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Research & Development Trend of Drug Delivery System (DDS)

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6.1 Introduction

Nowadays, symptomatic therapy such as surgical operation and drug therapy are given to patients. Medification is regularly done by oral administration, and intramuscular and venous injection. Injection usually causes pain and tissue injury, and it is difficult to give oral administration based on individual differences such as sex, age and disease condition. The administered drug distributes not only to the affected site but also to the normal cells (tissue), and decreases due to hepatic metabolism. Thus, only small part of the administered dosage reaches and acts on the affected site, and the drug distributed to the normal cells may cause adverse reactions. So, one administration or injection of the drug cannot maintain an effective concentration in the blood over many hours, causing a repeated dosage with more than the necessary dosage.

In recent years, as a measure to conduct safer and more effective drug treatment by inhibiting excessive drug use and adverse reactions, researches on a drug delivery system (DDS) that aims to supply the necessary minimum drug to the necessary site at the necessary time, are in the active. The DDS has two types of methods; one is a method to dissolve a drug slowly in the living body, and the other is a method to deliver a drug to the affected target site through the blood flow. To achieve the practical use of these methods, only the modification of drug is not enough. It is in need to develop matrix materials such as polymer materials or ceramic materials as carrier of drug. In the case of drug carried to the capillaries in the affected site through blood flow, the drug particle size including the drug and matrix material must be several nm to 200 nm (1 nm = 1/1 billion m) at maximum[1] because the diameter of the capillary is approximately 5μm and the absorbency of the drug increases with the decrease in the particle size of the drug.

For the treatment of cancer and regenerative medicine, utilization of polymer micelle and liposome as drug carrier shows a significant advancement, leading to a number of clinical studies. For bio-diagnosis/treatment and DDS in the gastrointestinal system, a practical MEMS was developed. At present, research and development of DDS has begun to bear fruit like this. Moreover, the research and development of DDS was taken up in the "Development and Application of Advanced Science Technology" (Nanomedicine Project) in the science technology policy of the Ministry of Health, Labour and Welfare in 2002, that is one example showing that it reached a breakthrough stage.

Therefore, in this report, we will introduce the present status of the research and development of DDS, prospect the future picture of DDS, and discuss the necessities of research and development on it, and arrangement of a research system.

6.2 Efficacy of DDS

From the standpoint of treatment and pharmaceutical development, the following efficacies are expected from the DDS technique[2].

(1) It is possible to take out only a particular action and to suppress the onset of a particular action. (Separation of actions)
(2) The efficacy becomes more exact. Reduction of the dosage and extension of the applicability of drug can be expected. (Increase of efficacy)

(3) A dropped out compound due to adverse reactions can be revived as a drug. (Reduction of adverse reactions, increase of safety)
(4) The burden on medical staff and patients can be reduced. The problem of no time to spare can be resolved. (Improvement of the convenience in use)
(5) Extension of the life cycle of products and reduction of medical expenses become available. (Economy)

In the research and development of DDS, according to the deeper understanding of the biomechanism and the advancement of material design technology, DDS is expected to provide more effective and safer treatment also in new therapies such as gene therapy and regenerative medicine, as well as in the use of genome products.

6.3 DDS to date

Various DDSs are considered as shown in Figure 1[3], and several DDSs have reached the stage of practical use. The material to carry the drug is of importance in considering DDS, and particularly in the administration via blood, the material to carry the drug requires the following properties.

(1) A large drug volume with a small particle size (100 nm).
(2) High water solubility.
(3) High stability of the structure.
(4) Ability of biodecomposition and bioabsorption after playing a role.

Polymer and ceramic materials having the above properties were developed, and, to date, the following DDSs have been put into practical use. If DDSs are roughly divided into two categories, one is the slow release of drug at a certain rate in a certain period of time (sustained release of drug), and the other is targeting of drug by selectively transporting the drug to the affected target site (targeting of drug).

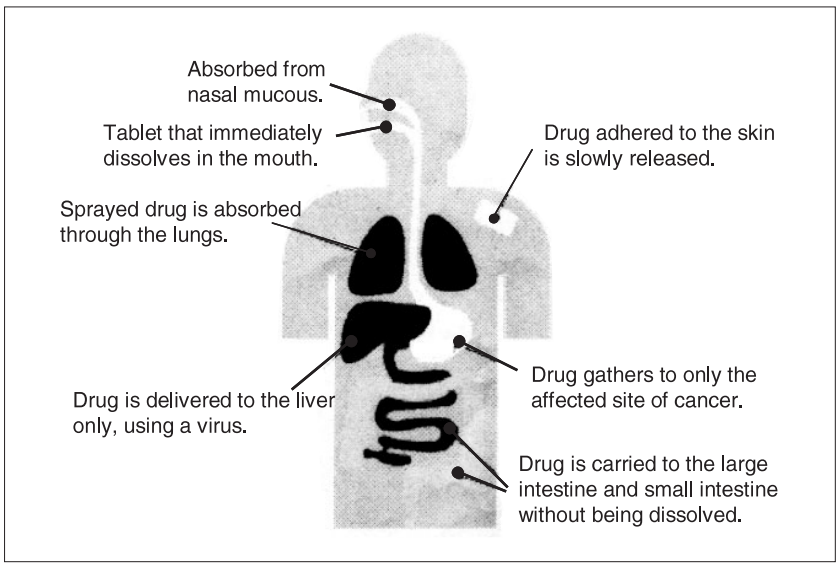
(1) Sustained release of drug

The purpose of the sustained release of drug is to keep a certain concentration of the drug in the blood over a long term. As basic principles of the sustained release of drug, there are a reservoir type and a monolithic type as shown in Figure 2.

