DAEWOONG

Open Collaboration for Innovative DDS Technology Development

Are you ready to become the real pharmaceutical scientist?

This integrated research program has been establishedsince 2020. This program will give a chance to the talented researcher and scientist in pharmaceutical field to do the collaboration research program with Daewoong Group as the biggest global healthcare group from South Korea. Research program will conduct in both Indonesia and Korea, and this program is fullyfunded program.

e-mail @

Register Now!

dwopencollabo@daewoong.co.kr

(Please check the detail requirement in the next poster)

For further inquiries please send us email to **2220265@daewoong.co.kr**

REGISTRATION GUIDELINE

ELIGIBILITY

- Currently an enrolled master/PhD student, researcher, or professor in the Pharmaceutical Faculty / Department
- Willing to do research related to the pharmaceutical product development
- No issue to travel abroad (some research period will be done in South Korea)
- Fluent in English for daily communication (able to speak in Korea can be an additional point)

BENEFITS

- Fully funded program (full research funding support, Supplying active ingredients and rare-chemicals on request, Technical and logistical assistance)
- After project evaluation, career development opportunities may be offered (Internship programs at Daewoong Site in Korea for 3~6 months)
- After project evaluation scholarship support and employment opportunities

REQUIRED DOCUMENTS

- Research proposal [Designation form]
- Certificate of enrollment / proof of active lecturer or researcher
- Personal CV [Free form]

REGISTRATION PROCESS

- Choose one research topics from the list
- Write your research proposal [**Designation Form**]
- Write your CV(curriculum vitae) form [**Free Form**]
- Please send all documents by email [**dwopencollabo@daewoong.co.kr**]
- Please be aware that all document must be in English!

Daewoong Pharmaceutical R&D promotional video

https://youtu.be/sAxVFJR2_UY?si=P_BcGZbulyhB9Ny1

RESEARCH TOPICS- I

Platform Technology Development for Intranasal Formulation & Device Technology

1. Objectives

① **Development of the intranasal (IN) formulation technology** to improve the drug delivery efficiency to the brain using the Nose-to-Brain(N2B) delivery route

