic hormone therapies are administered mainly by wearable electromechanical pumps. An important question is whether such electromechanical systems can be replaced by a totally implantable system that functions without the need for external energy. Such a system would be invaluable to those who require chronic treatment, which may last for years.

A step towards totally implantable systems is described in this issue by Professor Ronald Siegel and his colleague, Dr. Amardeep Bhalla, who characterize an autonomous biochemomechanical system consisting of a hydrogel that swells and delivers pulses of a drug at intervals that are similar to the normal endogenous rhythm [1]. Rhythmic behavior is due to a feedback interaction between an enzyme reaction that catalyzes the conversion of glucose to a hydrogen ion, and the effect of the hydrogen ion on swelling and permeability of the hydrogel membrane, which separates the enzyme from a constant activity glucose source [2]. This system is distinct from hydrogel based systems that have been designed to increase their release of insulin in response to a rise in glucose concentration, since its rhythmic behavior occurs in the presence of a constant glucose level. The operating principles underlying the rhythmic drug delivery system are highly nonlinear, and hysteresis in the hydrogel's response to the hydrogen ion is a crucial element in the mechanism. The authors show how the mechanism's ability to produce oscillatory behavior is limited to finite intervals of design and input parameters, as is often the case with nonlinear oscillating chemical reactions and other membrane oscillators. The sensitivity of the rhythmic system's periodicity to reaction products that build up and affect the mechanism is also studied.

To advance drug delivery technology to the next level, scientists in the field must address the difficulties facing the development of modulated delivery systems, such as pulsatile hormone delivery, sustained drug delivery for years without initial burst release, and true drug targeting [3]. Currently, most drug delivery scientists are focusing their research on nanoparticle technology. While such attention will help advance the field in the long run, current nanoparticle approaches seem to have reached a point of diminishing return. More researchers need to seek answers to problems that arise in developing truly self-regulated drug delivery systems. The work on rhythmomimetic drug delivery by Professor Siegel demonstrates how an understanding of polymer materials science, reaction design, and nonlinear dynamics can be used to produce release behaviors that are far different from the more commonly sought after zero order, single pulse, and stimuli responsive release patterns.

References

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Kinam Park
Purdue University
Departments of Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu

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