Development of Smart Drug Delivery Systems that Learn from Nature

Kakuji Tojo
Kyushu Institute of Technology College of
Computer Science and Systems Engineering
Ph.D., Professor, DDS Research Lab

Since nitroglycerine transdermal patches were introduced on the United States market in 1982 for the treatment of angina pectoris, controlled release (CR) systems have come into wide use throughout the world to treat a broad variety of diseases. The system design is in the form of pills, capsules, transdermal patches, implanted drug delivery systems, intravitreal inserts, subcutaneous implants, and injectables. These preparations take the forms of particles endowed with controlled release (CR) functions, films formed after evenly mixing drug powders into polymer bases, or implantable rods that are made by the advanced processing of particles.

When transdermal therapeutic systems started to use clinically about 20 years ago, the purpose of CR technologies was the constant-rate, long-term release of active agents. In other words, a major objective of CR technologies was to develop dosage forms which, with one dose, release active agents at a constant rate effective over a long time period. There were two major underlying reasons. First, the optimum tissue concentration and release characteristics of drug molecules were not fully understood for treating diseases, and second, owing to the large individual differences in pharmacokinetics (ADME: absorption, distribution, metabolism, and elimination) within the body, the accurate control of concentrations in blood and tissue did not make sense. Of course even today, although long-term constant-release systems are effective in gaining patient compliance and treating many diseases, timed drug release systems are increasingly necessary. Attention is focused especially on time-dependent release rate CR technologies that can address the time dependence of the state of a disease and undesired side effects, prevent drug tolerance, and set dose intermissions.

The active agents in pharmaceuticals are bioinformation molecules that control bodily functions by acting as signal or false-signal molecules. Generally these are produced in the body and are released for the maximum effect and without waste. Recently research has started to learn about not only drugs (bioinformation molecules) like these, but also how plants and insects economically and effectively use their bioinformation molecules. Knowledge turned up in this research is then used in CR technologies. This science is called biomimicry, and considered as a valuable new scientific field in the 21st, or biotech, century. [1]

For example, the chemical reactions, and the processes of release and movement of informational molecules within organisms, are the most efficient functions achieved by organisms through the long course of evolution. Biomimicry, or the imitation of these biological functions, will likely play an essential role in developing sustainable CR technologies.

However, it is certainly not easy to correctly understand the ingenious functions of organisms and exactly mimic them. Hence at this stage of research the main purpose of biomimicry would be to develop novel CR and drug delivery systems with the inspiration gained in the course of learning from nature. [2]

For that reason this paper explores controlled release processes for bioinformation molecules as related to CR technologies and the biomimicry concept. I examine biomimicry in CR technologies in relation to three items: (1) mimicking elements, (2) mimicking mechanisms, and (3) utilizing mechanisms. Mimicking elements means controlling bioinformation by using the active agents produced when necessary in the body, which has been the mainstream of pharmaceutical research and development to date. Mimicking mechanisms means understanding the mechanisms that use bioinformation molecules, and using them in CR technologies, thus making them similar to what nature does. Utilizing mechanisms, on the other hand, means using biological functions as is to develop highly economical CR technologies.
1. Mimicking Elements: Bioinformation Molecules

The molecules that organisms generally release for alarming or communication, or that they use to transmit information internally, are here defined as bioinformation molecules. Researchers have come to focus on using these bioinformation molecules, and on putting them to work in pharmaceuticals, pesticides, and other products after chemically modifying them into more potent molecules. Some examples are the insect pheromones used to control insect pests, synthetic progestins used as a contraceptive, steroid hormones such as estrogen, and peptide hormones of which insulin is representative. Devices that release these bioinformation molecules at a constant rate over a long period are the CR systems that have generally been developed to date. [3]

For example, pheromone CR systems have already been commercialized as eco-friendly insect pest control systems in forms that include films, hollow fibers, and microcapsules. [4] Meanwhile, researchers have developed a subcutaneous injection which includes LHRH in microcapsules of the biodegradable polymer PLGA. This therapeutic system is effectively used to treat prostate cancer and endometriosis. [5] Estradiol transdermal patches are used clinically to treat menopausal disorders and osteoporosis. [6] These CR devices are roughly divided into matrix and reservoir types. In both, however, the release process is governed by the diffusion of drug molecules in the polymers. In matrix-type pheromone CR devices, for instance, pheromone molecules evenly dispersed in the film undergo a prolonged release that is driven by the concentration gradient. Cumulative release amount Q for this type is proportional to the square root of time. Likewise in hollow fiber devices, Q is proportional to the square root of time if diffusion in the hollow tubes is rate-determined. Reservoir-type CR systems, by contrast, keep the release rate constant with a release rate control membrane, and resulting Q proportional to time. However, the difference between the release characteristics of the matrix and reservoir types has little effect on actual treatment systems and insect pest control systems. [7]

This is because the matrix-type release characteristics can be approximated as the initial burst and the subsequent constant-rate release. In fact, matrix systems have the advantages of no concerns about bursting release due to device destruction, and the easiness to adjust application area to fit the therapeutic efficacy.