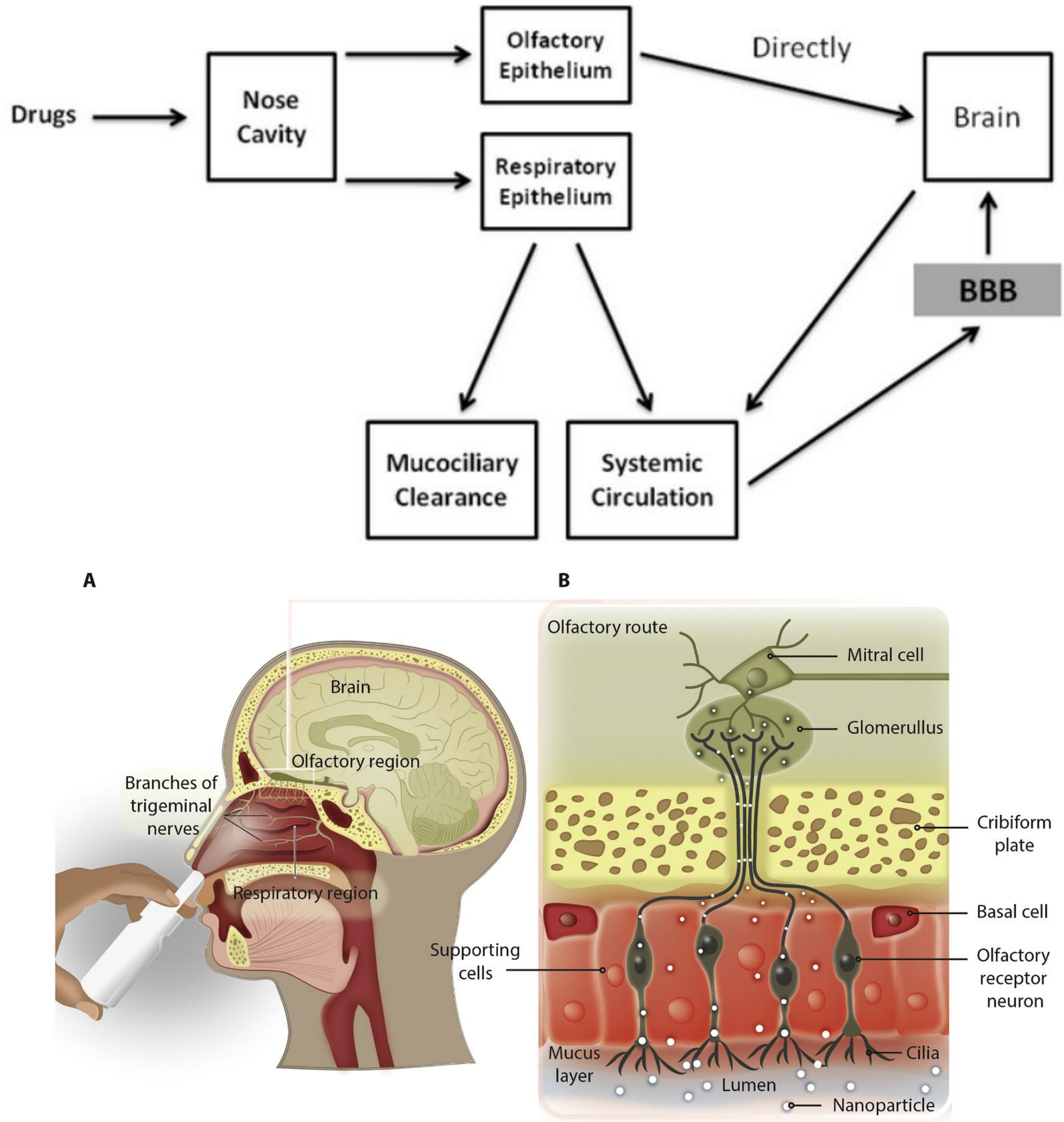
② Understanding the mechanism of drug transport from the nasal cavity to the brain and **generating engineering design ideas for a device technology** to target delivery of therapeutic agents to the olfactory region for direct Nose-to-Brain(N2B) pathway.

*** In case the device design-related ideations seem to be impractical, the overall objective would be to prioritize the formulation compatible with Nose-to-Brain(N2B) delivery addressing the challenges associated with the IN route.**

2. Background on the Intranasal Delivery

The main areas of the nasal cavity include the vestibular region, the respiratory region, and the olfactory region The olfactory area is located above the superior turbinate, while the rest of the area below is for respiration, and both areas are covered by mucous membranes. In terms of drug absorption through the nasal route, the respiratory mucosa and olfactory mucosa are the main target locations.

The respiratory mucosa occupies **80-90% of the surface** area and is rich in blood vessels, making it the **primary route for systemic absorption**. **The olfactory mucosa covers about 5-10% of the surface and provides a direct pathway to the brain's olfactory bulb through the olfactory system.**



3. Limitations with Nose-to-brain Delivery and Solutions

Limitation: The limited volume of formulation that can be applied to the nose, involves **poor drug permeability from nasal mucosa**, mucociliary clearance, the presence of a mucus layer, and local enzymes, and low drug retention time are some of the factors that can hamper drug absorption through the IN route.
Solution: IN formulations must be composed of biocompatible and odorless excipients and **avoid rapid elimination** due to mucociliary clearance and/or enzymatic degradation.

Formulations must present appropriate viscosity, physiological tonicity, and pH compatible with the nasal mucosa. Thus, different strategies have been explored to overcome the challenges of this route of administration. Most of these approaches aimed to enhance molecule absorption and permeability by increasing the time in which the dosage form remains in the nasal mucosa and promoting drug concentration in the CNS.