The reservoir type uses a method to control the amount of permeated drug by utilizing the permeability of the polymer membrane covering the drug. The monolithic type uses a method to control the diffusion of drug by dispersing the drug into a polymer or ceramic matrix.

When the drug is administered by a normal method, the concentration of drug in the blood shows a serrate-shaped change depending on the time and the number of administration, as shown in Figure 3. Immediately after administration concentration of drug rapidly increases, and

Figure 1: Mechanism of various DDSs



Source: Nikkei Homepage (http://www.nikkei4946.com/today/0105/12.html)

Figure 2: Basic mechanism of the sustained release of drug

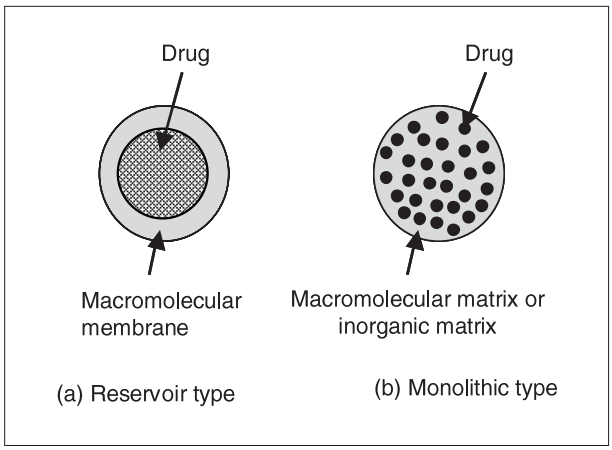
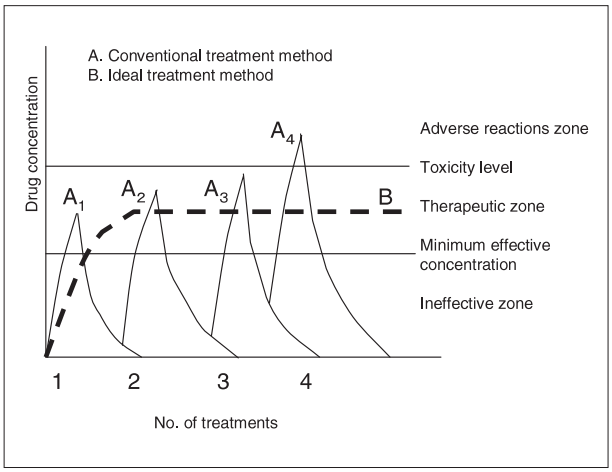


Figure 3: Temporal change of blood drug concentration



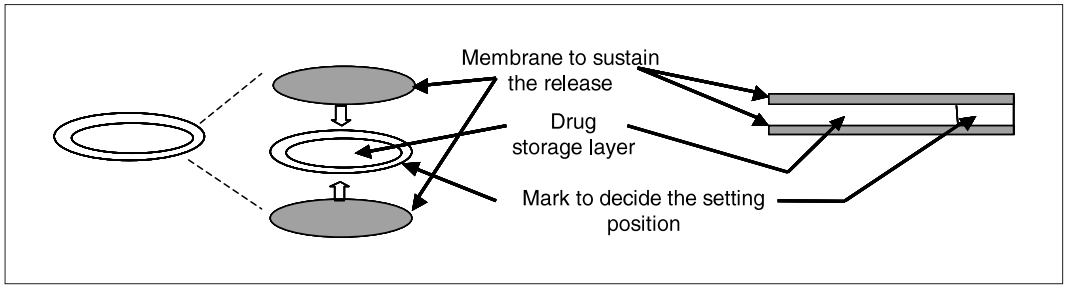
occasionally the concentration may reach a certain level with the risk of adverse drug reaction. Meanwhile, the drug in blood is metabolized in the tissues, and the concentration decreases by excretion, etc. If drug concentration becomes lower than the necessary minimum, therapeutic efficacy cannot be obtained at all[4].

T. Higuchi (Utah University), A. Zaffaroni (Alza Corp.) and others enclosed a drug for glaucoma (Pilocarpine) in ethylene-vinyl acetate copolymer (EVA) to be worn like contact lenses. As a result, an Ocusert system, which sustained the efficacy of the drug for 4-7 days, was put into practical use in 1974, and the product was launched in Japan in 1981. The annual sales of the system is more than 60 billion yen worldwide. In addition, as transdermal therapeutic systems (TTS) using PEVA membrane to control the absorption of drug through the skin just like patches, an antiangina drug Nitroglycerin and antihypertensive drug Clonidine (Catapres-TTS) were put into practical use in 1989. Recently, a TTS (Nicotinell-TTS) to assist smoking cessation was also put into practical use in 1998. This type of DDS has the advantage that it can be easily discontinued when a problem such as adverse reaction occurs. This advantage assisted the rapid progress to a practical use.

