BST licenses out DDS technologies to pharmaceutical companies having API, and co-develops. BST also gives licenses of DDS to contract manufactures working under GMP.

Abstract:

BST has novel oral and transdermal DDS technologies, Gastrointestinal mucoadhesive patch system (GI-MAPS) and Dissolving microple (DMP), for macromolecular drugs. Both DDSs are composed of pharmaceutical additives and so have high safety.

<table>
<thead>
<tr>
<th>Products &amp; Service</th>
<th>Stage</th>
<th>Outline</th>
<th>Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) GI-MAPS</td>
<td>Pre-clinical</td>
<td>Looking for pharmaceutical company to codevelop GI-MAPS for GLP-1</td>
<td>Bioavailability 3%, is obtained in beagle dog study</td>
</tr>
<tr>
<td>2) DMP</td>
<td></td>
<td>Circuits phase II study is proceeding with basic fibroblast growth factor, bFGF, DMP. About 20,000 DMP chips have been administered over 300 patients. There is no side adverse event.</td>
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<td>3)</td>
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</table>

Profile

2. Concept of the GI-MAPS

The concept of GI-MAPS is (1) to protect drug from the hydrolysis by the digestive enzymes and (2) to obtain high concentration gradient of drug and absorption enhancer between the intestinal mucosal surface by adhering to the target site of the intestine and enterocytes.

![Diagram of GI-MAPS](image)

- Protecting layer (Back layer, e.g. water insoluble film)
- Protect drug from degradation by digestive enzymes
- Drug-carrying layer (closed space)
- Adhesive layer (e.g. mucoadhesive gel-forming polymer film)
- Adhesive site-controlling layer (e.g. enteric polymer (pH sensitive) film)
- Adhere to the gastrointestinal mucosa
- Protect drugs from gastric juice in the stomach
- Dissolve at target site of small intestine

If you have any questions, please contact at: news-japan@eu-japan.eu
Providing innovating drug delivery technologies
for better lives

Providing solutions to poor bioavailability problems of API
by DDS technology
BioSerenTach (BT) has the original innovative drug delivery technologies, and provides pharmaceutical companies with drug delivery systems (DDSs) to develop and commercialize new pharmaceutical products.

By designing DDSs that break down the barriers inherent to many APIs in traditional delivery approaches, BioSerenTach helps to reduce the side effects, enhances the pharmacological activity of many drugs and improves QOL of patients in the world.

BT has developed a number of innovative DDS technologies and is interested in exploring possible partnership opportunities with pharmaceutical and biotech companies.

Solution for poor bioavailability problem of API
With the aid of microfabrication technology, Professor Takada made it possible to prepare microparticles including microcapsules and microspheres individually, i.e. one by one, and as a result high drug loading efficiency, theoretically 100%, was attained. Therefore, each microparticle has the same shape and size. Especially, Professor Takada innovated two kinds of microparticles.

- Three-layered microcapsules for
  1. Oral preparation designates as “Gastrointestinal mucoadhesive patch system GI-MAPS™
  2. Injection preparation to obtain long-term sustained release of API

- Dissolving micropiles as transdermal drug delivery system (TDDS)

Pharmaceutical preparations

- Recent advance in microfabrication technology
- BioSerenTach has Two key technologies

Three-layered microcapsules
Dissolving micropiles
**1. Introduction**

The technology, which improves the bioavailability (BA) of poorly absorbable drugs from the gastrointestinal (GI) tract, has been recognized as an important strategic tool to optimize oral drug therapy and to improve the patient compliance. Protein/peptide drugs are the representative low BA drugs.

To elucidate the pharmacological activity of protein/peptide drugs, two barriers, i.e. hydrolysis in the GI tract and low membrane permeability, must be conquered. Oral administration destroys all physiological activity of the protein/peptide drugs and explains why typical oral BA of protein/peptide drugs is usually less than 1-2%.

To improve the oral BA of protein/peptide drugs, some technologies such as absorption enhancers and enzyme inhibitors and enteric-coated formulations, have been challenged. However, no technology has been launched yet. Recent studies have indicated that the dilution and spreading of absorption enhancer in GI tract reduce the enhancing effect of the absorption promoter (1, 2).

Professor Kanji Takada (Kyoto Pharmaceutical University, Department of Pharmacokinetics) has invented a novel DDS technology to improve the BA of protein/peptide drugs. This technology is based on the patch formulation, which creates a closed space on the target site of GI mucosa by adhering to the mucosal membrane.