4. Strategies to Achieve the Objectives

Below are the Formulation strategies:

① Sol-gel technology

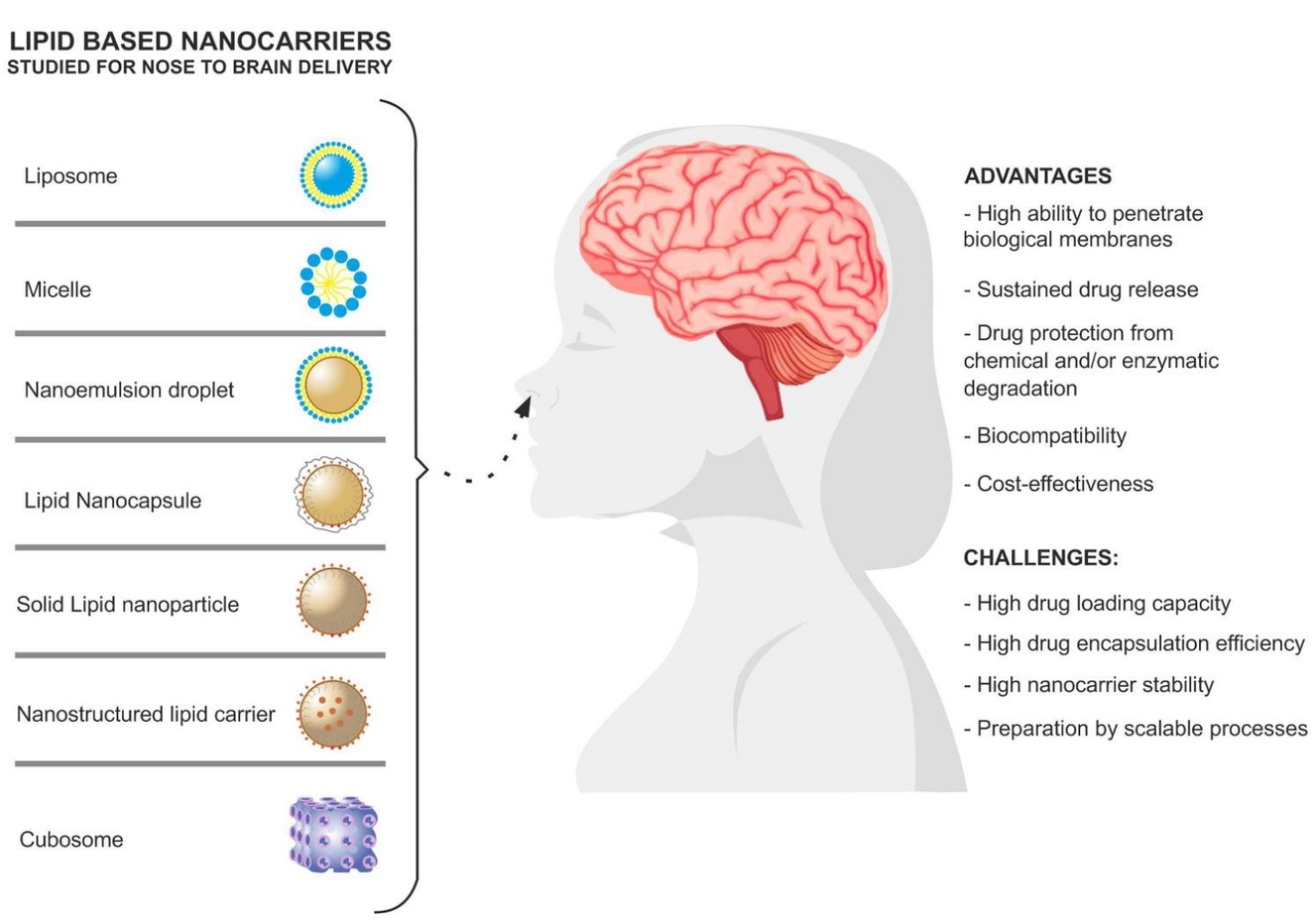
Sol-gels are administered through the nose and quickly become a gel upon contact with the mucosal tissue. This allows direct delivery from the nose to the brain. By bypassing the stomach and intestines, the gel avoids first-pass

metabolism, potentially leading to **much better absorption** - even better than nasal sprays and other advanced methods. Moreover, the gel remains in the nasal passages, gradually releasing the drug and keeping it effective for several days, making it **suitable for a sustained-release system.**
This technology offers distinct advantages such as increased patient compliance, improved safety, **lower dose requirements** than oral administration, rapid onset of action, and minimized systemic exposure, reducing the risk of peripheral toxicity.