In 1992, for prostatic cancer, Takeda Chemical Industries, Ltd. put a drug named Ryuprin into practical use, which allows the retention of blood drug concentration for 4 weeks. It has been used in more than 70 countries across the world, and annual sales reached more than 150 billion yen. In addition, Ryuprin SR Injection Kit 11.25, which allows the retention of blood drug concentration for 12 weeks by changing the material enclosing a drug, was put into practical use in August 2002[5].

Diabetes patients must receive insulin injections several times every day. However, in 1953, Novo Nordisk A/S mixed two types of insulin crystals, i.e., easily soluble and hardly soluble, making it possible to decrease the number of injections to once daily. If insulin is administered excessively or blood glucose concentration decreases too much, it may lead to a life-threatening condition (hypoglycemia) such as cerebral function disorder, so it is necessary to conduct insulin treatment at an appropriate dose according to the glucose concentration. Therefore, research and develop-

Figure 4: Ocusert System (treatment for glaucoma)



ment activities are being conducted on a material and system to release insulin according to the blood glucose concentration, but the system have not been put into practical use as yet [4].

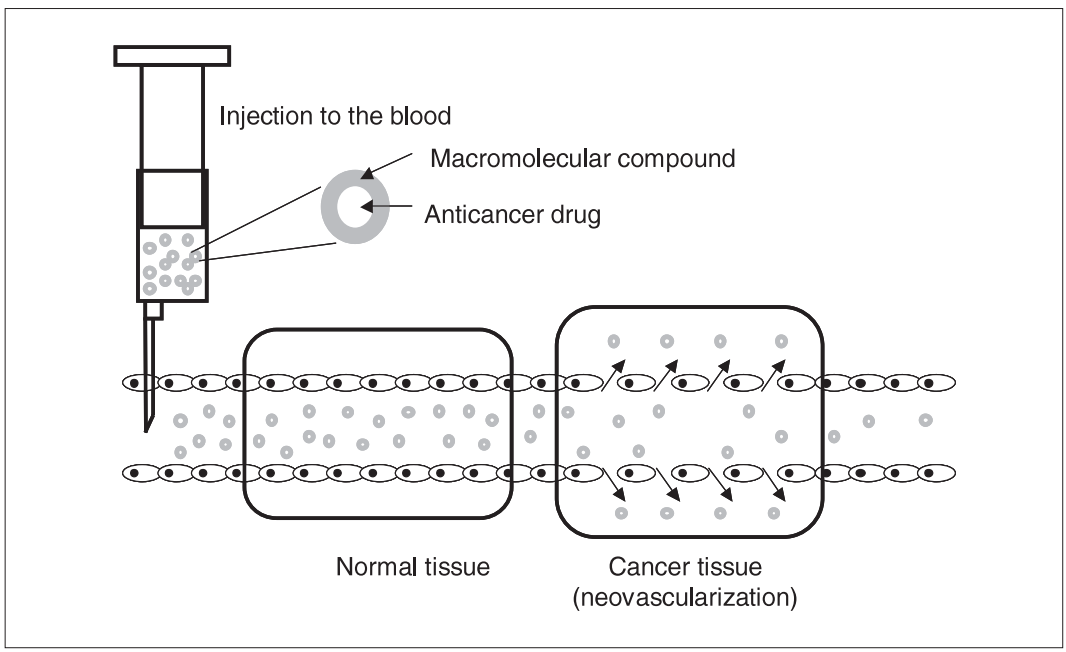
(2) Drug targeting

The targeting of drug is also called missile therapy, and it is a method of carrying a drug effectively to the targeted inflammatory site or cancer cells to demonstrate the drug's action. In 1988, Yutaka Mizushima (DDS Research Institute, Jikei University) developed a lipo product with particles (liposome) enclosing drugs within an artificial phospholipid membrane with multiple layers. This attracted people's attention as the first targeting product in the world. The lipo product utilizes the characteristics in which lipid particles often gather at the vessel having arteriosclerosis or at the inflammatory site. Lipo prostaglandin E1 (PGE1) products (first generation) enclosing PGE1, which is very effective for arteriosclerosis in lipid particles, was put into practical use. From 1992 to more recent years, annual sales in Japan of approximately 35 billion yen has been maintained. In PGE1 products, the drug is enclosed in soybean oil, and the surface is capsuled with lecithin. Except for the above products, steroid hormones and non-steroid analgesic/inflammatory drugs were put into practical use. At present, for the second-generation PGE1 product produced by esterifying PGE1, Mitsubishi Pharma Corporation is conducting phase 2 and phase 3 of the clinical studies in the United States and Japan[6].

On the other hand, research and development activities on drugs targeting cancer cells have been conducted based on a principle of active targeting to accumulate the anticancer drug to cancer, utilizing the antigen-antibody reaction with cancer cells. A certain level of achievement in the laboratory was obtained, but no success in animal tests has been obtained. The reason is because an antigen similar to the target cancer antigen exists in the blood and on the surface of other normal cells, and, therefore, the necessary amount of drug cannot be concentrated onto the target site.