Sustained CR systems described above are examples of biomimicry that use bioinformation molecules as mimicking elements. However, long-term release of bioinformation molecules is quite wasteful, and less efficient and economical, compared to its release processes occurring within organisms. Recent research has revealed that insect pheromones, peptide hormones (such as insulin), and other substances are not released at constant rates within organisms. [8] For example, insulin releases for controlling blood glucose concentration come in pulses, starting and stopping in approximate 14-minute cycles even if the blood glucose level continually increases. [8] When the relationship between drug concentration and therapeutic efficacy follows a sigmoid profile, it is more efficient to deliver the drug at high concentrations by starting and stopping in cycles than to continually release it at low concentrations. Further, by delivering insulin in short cycles, it is possible even at the same concentration in the bloodstream to tell when it is rising or falling, thereby curbing excess insulin releases on the downswing and preventing hypoglycemia-induced coma. As this shows, it is generally more economical for organisms to release bioinformation molecules in pulses, and this suggests that in order to imitate such “elements” and use them in CR and drug delivery technologies we must properly learn about their release mechanisms as well.

2. Using External Energy for CR Time Control

Many of the DDS and CR systems currently in clinical use are designed, as shown in Fig. 1, to release the active substances according to a preprogrammed release pattern. [9] Accordingly, their design does not allow them to respond to environmental changes or...
changes over time in the body's internal dynamics. In the treatment of pain, for instance, a DDS that can respond to sudden pain would have to time-control the release of the drug molecules in accordance with the pain. With such a DDS, time control would be possible by adding external energy to the energy source in Fig. 1. Ultrasound and electric fields are effective as this added energy. An in vitro membrane penetration experimental apparatus as shown in Fig. 2 was used to investigate the effect of ultrasound exposure on LDPE membrane penetration by a drug (benzoic acid). Fig. 3 shows the time course of the cumulative penetration when applying ultrasound for 10 min at three different frequencies. At 100 kHz penetration was hardly enhanced by ultrasound at all, but at 28 kHz and 45 kHz the penetration rate during exposure was, respectively, 3.5-fold and 5.5-fold more than the non-exposure intervals. It is interesting to see that when the ultrasound was switched off, the penetration rate instantly dropped to the same rate as the control. [10] In a membrane penetration experiment with continuous exposure the diffusion coefficient was determined from the time lag. We found that enhancement of penetration by ultrasound was mainly due to a rise in the drug diffusion coefficient, while the effects of temperature increase, solubility (distribution improvement), or other phenomena can be almost negligible.

Ultrasound exposure can also be used for the timed release of drugs from drug delivery systems implanted subcutaneously. Takasaki et al. developed an implantable biodegradable system with indomethacin dispersed in small poly lactic acid rods 1 mm in diameter and 3 mm long, and succeeded in enhancing timed release with exposure to 1 MHz ultrasound. [11]

Researchers in various fields are also working on iontophoresis, which enhances penetration, by using electric fields for the cutaneous absorption of watersoluble drugs and large molecules. Akagi et al. used a vertical in vitro diffusion cell (Fig. 4) to elaborate the effect of an electric field on the penetration rate through hairless mouse skin. They determined the relationship of penetration enhancement to the intensity of electric field and the duration of current application (Fig. 5). CR systems using external energy such as ultrasound and electric field, constitute a new

![Fig. 2](https://example.com/fig2.png)

**Fig. 2** Experimental setup for measuring the effect of ultrasound on the membrane permeation of drugs. The side-by-side diffusion cell system is placed in the ultrasonic water bath washer.

Model drug: benzoic acid; donor concentration: saturated concentration; effective volume: 68 ml; effective area: 12.5 cm²; membrane: LDPE (50 µm in thickness); temperature: 37°C.

![Fig. 3](https://example.com/fig3.png)

**Fig. 3** Time course of cumulative amount of benzoic acid penetrated across an LDPE film. Ultrasound was applied for 10-minute intervals at 0, 20, 40, 60, 80, and 100 minutes (shaded areas). Key: (●) control (no ultrasound), (□) 100 kHz, (○) 28 kHz, (▲) 45 kHz.