② Nanoparticles Formulations

Nanoparticle-based drug delivery systems have shown to be a valuable tool to promote drug accumulation in the CNS through an increased permeation across the olfactory region.
There is extensive research on using low-molecular-weight compounds, proteins, peptides, nucleic acids, and more for delivery through the Nose-to-Brain route. This approach offers several advantages such as minimizing drug degradation, maximizing bioavailability, increasing residence time, controlling drug release, and reducing systemic side effects. Typically, nanoparticles in the range of 100-200 nm demonstrate good N2B delivery efficacy.
Lipid and biomolecule-based nanoparticles: These are commonly used for N2B delivery.

- Lipid-based nanoparticles: Liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, polymeric nanoparticles (chitosan / PLGA / PEI), albumin nanoparticles, etc.
- Nanoemulsions & Microemusion

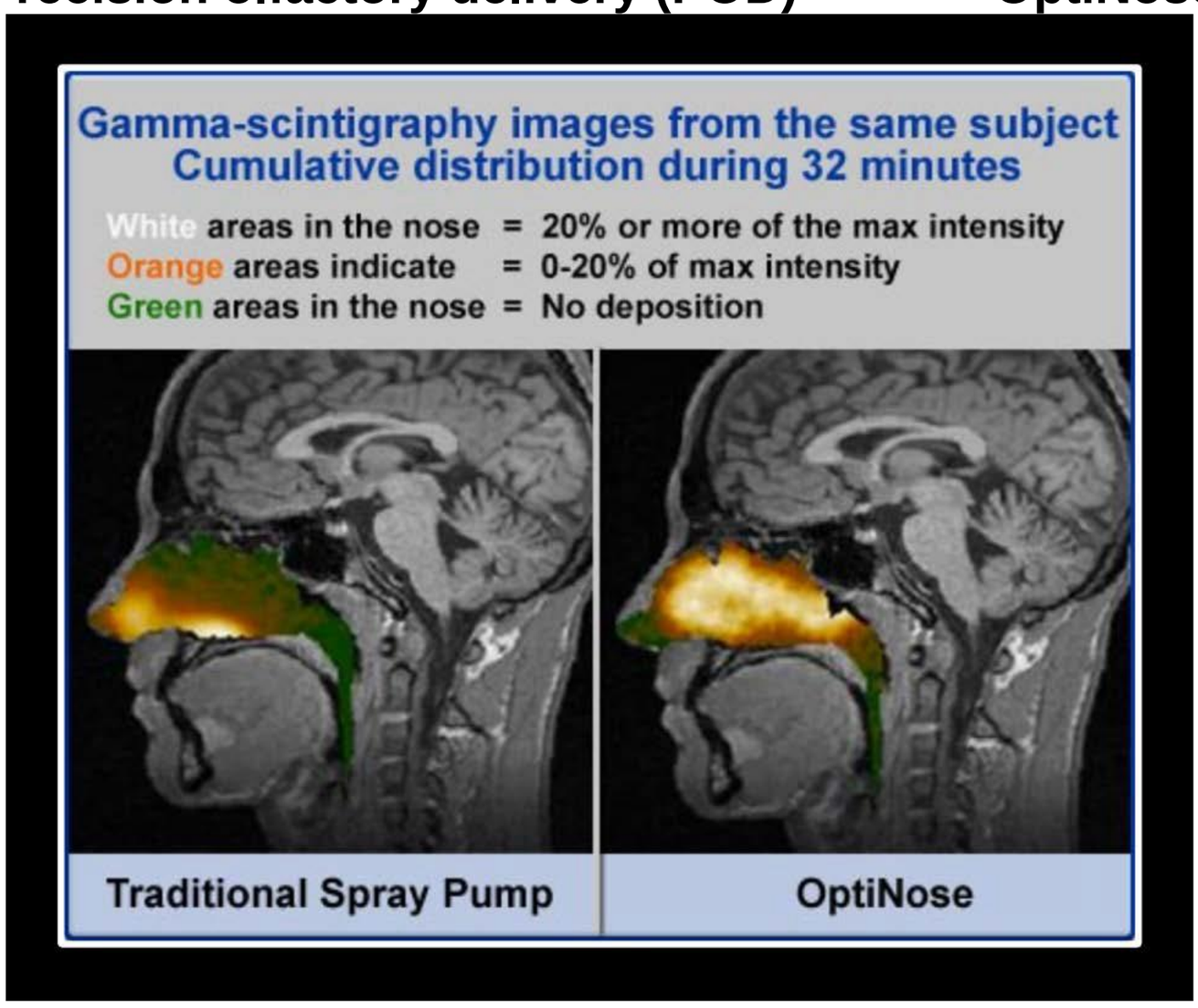


③ Device Technology

There are only a few devices available in the market that specifically target the olfactory bulb. As shown below, Impel Pharm. has developed its proprietary Precision Olfactory Delivery (POD®) technology to target the vascular-rich upper nasal space, with multiple clinical trials suggesting rapid absorption and consistent drug bioavailability with ease of use in mind for a patient, provider, or caregiver.

Precision olfactory delivery (POD)

OptiNose



5. Co-development Program Action Plan & Development Conside rations

- **Selection of the model drug for the project**

- Psychedelic and CNS drugs are most preferred for N2B delivery. A few sugges ted candidates are

① Cannabinoid, LSD, Ketamine, and R-ketamine [Psychedelics]

② Antimigraine drugs- Zolmitriptan, Somatriptan

③ Apart from CNS, Naloxone OTC can also be a good candidate

- **Pre-formulation Studies (API Solubility)**

The API needs to be formulated with excipients that enhance adhesion and, therefore, absorption in the nasal mucosa.

- **Nasal formulations**

Appropriate and compatible formulation technology selection is highly required to address the challenges related to IN formulations.
General Considerations for formulation characterization:
Absorption enhancers: surfactants, cylodextrins, bile salts, tight-junction modifiers
Osmolarity:
Iso-osmolarity: ~280 mOsm/kg
Hypo-osmotic (<50 mOsm/kg): can improve absorption, but also increase

potential for epithelial damage

Hyper-osmotic (>900 mOsm/kg): increase in mucus secretions

pH:

Nasal cavity is slightly acidic, pH 5.5-6.5