Since Hiroshi Maeda (Dept. of Medical Researches, Kumamoto University Graduate School) et al. advocated the enhanced permeation and retention (EPR) effect in 1986, research on the targeting to solid cancer has significantly changed. As shown in Figure 5, new blood vessels in cancer tissue have a higher permeability than blood vessels in normal tissue, so that more polymer compound with a large molecular size permeates and transfers into cancer tissue. In addition, the recovery mechanism of polymer compounds through lymph vessels is incomplete in cancer tissue, so retention of a polymer compound within the cancer tissue may easily occur [7]. This is called an EPR effect. By this effect, passive targeting to

Figure 5: Selective delivery of anticancer drug to the site of solid cancer (EPR effect)



have cancer cells take in a drug in the blood became possible. As a result, in 1986 and after, the targeting to solid cancer made a new start as passive targeting by inhibiting the metabolism in the liver and kidney and using the sustained release, in contrast to the conventional active targeting by the antigen-antibody reaction.

6.4 Current status of research and development of DDS

As stated above, the research and development of DDS to date may be roughly divided into two; sustained release of drug and targeting to the affected target site, and these are considered individually. However, after the EPR effect was advocated for the targeting of solid cancer, the research and development came to be conducted not only for targeting to cancer cells but also for the system associated with the sustained release function.

6.4.1 Status of research and development of DDS in Japan

(1) Targeting to cancer cells

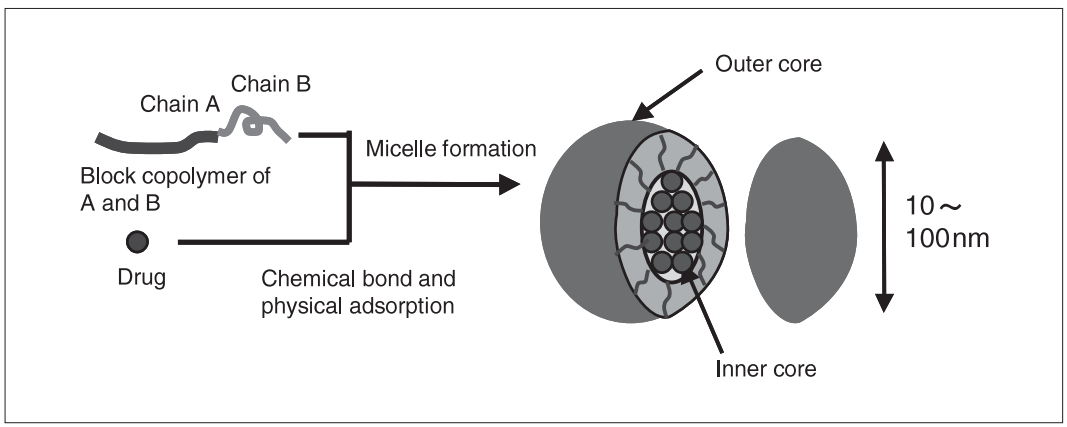
Kazunori Kataoka (Graduate School of Engineering, University of Tokyo, and the Biomaterials Center of National Institute for Materials Science, Japan) et al. obtained a significant increase in anticancer activity in the living body using polymer micelle enclosing an anticancer drug (Adriamycin), and confirmed the accumulation with a high selectivity to cancer tissue. As shown in Figure 6, in their study of a block copolymer using polyethylene glycol in chain A and poly (aspartic acid) in chain B, Adriamycin was chemically bound to the part of chain B to form polymer micelle (aggregate) of several dozen-nm uniform particle size with chain A as the outer core, and Adriamycin was also adsorbed physically to the inner core.

When aqueous solution containing polymer micelle capsuling Adriamycin was administered in mice with transplanted human colon cancer cells, the degree of accumulation of Adriamycin in cancer cells was more than 10 times higher than in single agent treatment with Adriamycin owing to the EPR effect, and a high anticancer effect was confirmed. Currently, phase 1 of the clinical study is in progress, and the micelle is highly expected as a targeting DDS to solid cancer. Moreover, the system of polymer micelle is really a general-purposed system that is easily applicable to cisplatin and other anticancer drug hardly soluble in water. The system is being studied to apply to gene therapy in which gene-encoding protein for treatment is enclosed in the micelle and carried effectively into the target cell.

(2) Application to regenerative medicine

Except for blood cells, most cells adhere to the scaffolding material, i.e. extracellular matrix, for proliferation and differentiation in the living body. When the tissue has a large defect, the scaffold is also lost. In this case, even if only cells are supplemented to the defect site, regeneration of the tissue cannot be expected. In order to regenerate the tissue, a tentative scaffold of cells must be supplied to the defect site, and, at the same time, a cell growth factor to proliferate the cells must be used. However, the cell growth factor is protein, and the life span in the living

Figure 6: Macromolecular micelle containing drug



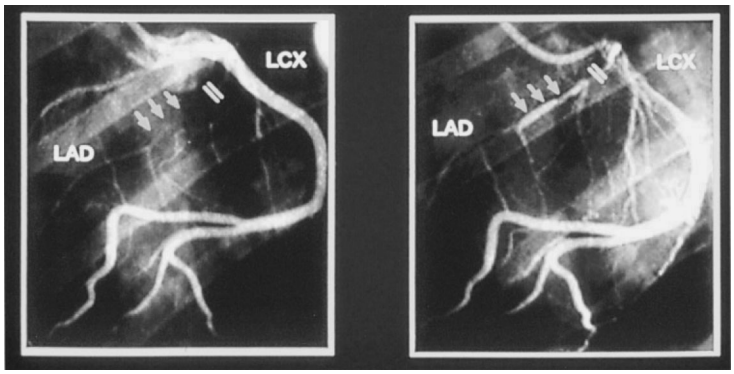
body is short and unstable. To solve these problems, if the cell growth factor or the related gene is capsuled in a bioabsorbent material to sustain the release in the regenerated site, it is considered that regeneration of the tissue will accelerate. Researches of regenerative medicine using DDS are being conducted actively, and here we introduce a part of them.

