SMART DRUG DELIVERY SYSTEMS LEARNED FROM NATURE

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Introduction

When transdermal drug delivery systems were first introduced clinically about 25 years ago, the purpose of controlled release technologies was the constant-rate, long-term release of active agents; 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 optimum release characteristics of drug molecules were not fully understood for treating diseases, and second, owing to the large individual differences in pharmacokinetics within the body, the accurate control of concentrations in blood and tissue did not make sense. Of course even today, long term constant-release systems are effective in gaining patient compliance and treating many diseases. However timed-drug delivery systems are increasingly necesary.

The active agents in pharmaceuticals are bioinformation molecules that control bodily functions by acting as signal or false-signal molecules. These are frequently produced in the body and released for the maximum effect and without waste. Recently research has started to learn about not only drug molecules but also how plants and insect economically and effectively use their bioinformation molecules. This science is called biomimicry and considered as a valuable new field in the 21st biotech century [1].

For example, the chemical reactions, and the processes of release and movement of information molecules within our body, are the most efficient functions achieved by living creatures 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 understanding the ingenious functions of the living creatures 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.

This paper examines biomimicry in CR technologies in relation to three items: (1) mimicking elements, (2) mimicking mechanisms, and (3) utilizing mechanisms. Mimicking elements means discovering drug molecules produced when necessary in the body, which has been the main stream of pharmaceutical research and development to date. Mimicking mechanisms means understanding the mechanisms that use bioinformation molecules, and using them in DDS technologies, thus making them similar to what nature dose. Utilizing mechanisms on the other hand, means using biological functions as is to develop highly economical DDS.

1. Mimicking Elements

The molecules that living creatures generally release for alarmaing or communication, or that they use to transmit information internally, are here defined as bioinformation

molecules. Researchers have increasingly focused on using these bioinformation molecules, and on putting them to work in pharmaceuticals, pesticides, and more potent molecules. Some examples are the insect pheromones, systhetic progestines and estrogens, and a variety of proteins and peptide hormones. 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.

For example, pheromone CR systems have already been commercialized as eco-friendly insect pest control systems in forms of films, hollow fibers, and microcapsules. Estradiol transdermal patches are used clinically to treat menopausal disorders and osteoporosis. 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 driven by the concentration gradient. The 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 contract, 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. This is because the matrix-type release characteristics can be approximated as the initial burst and the subsequent constant-rate release.

CR systems described above are examples of biomimicry that use bioinformatiaon molecules as mimicking elements. However, constant release of bioinformation molecules is quite wasteful, and less efficient, compared to its release processes occurring within living creatures[2]. It is generally more economical for us 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 Time-Control

Many of the DDS and CR systems currently in commertial use are designed to release the active agents according to a programmed release pattern. Accordingly, their design dose 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 suddwn pain would have to time-control the release of the durg molecules in accordance with the pain. With such a DDS, time-control would be possible by adding external energy. Ultrasound and electric fields are effective as this added energy. An in vitro skin penetration experimental apparatus was used to investigate the effect of ultrasound exposure on skin penetration. Fig.1 shows the time course of the cumulative penetration when applying ultrasound for 10 to 60 minutes.

Researchers in various fields are also working on iontophoresis, which enhances penetration, by using electric fields for the cutaneous absorption of water-soluble drugs and large molecules. CR systems using external energy such as ultrasound and electric field, constitute a new technological 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 sciences.

3. Mimicking Mechanisms

The bombardier beetle has a marvelous defense against enemies [13]. The beetle has two chambers in its abdomen. One stores hydrogen peroxide and hydroquinone, and 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. It is a living microbioreactor 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 that replaces the bombardier beetle's abdominal chemical storage layer and the reaction chamber with polymer reaction membranes, and has a impermeable separation membrane between the other membranes (Fig.2). 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 long-term 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 chronophrmacology 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 adhesive layer, and thus maintaining the effective absorption rate, then it would be possible to set the intermission period by repeated once-a-day application. 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.3).