Irritation can occur outside the physiological range

Viscosity: Can increase residence time in the nasal cavity, but also affect spray characteristics (droplet size)

- **Device Technology or Supply**

For IN formulations, the Device is the most important part of the development. Considering the fact that device development is not feasible in a limited time, we highly encourage engineering or designing ideas suited to our objective of delivering drugs to the superior nasal cavity. If we could be able to compile the device design ideas, the third party (device manufacturers e.g. Nemera, Aptar, Recipharm, etc.) may help develop such proprietary devices for us.
If the device ideation is not feasible, we also encourage focusing primarily on developing a stable and compatible IN formulation for enhanced delivery.

- **Co-Development of Formulation and the Device**

(Drug-device combination)

Successful development and launch of a nasal drug delivery system requires cooperation between teams that are involved in formulation and device development. This ensures that data generated during the drug development and testing phases will be relevant for manufacturing and product launch.
The intended deposit location in the nasal cavity is important for efficacy and will depend on both the formulation and the device. The delivery device, whether a spray pump, must be effective for delivering a **precise dose to the target area of olfactory mucosa with minimal loss**. The device should also be easy to use by the intended patient population.
Drug deposition tests must be performed to analyze how the drug is distributed in the nasal cavity upon spraying.

- **Device Performance:**

US FDA or KFDA recommended device tests have to be performed and these tests are Pump Delivery, Spray Content Uniformity, Spray Pattern, Plume Geometry, Droplet Size Distribution, Particle Size Distribution (Suspension), Particulate Matter, Stability and Leachable, etc.

- **Initial and Final Combination Prototype Development**

With the completion of 6-months of stability testing, final prototypes can be acquired.

- **Scale Up and Tech Transfer**

The research group in Indonesia will help transfer the product from the Indonesia Site to the Daewoong Site in Korea or another CMO for scaling up and clinical batch manufacturing.

RESEARCH TOPICS- Ⅱ

Platform Technology Development for Long Acting Injectables

1. Objectives:

The aim is to collaboration is talents within emerging pharmaceutical technologies. These areas include Long acting injectables(LAI) and Polymeric microsphere systems(PoLMis™).