![Fig. 4](https://example.com/fig4.png)

**Fig. 4** Experimental setup for in vitro skin penetration by iontophoresis. The skin specimen was prepared from abdominal hairless mouse skin.
technology field that integrates information technology and biotechnology. This new area of research will likely be important as biomimetic drug delivery and CR systems in a broad array of medical treatments and insect pest control.

3. Mimicking Mechanisms

The bombardier beetle, a 1 cm-odd long insect that is seen in fallen leaves, under stones, and other places, has a marvelous defense against enemies. Eisner [13] notes that the beetle has two chambers in its abdomen. One stores hydrogen peroxide and hydroquinone, while the other is a reaction chamber enclosed by the enzyme catalase. When the beetle detects an enemy, it immediately sends the two chemical substances from the storage chamber to the reaction chamber, where it uses the enzyme to bring about an instantaneous exothermic oxidation reaction. The tissue surrounding the reaction chamber is not harmed by the heat because it is chitinous. In this way the insect fires rapid pulses of the toxic substance benzoquinone as hot as 100°C at targets without harming itself (Fig. 6). It is a living microbiochemical reactor system controlled exquisitely.

We have learned from the bombardier beetle’s defense mechanism in developing a new multi-layer, timed-release transdermal drug delivery system [14] that replaces the bombardier beetle’s abdominal chemical storage layer and reaction chamber with polymer reaction membranes, and has an impermeable separation membrane between the other membranes (Fig. 7). This separation membrane is removed just before use. In conventional design, an absorption-enhancing chemical is added to the adhesive layer of the transdermal therapeutic system. Depending on the properties and concentration of the substance, it sometimes impairs the stability of the drug during the storage period. With this device design, however, long-term stability is maintained because the drug molecules and enhancer come into contact just before use. Setting the drug absorption time lag with the lower drug storage layer (membrane B) makes it possible to develop new transdermal therapeutic systems that can control intermission periods for drug absorption or that take chronopharmacology into account. If an appropriate time lag can be set in transdermal absorption with the time lag control membrane while also lowering stratum corneum resistance to diffusion with the penetration enhancer dispersed in the adhe-
sive layer, and thus maintaining the effective absorption rate, then it would be possible to set the intermission period by repeated once-a-day application of the system. For example, in ethylene vinyl acetate copolymer membranes, the diffusion coefficient of the drug is constant because it is independent of the vinyl acetate content; solubility alone increases with vinyl acetate content. We have taken advantage of this property and confirmed with laboratory animals that the new system can set the time lag at about 8 h without lowering the steady-state penetration rate (Fig. 8). [14]

Transdermal therapeutic systems like this can be applied not only to setting intermission periods for transdermal treatments in which drug tolerance is a problem, but also in new time-control transdermal therapeutic systems which take circadian rhythms into account and avoid medication at unnecessary times (such as nicotine absorption during sleep with the nicotine patches that help people quit smoking). Another possibility is time-control systems that prevent drug transport to the bloodstream during sleep, and begin maintaining the effective concentration in the blood just before getting up in the morning. Users would accomplish this by merely changing their patch once daily just before retiring.

Further, research on the recently developed iontophoresis technology, which uses an electric field to time-control the cutaneous absorption of drugs, has shown for example that it is possible to deliver effective agents to the bloodstream in pulses or in any time-dependent manner by turning an electric field on and off, and that bioinformation molecules in the skin can be extracted by reversing electrode polarity.

Optimizing new drug delivery technologies like these might in the near future bring about novel therapeutic systems with feedback functions as illustrated in Fig. 9.

Fig. 9 Advanced drug delivery system with negative feedback control loop. Feedback signal may be the concentration of bioinformation molecules extracted from the body.

4. Utilizing Mechanisms

Australia's mountain ash is the world's largest tree, sometimes attaining a height of 100 m. Its leaves are believed to transpire as much as 1,000 L of water per day. [15] To keep its leaves from withering, the tree constantly brings water up from its roots, sends it via the trunk to the branches, and from there to the leaves. This is truly an amazing feat of nature, because the tree carries this on without producing any noise or vibration. One time I had the idea that it might be possible to use such economical natural mechanisms to efficiently deliver nutrients and insecticides or other active agents to an entire tree, and I decided to develop a "pesticide patch" that would deliver pesticides to the tips of a plant's leaves by absorbing them through stems (Fig. 10). [16] Literature survey indicates that less than 1% of generally used pesticide sprays are actually delivered to target insects. [7] Nearly all the applied pesticide instead contaminates not only the plants, but also the air, water, and soil. When pesticides are applied as granules by spreading them on the soil, they are washed away by rain, and soil contamination is unavoidable. This led to the idea of a transdermal absorption system for pesticide, or pesticide patch, that is applied to the bottom of a plant stem, where the pesticide is absorbed and then delivered through vessels to the entire plant. The pesticide’s active agent imidacloprid and additives (penetration enhancers) are well dis-
persed into an adhesive polymer base, and then made into a thin-film preparation using the doctor blade method (Fig. 11). The two small-scale, automatic manufacturing devices shown in Fig. 16, using the solvent and hot-melt methods, have been developed to make preparations for field and clinical trials. This patch was applied to the in vitro pesticide stem penetration apparatus shown in Fig. 12 to measure the imidacloprid stem absorption rate. Penetration enhancers were $\alpha$-menthol and d-limonene, for each of which we developed a high- and low-absorption pesticide patch. Fig. 13 plots the effects of different $\alpha$-menthol concentrations on the enhancement of imidacloprid stem penetration on eggplant.