**2. Concept of the GI-MAPS**

The concept of GI-MAPS is (1) to protect drug from the hydrolysis by the digestive enzymes and (2) to obtain high concentration gradient of drug and absorption enhancer between the intestinal mucosal surface by adhering to the target site of the intestine and enterocytes.
3. Concept and function of GI-MAPS

- After oral administration of gelatin capsule containing GI-MAPS, drugs in the formulation are protected from the gastric juice in the stomach by enteric film on the adhesive layer (adhesion site controlling layer) and protection layer.
- When GI-MAPS is transferred to the small intestine, the adhesion site controlling layer of GI-MAPS is dissolved at the target site of the small intestine, and GI-MAPS adhere to the intestinal mucosal membrane.
- As a result of adhesion, the drug carrying layer of GI-MAPS existing between protecting layer and adhesive layer forms a closed space. Drugs in the closed space are protected from the attack of the digestive enzymes in the intestinal lumen.
- Dissolution of drug in the drug carrying layer forms the high concentration gradient of drug between the GI-MAPS and the enterocytes, and consequently formulated drug can be efficiently absorbed.
- In addition, when an absorption enhancer is formulated with a drug in the drug carrying layer, the concentration of absorption enhancer as well as drug in this closed space reaches to high level. Under this condition, optimal absorption enhancing effect can be obtained.

4. Proof of the concept of GI-MAPS

A peptide drug, desmopressin, was formulated in GI-MAPS and applied to the dog intestinal lumen after abdominal incision where the GI-MAPS was adhered to the intestinal membrane by surgical glue. After application, blood samples were obtained and plasma drug concentrations were measured by a LC/MS method. By comparing to the iv data, the BA of the peptide drug from GI-MAPS was 46%, though that from the co-administration with absorption enhancer was 10%.

5. Improvement of oral availability of protein/peptide drugs by GI-MAPS

1) Granulocyte colony stimulating factor (G-CSF)

G-CSF (125 μg) loaded GI-MAPS was orally administered to beagle dogs. Total white blood cell (WBC) count in the systemic circulation after administration significantly increased. In contrast, WBC after oral administration of G-CSF solution did not significantly change from the pre-dose level. The pharmacological availability of G-CSF from GI-MAPS was 23% as compared to the intravenous administration of the same dose of G-CSF (3, 4).
2) Interferon-α (IFN)

IFN loaded GI-MAPS was orally administered to beagle dogs at a dose of $5 \times 10^6$ IU. After administration, serum IFN concentrations were measured.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (pg/mL)</td>
<td>$310 \pm 58$</td>
<td>$343 \pm 61$</td>
<td>$107 \pm 37$</td>
<td>$52 \pm 11$</td>
<td>$50 \pm 17$</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.E. of three subjects.

6. Adhering of GI-MAPS to the intestinal mucosa

At 1, 2, 3, 4, 5 and 6 hr after administration of GI-MAPS into the rat duodenum, the rats were sacrificed. The whole small intestine from pyloric sphincter to the ileo-cecal junction of each rat was divided into five portions (#1-#5) and the remaining GI-MAPS in the GI tract was visually detected.

GI-MAPS was transferred from section #1 to #4 gradually. It took approximately 4 hr. Therefore, GI-MAPS$^{TM}$ adhered to section #2 and retained there for approximately 2 hr. (6)
7. Application of GI-MAPS to non-protein/peptide drugs

GI-MAPS technology can be applicable to not only poorly absorbable drugs such as HIV protease inhibitors and peptide-mimetic drugs but also non-absorbable drugs like gentamicin etc. Pharmaceutical industry has many drug candidates. However, most of them are dropped out because of low- or non-absorbability from the GI tract. GI-MAPS™ is a sophisticated technology to solve the low BA problem of these drug candidates.

8. Human study of GI-MAPS containing caffeine as a model drug

To study the absorption enhancing effect of GI-MAPS, 50 mg of caffeine was formulated in GI-MAPS and was administered to human volunteers. After ingestion, saliva samples were collected consecutively for 12 hr and salivary caffeine excretion rates were measured by a HPLC assay method. As a control, enteric capsule containing 50 mg of caffeine was used. The salivary caffeine excretion rate after oral administration of GI-MAPS was significantly increased as compared to that obtained from enteric capsule.

From these results, GI-MAPS can be applicable to oral sustained-release preparation of clinically important drugs, for example theophylline. (7)

Salivary caffeine excretion rate-time profiles after oral administration of caffeine in GI-MAPS and enteric capsule to there human volunteers.