[1] Sustained release of cell growth factor using bioabsorbent polymer hydrogel

This is a technique to prepare hydrogel by cross-linking gelatin or collagen, or polymer mixtures such as hyaluronic acid and alginic acid, and fix the aqueous solution of cell growth factor within freeze-dried polymer hydrogel. The hydrogel is decomposed over time in the living body, and the decomposition rate can be controlled by the degree of the cross-linking of hydrogel.

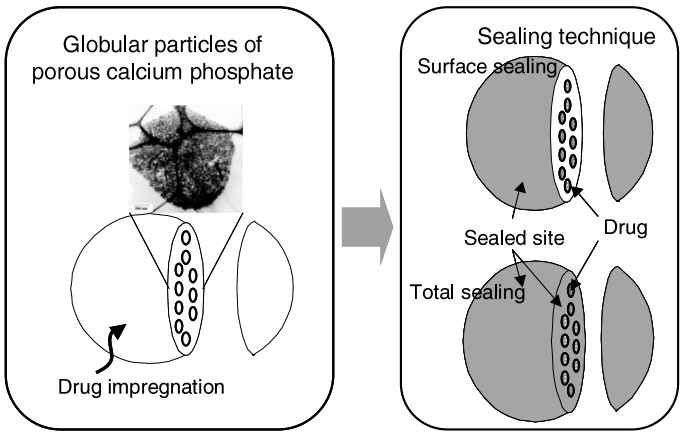
Yasuhiko Tabata (Institute for Frontier Medical Sciences, Kyoto University) et al. are conducting a study of sustained release of cell growth factor utilizing the bioabsorbent gelatin hydrogel with less toxicity in the living body. They consider that neovascularization can be induced by sustained release of basic fibroblast growth factor (bFGF), which is one of the angiogenesis factors, from gelatin hydrogel. In order to attempt regeneration of the coronary artery in the heart, at one week after the furcation of the left anterior descending artery was ligated in dogs, bFGF impregnated gelatin hydrogel particles were administered. As

Figure 7: Effect of bFGF impregnated gelatin particles on coronary arteries in the heart



Source: Department of Biomaterials, Department of Molecular Interaction and Tissue Engineering, Institute For Frontier Medical Sciences, Kyoto University; homepage of Tabata Laboratory: http://www.frontier.kyoto-u.ac.jp/te02/studies/research/heart.html

Figure 8: Sustained release system using inorganic materials



shown in Figure 7 [8], at one week after treatment, the blood flow resumed within the cardiac muscle and neovascularization was confirmed. This technique is a very useful method to supply oxygen and nutrition to ischemic disease or transplant cells, and to maintain the functions. [9]

[2] Sustained release of cell growth factor using bioabsorbent ceramic material

Yutaka Mizushima, Junzo Tanaka (Biomaterials Center, National Institute for Materials Science, Japan) and others are conducting the development of carrier materials for regenerative medicine using materials existing in hard tissues in the living body such as calcium phosphate and calcium carbonate. These materials are characterized in that the carrier is dissolved in the living body after sustained release of drug and shows no toxicity within the living body after being dissolved. In a product using calcium carbonate, sustained release of steroid hormones and basic protein was successfully achieved.

In recent years, they have developed the drug sustained release technique (plug up the pore of material) for apatite porous particles (pore diameter, 1-10 μm) existing in the hard tissue (particularly, bones) in the living body. As shown in Figure 8, in this system, after a drug is enclosed in the pore of calcium phosphate particles, the surface and inner pores are closed using a material without biotoxicity such as polysaccharides and calcium carbonate to increase the sustained release. This can be applied to regenerative treatment such as subcutaneous and intramuscular sustained release of protein products, local treatment, and local retentive sustained release. Two-week sustained release was successful in erythropoietin to increase red blood corpuscle, and in brain neurotropic factor essential for the survival of neuron of corpus striatum in the brain. These products were produced by focusing on the good adsorption of protein by calcium phosphate. Application to many protein products are expected after this.

(3) Application to gene therapy

In gene therapy, detoxicated viruses are currently used as the transgenic agent (vector) in many cases. However, occasionally it is difficult to completely eliminate the toxicity of the virus, or the virus may mutate later causing to obtain toxicity. Due to such problems, research and development activities on non-virus transgenic agents are conducted.