Further, research on the recently developed iontophoresis technology, which uses an electric field to time-control the cutaneous absorption of drugs, has shown possible time profile of drug release in pulses or in any time-dependent manner by turing an electri field on and off (Fig.4).

4. Utilizing Mechanisms

Literature survey indicates that less than 1% of generally used pesticide sprays are actually delivered to target insects. Nearly all the applied pesticide insteady 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 unavoidable. This led to the idea of a transdermal absorption system for pesticide, or pesticide patch, that can be 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 dispersed into an adhesive polymer base, and then made into a thin-film preparation using the doctor blade method.

We applied this pesticide patch to the stems of model plants: tomato, eggplant, and

chrysanthemum plant about 5 cm above ground level. Insecticidal efficacy was then measured by putting 10 aphids each on the tops and undersides of leaves, and counting them each day. We found that the insecticidal efficacy was time-controlled by the device design and the penetration enhancer. Because the insecticidal agent is stored in the polymer matrix, 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.

Conclusion

This paper has shown how biomimicry plays an important role in developing novel drug delivery systems that can time-control release and delivery rate. Further three approaches were explained for developing the transdermal DDS learned from nature: (1) mimicking elements, (2)mimicking mechanisms and (3) utilizing mechanisms.

References

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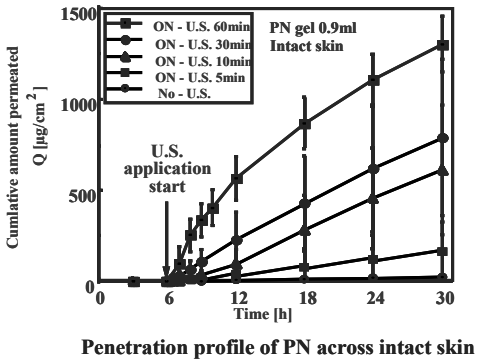

Fig.1. Effect of ultrasound application on the skin penetration of prednisolone(PN)

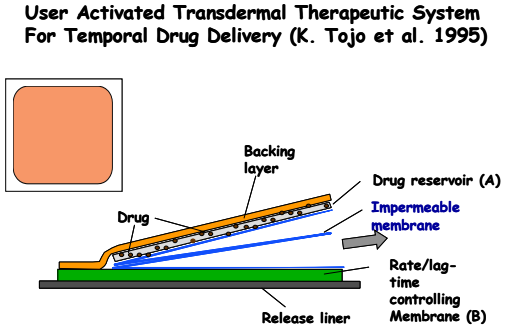

Fig.2. Patient-activated temporal transdermal drug delivery system

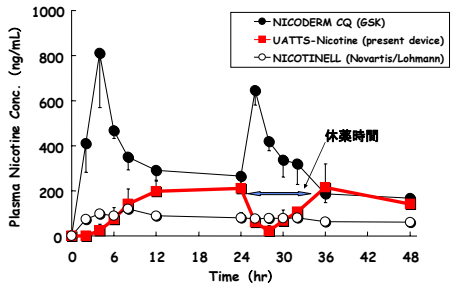

Fig.3. Plasma concentration profile of time-lag transdermal delivery of nicotine using the patient-activated TTS(in vivo rats)

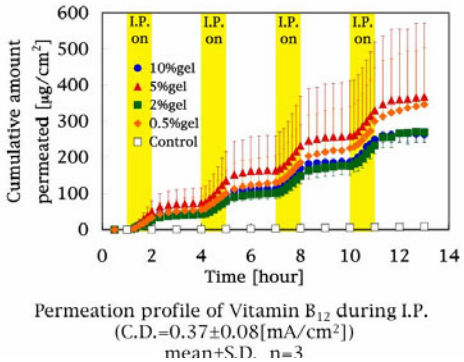

Fig.4. Time-control of skin penetration of drug by iontophoretic transdermal delivery. (in vitro)