9. Production of GI-MAPS

With Toray Engineering Co., Ltd., BT codeveloped a micron size GI-MAPS producing machine with the aid of big grant from the government in which drug can be formulated as solid or semisolid state.

BT has an alliance with Nipro Co., Ltd. to produce GI-MAPS under GMP condition. Nipro has a contract manufacturing function of GI-MAPS.

With this machine, the applied area of GI-MAPS has been enlarged as follows:
- Colon delivery of steroids etc. for the treatment of inflammatory bowel disease (IBD) where Eudragit S100 is used as the surface membrane.
- Targeting of metronidazole and ampicillin to the stomach for the treatment of *Helicobacter pylori* infection where mucoadhesive polymer is used as the surface membrane.
- Oral sustained-release preparation where water-insoluble semipermeable membrane like ethylcellulose or cellulose acetate membrane is used as the surface membrane.

![GI-MAPS producing machine](image)

**Patents**

Patents on GI-MAPS were obtained in USA and Japan.

US patent: 7,097,851 B1, granted on August 29 in 2006
Japan Patent: 4497725, granted on April 23 in 2010
Japan Patent: 2017-125572

![Capsule containing GI-MAPS](image)
Dissolving micropiles

To increase the skin permeability, many different approaches have been studied. For example, chemical/lipid absorption enhancers, iontophoresis and electroporation are under investigation. However, the success of these transdermal drug delivery systems has been limited because of low membrane permeability of drugs through the skin. On the other hand, based on the development of micro-fabrication technology, the use of micron-scale piles showed a dramatically increase of the skin permeability of drugs. Solid microneedles made of stainless steel have been shown to increase the transdermal permeability of drugs with “poke with patch”, “coat and poke” and “dip and scrape” delivery systems. BioSerenTach’s microneedle technology differs from those systems. Micropile is made of self-dissolving polymers having thread-forming property. The polymers are (1) proteins like albumin etc, (2) polysaccharides like dextran, chondroitin sulfate, hyaluronic acid etc, and (3) others. Strictly speaking, BioSerenTach’s microneedle is not a microneedle but is a micropile. Dissolving micropile can be easily prepared under room temperature. Therefore, this system, dissolving micropile, can be applied to drugs that are sensitive to high temperature such as peptide/protein drugs, i.e. insulin, erythropoietin, growth hormone etc. In addition, dissolving micropile can be also applicable to genetic materials, i.e. oligonucleotide delivery, and vaccines including both protein and DNA vaccine.

Dissolving micropile was applied to insulin and the pharmacodynamic evaluation was performed. Insulin was formulated into thread-forming polymer and pen-type dissolving micropile was prepared under room temperature as shown in the photo. Dissolving micropile was administered to the dog skin, 1.0 and 2.0 IU/dog. Blood samples were obtained for 6 h. Plasma glucose levels were measured and the results are shown in the following figure, where insulin solution was subcutaneously (sc) injected as a positive control preparation. The physiological availabilities of dissolving micropile were 75-99 %.

[Graph showing plasma glucose levels vs. time profiles after application of dissolving micropile to dogs]
With erythropoietin (EPO), dissolving micropile was also evaluated in rats. After percutaneous administration of EPO-micropile, 100 IU/kg, serum EPO level gradually increased and reached to the peak level at 8 hr after administration. The bioavailability (BA) was calculated to be 99%.

Dissolving micropile was also applied to human growth hormone (hGH). After the percutaneous administration of hGH-micropile to rats, 200 μg/kg, plasma hGH level showed its maximum level at 1 hr and the BA was calculated to be 87.5%.

BioSerenTach developed a machine to prepare dissolving micropile array chip as shown in the photo.

Each micropile has a cone shape and is composed of API and pharmaceutical additives.
Micropiles dissolve rapidly and completely in the epidermis of the skin and can deliver API into the systemic circulation with high bioavailability.

As an example, insulin dissolving micropile array chip was prepared and was administered to the rat skin by pressing with fingers and pharmacodynamic study was performed by measuring plasma glucose levels at the insulin dose of $1.73 \pm 0.17$ IU. As a positive control, insulin solution was sc injected to another group of rats, $1.0$ IU/kg. By comparing the total areas above the plasma glucose level vs. time curve (AAC), relative pharmacological availability of $52.2\%$ was obtained.

Two-layered dissolving micropiles

To increase the availability of API formulated in the preparation, BioSerenTach developed two-layered dissolving micropiles as the 2nd generation dissolving micropile array chip where API was localized at the distal part of micropiles.