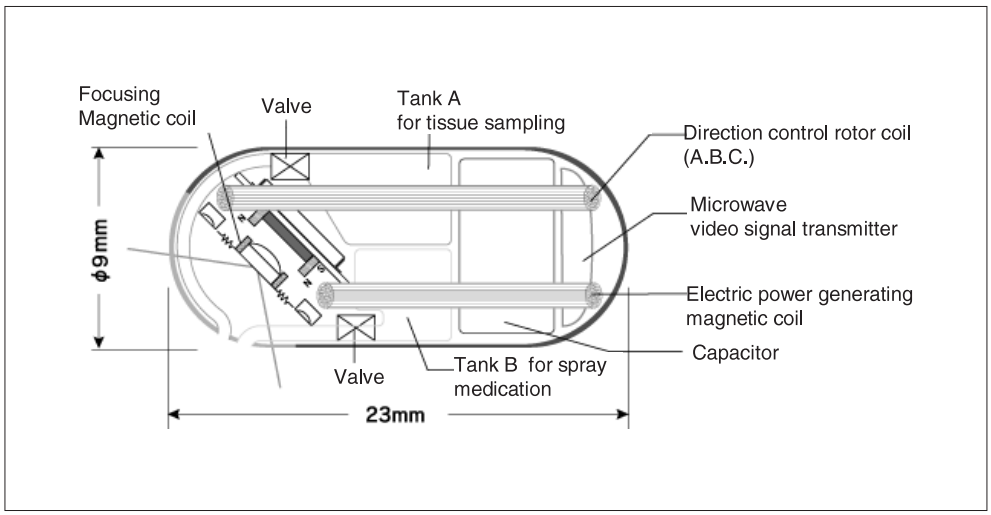
Kazunori Kataoka et al. are conducting the development of a non-virus transgenic agent in which a polymer compound mainly consisting with polyethylene glycol which has biocompatibility, covers around calcium phosphate taking in the gene. If this is mixed with human culture cells, the transgenic agent will be spontaneously taken into the cells. In cells with low calcium concentration, calcium phosphate will dissolve and the gene is expected to be released. In vitro experiments revealed that the transgenic agent could introduce a gene into cells and exhibited no toxicity to the cells. Following this, they plan to start experiments using animals such as mice.

Masahito Nakanishi (Gene Function Research Laboratory, National Institute of Advanced Industrial Science and Technology) et al. are aiming to develop a new transgenic system necessary for human gene therapy by membrane-fusion- liposome utilizing the membrane fusion activity of Sendai virus. The Sendai virus prolongs a very stable infection without killing the host cells. The membrane-fusion-liposome prepared using the Sendai virus has the outer membrane originating from the Sendai virus, so that it is directly fused with cell membrane, and can transport the inner substance to the objective cell.

(4) Drug targeting by MEMS

As for drug targeting using micro-electro-mechanical systems (MEMS), a capsule-type endoscope for the gastrointestinal system without batteries "NORIKA v3" [10], was announced in the autumn of 2002 by RF System Lab. (Japan), a medical camera manufacturer, with a catch phrase "A robot submarine enters the living body to give diagnosis and treatment," as shown in Figure 9. NORIKA v3 has a built-in electric power generating magnetic coil and electriccondensor in a 9ϕ~23mm capsule, and can be driven and controlled from outside of the patient's body using electromagnetic waves. By employing a CCD device for the imaging sensor, and by combining white and infrared lights and additional light with

Figure 9: MEMS for the gastrointestinal system



Source: Homepage of RF-System Lab., http:// WWW.RFNORIKA.comindex1.html

a different wavelength, high-quality moving pictures just like home videos are able to be obtained. The capsule has two tanks sharing 40% of the total volume which is for the administration of drug solution at the desired position by an exclusive valve control, that enables it to function as a DDS in the gastrointestinal system. As for the prices of NORIKA v3, the capsule will be launched at 100 U.S. dollars, with the extracorporeal control device at around 10,000 dollars. In December 2002, samples will be shipped for clinical studies.

On the other hand, for the cardiovascular system, because the size of the MEMS must be several hundred nm, the diameter of the capillary is as small as 5μm. It would be difficult to manufacture MEMS of such size even though current nanotechnology is utilized. Therefore, modification of liposome and polymer micelle with the nanomachine utilizing the morphological change of the nano-structure molecules are conducted to obtain a drug targeting nano-machine. In this case, the valve for control release of drug is intend to open and close utilizing the molecular morphological change.

6.4.2 Status of research and development of DDS in the United States and Europe

Research and development of DDS was also actively conducted in the United States and Europe as well as in Japan, aiming for application in cancer therapy, gene therapy, regenerative medicine, and AIDS therapy. Also in these countries, the employed polymer structures are micelle, dendrimer (dendriform structure), and liposome, etc. These polymer structures are characterized in that they can carry larger amount of drugs than other structures. The combinations of the polymer structure and drug are varied according to the employed methods; targeting to the affected site and sustained release of drug. As an example, the following may be given[11].

(1) Targeting to cancer cells

- R. Duncan (Cardiff Univ.) et al. in U.K. developed an anticancer drug for solid cancer and metastatic cancer tissue. An anticancer drug is bound to polyethylene glycol and N-(2-hydroxypropyl) metacryl (hydrophilic polymer by peptide bond) by peptide bond, which allows this to circulate in the blood for 24 hours.
- James R. Baker Jr. (Univ. of Michigan) and Jean M.J. Frechet (Univ. of California, Berkeley) et al. in the United States have already evaluated the use of an anticancer drug such as cisplatin and methotrexate bound to dendrimer (dendriform structure). The dendrimer is considered to reach the tissue easier owing to its small particle size of several nm.
- Glen S. Kwon (Univ. of Wisconsin) et al. in the United States evaluated an anti-AIDS agent, amphotericin B combining with micelle of polyethylene glycol-poly (L-amide asparate) with 30-50 nm in diameter for the use in AIDS therapy.