We also applied this pesticide patch to the stems of model plants: tomato, eggplant, and chrysanthemum plants about 5 cm above ground level. Insecticidal efficacy was measured by putting 10 aphids each on the tops and undersides of leaves, and counting them each day (Fig. 14). Fig. 15 compares the results from several devices. With the preparation containing no pesticide the number of aphids clearly increased day by day. This contrasted with the insecticidal characteristics of the pesticide-loaded preparations, with the high-absorption type (containing $\alpha$-menthol) being fast-acting, and the low-absorption type (containing d-limonene) being time-lag. Although no figure is included here, measuring the insecticidal effect of the high-absorption preparation on aphids infesting chrysanthemum plants showed that all aphids died within three days. No harm to the plants was discerned.

We also found that using pesticide patches allowed a reduction of pesticide application amount of between 1/20th and 1/10th the amount applied in granular form. [17] Because the insecticidal agent is stored in the polymer base, its effectiveness is not influenced by rain, wind, or other weather conditions. Further, there is no environmental contamination because the pesticide is not lost to the soil or air. It is possible to develop totally new delayed-release pesticide delivery systems that allow time control of the insecticidal effect by controlling the absorption rate, thereby promising to raise the users' quality of life.

![Fig. 10 Concept of biomimetic pesticide delivery through plant stems.](image)

![Fig. 11 Laboratory process for manufacturing pesticide patches.](image)
In vitro system for measuring the pesticide penetration rate through plant stems. The adhesive pesticide delivery system is applied to the surface of the hollow stem.

Effect of l-menthol, a penetration enhancer, on the stem penetration of imidacloprid. Model plant: eggplant (Solanum melongena L. cv. Senryo No. 2, eight weeks after germination)

Time variation in the ratio numbers of aphids surviving the acrylic adhesive delivery of imidacloprid through the stem of eggplant. Ten aphids were initially placed on both sides of each leaf (No=10).

Laboratory-scale equipment for manufacturing transdermal drug delivery devices. (a) Solvent method, (b) hot-melt method.
Conclusion

This paper has shown how biomimicry, or learning from nature, plays an important role in developing novel drug delivery systems that can time-control release and delivery rates. Further, examples were used to explain in general the three approaches for developing the DDS's that learn from nature: (1) mimicking elements, (2) mimicking mechanisms, and (3) utilizing mechanisms. The time-controlled release of bioinformation molecules is an efficient and economical process acquired by organisms over the long course of evolution, and organisms take ingenious advantage of both their internal and external environmental conditions, which change from moment to moment. When we learn from living functions and develop new DDS, we must keep in mind not only the functions of individual organisms, but also the roles of organisms as systems and the “natural systems” that comprise organisms and their surrounding environments. Living creatures make smart use of natural systems to achieve their efficient and economical release and delivery systems for bioinformation molecule. Accordingly, only when we study biomimicry by taking natural systems into account can we minimize the risk inherent in mimicking only certain facets of intricate natural functions.

References

Kakuji Tojo

Dr. Kakuji Tojo is a professor of Biosystems Engineering at Kyushu Institute of Technology and is the Director of the DDS Laboratories at the Center of Iizuka Research and Development (CIRD). He graduated in Chemical Engineering from University of Osaka Prefecture (1969). He was a postdoctoral researcher at Kansas State University and later joined Rutgers University College of Pharmacy where he had been an Assistant Professor and tenured Associate Professor. He accepted a professorship at National Kyushu Institute of Technology in 1990, and served as the Regent Professor, 1995 to 98. His research interests include transdermal drug delivery, ophthalmic drug delivery and biomimicry in controlled release technology. He had served as a member of the Board of Governors, Controlled Release Society, 1991 to 1994. He is an editor or editorial board member of international journals including European Journal of Pharmaceutics and Biopharmaceutics, Archives of Pharmacal Research (Korea) and Journal of Chemical Engineering of Japan.