Proof-of-concept experiment

The following two kinds of dissolving micropile array chip where insulin was formulated at the acral portions, $180 \mu m$ and $210 \mu m$ from the top of micropiles, were prepared and evaluated in rat experiment.

<table>
<thead>
<tr>
<th>Physicochemical characteristics of insulin loaded dissolving micropiles</th>
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<tbody>
<tr>
<td>Dissolving micropiles</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>$180 \mu m$ length</td>
</tr>
<tr>
<td>$210 \mu m$ length</td>
</tr>
</tbody>
</table>

Each value represents the mean $\pm$ S.E. ($n=4-5$)

180 $\mu m$ length dissolving micropiles

Before administration

After administration

210 $\mu m$ length dissolving micropiles

Pharmacodynamic analysis by comparing the areas above the plasma glucose concentration vs. time curve, AACs, obtained after percutaneous administration of insulin dissolving
micropile array chips and sc injection of insulin solution, relative physiological availability (RPA) of insulin was determined to be 98% in both dissolving micropiles.

**Plasma glucose level-time curves after subcutaneous injection of insulin solution and percutaneous administrations of dissolving micropiles to rats**

Functions of dissolving micropile array chip

(1) Painless administration of drugs by percutaneous route
(2) High pharmacological availability and high bioavailability
(3) High safety (no fear of HIV infection)
(4) Percutaneous delivery of peptide/proteins
(5) Skin vaccine

Related technologies

To enhance the skin permeability of drugs, absorption enhancers, iontophoresis, electroperoration and ultrasound have been studying. TDDS is severely limited by the poor permeability of drugs through the human skin, i.e. most drugs do not permeate through the skin at therapeutically relevant rates. Microneedles made of metal and polymers like poly(lactic acid) belong to the category of medical device.

Two-layered dissolving micropile array chip producing machine

Producing machine of two-layered dissolving micropile array chips that assumes to work under GMP condition was developed in 2011 by the fund of Japan Science and Technology Agency (JST).
**Application of dissolving micropile to local therapy drug**

Lidocaine was formulated as local anesthesia and pharmacodynamic study was performed in rats where lidocaine cream was used as a positive control. After the administration of lidocaine dissolving micropiles, 50% reduction of idiospasm was obtained at 5 min after administration, though it took 30 min in lidocaine cream. The onset time has been greatly improved.

**Use**  
Dosage form: Transdermal drug delivery system (TDDS)  
Applicable drugs: Drugs of which clinical dose is lower than 10 mg  
*Peptides, Proteins, Vaccine, Hormones, Organic compounds*

**Patent application**  
29 patents including 8 world-wide have been applied. Two of them are granted.  
- JP 4913030, US 8,506,980, Canada 2,595,894  
- JP 5538897, US 8,491,534, Canada 2,706,404, Australia 2008327083, Korea10-1555391

**Public information**  
Dissolving micropile array chip developed by BioSerenTach is recognized as a representative innovation of Japan and is introduced globally through the website related to the Ministry of Foreign Affairs of Japan.  

**Cosmetics**  
Dissolving micropile array is applied to cosmetics. Dissolving micropile array sheet made of hyaluronic acid is on the market in Japan for wrinkle treatment. Dissolving micropile array chip containing vitamin C is used for the treatment of fleck.
Three-layered long-term sustained-release microcapsules

Microcapsules are used to obtain sustained-release nonparenteral preparations, especially subcutaneous injections. Among them, leuprolide acetate microcapsule is a representative preparation. After sc injection, leuprolide acetate is released from microcapsules for long term, one month or 3 months. Strictly speaking, this system is not microcapsules, i.e. microspheres. Microspheres are prepared by formulating leuprolide acetate into poly(lactic acid) and/or poly(lactide-co-glycolide), PLGA. PLGA microspheres are not applicable to other drugs because of low loading problems. BioSerenTach developed a new microcapsule with three-layered structure. Between surface layer and backing layer, drug is loaded. The advantage of our Three-layered long-term sustained-release microcapsules are as follows:

1. Loading efficiency is 100%
2. No burst phenomenon

FITC-dextran was used as a model macromolecular drugs and in vitro release study was performed. As shown in the following figure, long-term sustained-release characteristic was obtained.

Patents
- JP4990465

*In vitro release profiles of FITC-Dextran from three-layered microcapsules*

Each value shows the mean ± S.E. (n=3~5)