(2) Application to regenerative medicine

- Jeffrey A. Hubbell (Swiss Federal Institute of Technology, ETH) et al. evaluated the application of material such as fibrin whose structure turns to gel from liquid in the living body to regenerative treatment such as neovascularization, bone regeneration, and nerve regeneration. Cell growth factors (VEGF, etc.) are taken into the material.

(3) Application to gene medicine

- Alexander T. Florence (Univ. of London) et al. in U.K. developed a dendrimer aggregate (complex) such as dendrisome and dendriplex to bind with DNA, and attempted the application as a transgenic agent.

(4) Drug targeting MEMS

- Given Image Inc. in Israel published the development of a battery-driving capsule camera "M2A" in May 2002. However, several problems were pointed out including picture resolution, battery life span, retention of the capsule in the living body, and the sufferings of the battery's chemical substances, and it was reported that it would take several years to resolve such issues.

As stated above, research and development of DDS were also conducted extensively and actively in the United States and Europe. As a general evaluation of the research and development of DDS in Japan, in the 1950s when the concept of DDS was born, development of new pharmaceutical was highly evaluated but DDS was not appropriately evaluated. Therefore, the level of research and development of DDS was behind the United States and Europe. However, in the 1980s and after, when the new DDS gained general appreciation, the study of DDS significantly increased and achieved the present level in Japan not inferior to that of the United States and Europe but likely equivalent or superior to their level.

6.5 Measures taken by the government

From the 1980s to 1990s, research and development activities of DDS were covered mainly by the Grant-in-Aid for Scientific Research of the Ministry of Education. For 6 years from 1982, research and development activities on materials for DDS were conducted with the grant for special research (Teiji Tsuruta, professor emeritus of the University of Tokyo), etc. In addition, for 3 years from 1999, "Biomolecular design for biotargeting" in "Research of special area (A)" (Takeshi Kobayashi, representative of the Area and belonging to the Graduate School of Engineering, Nagoya University) was conducted and the targeting function was examined from a chemical point of view and the DDS was reconstructed using engineering knowledge.

It was taken up in the research project "Development and the application of the advanced science and technology (Nanomedicine project to apply nanotech to medicine)" of the science and technology policy by the Ministry of Health, Labour and Welfare in 2002. As application of nanotechnology to the medical field, DDS development is advanced by the understanding of diseases such as cardiovascular disease and of the function of cell receptors. As application of nanodevice to the medical field, the research and development of small precision therapeutic instruments are advanced. Those are important from the viewpoint of reinforcement of international competitiveness.

In the Japan Science and Technology Corporation, in the research area "Invention of new materials for chemical and biological systems" of the Core Research for Evaluational Science and Technology (CREST), as part of "Aiming to invent chemical and biological innovative functional materials, molecular machine, biodevice, biosensor technique in the nano scale" (Masuo Aizawa, research supervisor and belonging to the Tokyo Institute of Technology), "Invention of nano-structure device functioning as a gene vector" was proposed and taken up by Kazunori Kataoka et al. in 2001. The purpose is to create a safe and high-function "gene

vector" carrying various drugs including gene to targeted tissue in the living body, and conducting treatment and diagnosis. The vector is prepared by the exact self-organization of polymers and lipid molecules.

In addition, in 2002, the proposal of Tokuko Haraguchi (Communications Research Laboratory) et al. concerning the "Invention of artificial cell nucleus as a gene delivery system" was taken up in the "Construction and utilization of advanced function structures of soft nanomachine" (Hirokazu Hotani, research supervisor and belonging to the Graduate School of Science, Nagoya University). The research aims to develop a gene delivery system with a special function useful for gene therapy and drug treatment. Beforehand, understanding of the formation mechanism of the nuclear membrane around the chromosome and development of an artificial cell nucleus with a special function are conducted.

In the National Institute for Materials Science, Biomaterials Center was started in October 2001, aiming to realize a society with advanced medicine. At the center, extensive and comprehensive research and development activities on biomaterials are conducted. Application of polymer micelle to targeting to cancer and to gene therapy and that of ceramic materials to regenerative treatment are conducted for DDS. At present, they collaborate with 20 engineering departments of universities (including 4 foreign universities), 15 medical departments of universities (2 foreign) and 15 companies (2 foreign), aiming to be the main foothold of research and development of biomaterials in Japan[12].

6.6 Picture of DDS in the future

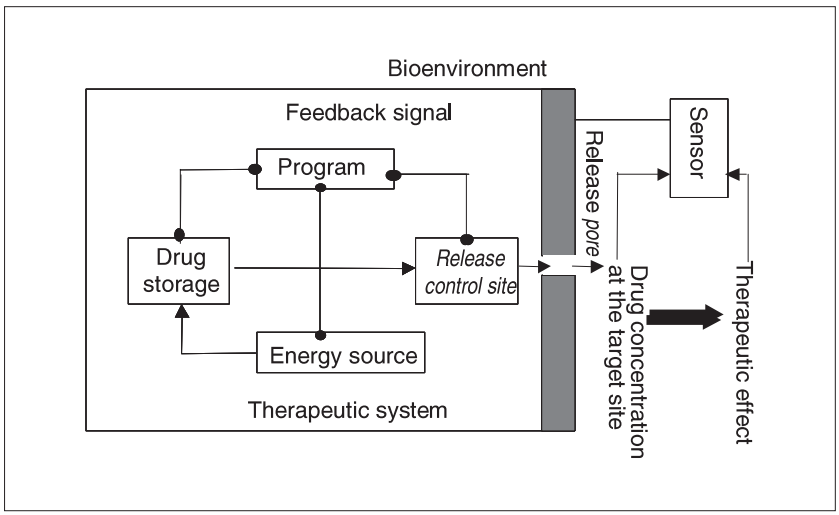
What is desired for the future DDS is to control the drug transfer and reaction within the living body according to a patient's individual differences, i.e., what amount, what speed, and where and how the drug is released. For example, in the treatment of diabetes, as stated above, it is necessary to release insulin according to the glucose concentration in the blood. The system shown in Figure 10 is an ideal drug controlled release system. To realize this system, the system must have the following functions.

(1) Sensing function for the therapeutic effect and drug concentration (Sensor development)
(2) Function for data processing and setting release patterns (Data processing development)
(3) Precision release function based on the above setting (Precision release device development)

It is also required for materials to have reliability and safety to keep functions (1) to (3).

Not only research and development of material sciences such as polymer and ceramic materials to be combined with drug, but also the development of sensing function, microanalysis, and precision machine engineering are important. The following research and development may be suggested.

Figure 10: Ideal drug controlled release system



- Development of nanomachine for targeting DDS, which has a drug-release control valve driven by the morphological change of molecule. It may be enabled by the modification of liposome and polymer micelle with nanomachine utilizing the morphological change of nano-structural molecule, drugs, and proteins having a sensing function.
- Research and development of a drug releasing MEMS associated with the sensing function, data processing, and precision release device.

6.7 Present status of examination of DDS products

The "examination of DDS products" in the Ministry of Health, Labour and Welfare is not considered very much. The present status of the "examination of DDS products" is as the following[13].

- According to the notification from the Director General in April 1999, regulations concerning new active ingredients, new compounding ingredients, new route of administration, new virtues, new dosage form, and new dosage are provided, but there is no peculiar regulations corresponding to DDS products.
- In the regulation for the new dosage form which is considered to be most related to DDS products, toxicity tests, and efficacy pharmacology and general pharmacology tests are not necessary. However, those tests are necessary for DDS products that provide significant efficacy owing to excellent ideas and technology.
- In the case of DDS products secondly put on the market, even if the ingredients are different from the advanced product, it is examined and permitted in the same way of conventional drugs.
- The guidelines for the examination of sustained-release drugs were publicized in 1988, but the revision of the guidelines is not conducted.

Therefore, the Japan Society of Drug Delivery System submitted the "draft guidelines for the examination of DDS products" to the Ministry of Health and Welfare in July 1999. The guidelines suggests that the characteristics of DDS products should be understood well, logically necessary basic and clinical tests should be sufficiently conducted, and unnecessary ones should be omitted to shorten the examination period[13].

An actual problem is that the period of examination of pharmaceutical manufacturer in our country is so long that the drugs are sometimes re-imported after receiving permission in the United States and European countries. The long duration for the examination of new drugs in Japan delays the practical use of drugs, that is likely to be one of the causes for the lower competitiveness of the medical industry of Japan than that of the United States and Europe.

6.8 Conclusion

In the case of sustained-released type DDS, almost all of the products with less difficulties in the development are already introduced and put into practical use. In the case of targeting DDS to cancer cells that was stagnant, its development rapidly progressed and the results came to be applied clinically. In the field of regenerative treatment and gene therapy, not only gene but also cells are recognized as a drug, and a system to carry this to the targeted affected site is demanded. Moreover, MEMS being able to be used as a DDS for the gastrointestinal system was developed. Under these circumstances, projects for DDS were taken up and proceeded in the research project of the science and technology policy (Nanomedicine project to apply nanotech to medicine) of the Ministry of Health, Labour and Welfare, and in the Core Research for Evaluational Science and Technology of the Japan Science and Technology Corporation. In addition, in the "New industry created by nanotech" — n-Plan 2002— published in November 2002, Nippon Keidanren proposed that in order to maintain Japanese technological competitiveness being high in the field of nanomedicine, which is expected to develop in the future, the government should head the frontline of the research and development in the nanomedicine field and tackle the arrangement such as review and rapid operation

of the medicine-related system, as well as close cooperation between medical and engineering fields.

The research and development of DDS is an interdisciplinary area, and requires close cooperation among medical science, pharmacy, material science, bioengineering, precision mechanical engineering, electronics, computer and information science and so on. The achievement of cooperation among such wide fields cannot be expected by the effort of only one corporation, one university, or one institute. Therefore, followings are necessary to maintain and raise the level of Japan's high technological competitiveness. Constructing an organization to play a key role in the cooperation under the strong leadership of the government as soon as possible, gathering highly competent researchers, arrangement of an environment and system, and advancing the research and development of DDS by a joint industry-university-government project. Under the circumstance, the "Biotechnology Strategy Meeting" proposal of fundamental principles suggested the increase in funds of bioresearch (double in 5 years) and the relief of regulations including the reduction of the period for the examination of new drugs. This proposal is an important policy to promote the research and development of DDS.

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