2. Introduction:

Daewoong Pharmaceutical has a vision of becoming the global leader in the pharmaceutical technology sector by 2030, focusing on future promising drug synthesis technologies. In the short term, our goal is to invest in our current technologies such as combination therapies, sustained-release formulations, and route of administration enhancements. In the long term, we aim to concentrate on advanced technologies such as **long-acting injectables**, intranasal spray formulations, and micro-needle technologies. Our objective is to secure a global platform technology by 2030.

We are determined not to rely solely on our own technology, facilities, and capabilities, but also to utilize global open collaborations to achieve this vision.

First, I would like to introduce the collaborative research program for **the development of platform technologies applicable to long-acting injectables.** These drug delivery system are specially designed to be gradually released over a long period of time, compared to general injections. They refer to injectable dosage forms that are administered to patients with low medication adherence in order to induce better clinical outcomes. Daewoong Pharmaceutical possesses facilities and patented technologies for research and production of long-acting injectables.

It is significant achievement to obtain research papers and patents through this collaborative research program. However, there would be nothing more gratifying than **discovering long acting injectable products to treat patients in Indonesia** in the near future. So, we would like to choose a research topic that actively reflects the local situation in Indonesia. It holds great importance as the first step towards Daewoong Pharmaceutical's vision for Indonesia. Therefore, **we will focus on two main topics to develop long-acting injectables.**

First, the development of diabetes and obesity treatments using GLP-1 agonist.

Second, the development of treatments for patients with mental disorders such as schizophrenia.

We plan to utilize drug delivery systems such as microspheres or suspension formulations using biocompatible polymers and wet milling technologies. In addition, **Daewoong Pharmaceutical is ready to positively review any proposals and ideas related to research topics that may be hesitant due to specific reasons or <u>any research topics that professors wish to develop.</u>**

By developing these platform technologies, we hope to meet the unmet needs of patients, improve patient convenience, lead the advancement of medical/pharmaceutical industry in Indonesia.

RESEARCH TOPICS- Ⅲ

Platform Technology Development for Oral Sustain Release Drug Delivery System

1. Objectives:

① Development of formulation platform technology that improves the gastrointestinal absorption rate of drugs by extending the residence time in the gastrointestinal tract.

② Improved patient compliance by reducing the frequency of dosing from sustained and controlled release of drugs in stomach

③ Securing various formulation technologies to develop more sustainable oral sustained-release tablets ex. Colon delivery system,

2. Probable Approaches to Achieve Objectives:

1. Formulation Technologies:

① Matrix system

Monolithic matrices are the most common version. These systems comprise one or more release-controlling agent with one or more drugs uniformly dispersed in the matrix.

1) Hydrophilic matrix systems: Drug particles are dispersed in hydrophilic polymeric matrix, drug release occurs by dissolution of the drug, diffusion through the gel layer (formed upon exposure of GI fluids), and/or erosion of the matrix

2) Insoluble matrix Systems: Drug is dispersed in a matrix of water-insoluble polymers and waxes, drug release occurs as the GI fluid permeates the matrix and dissolve the drug

② Reservoir system

A drug containing unit (core) is enclosed by a polymeric barrier coat. Two key reservoir systems have been commonly used:

1) In simple diffusion systems, a drug-containing core is surrounded by a water-insoluble polymer coating. Drug release is achieved by diffusion of drug through the coating.

2) OSMOTIC SYSTEMS contain osmotic agent in the coated drug core. Drug-release occurs through an orifice in the coating layer due to an osmotic pressure gradient generated as the GI fluids permeate into the core.

③ High-density system

The density of dosage form plays an important factor in the formulation of

the GRDDS. A high-density system uses its weight as a retention mechanism. To enhance the gastric residence of a drug in the stomach, its density must exceed the normal stomach content 1.004g/mL.

④ Floating or low-density system

These systems remain buoyant due to lower density and provide continuous drug release. It’s prepared using effervescent compounds along with hydrophilic polymers. These dosage forms involve encapsulation of drugs in hydrophilic polymers like ethyl cellulose and eduragit RS-100 with effervescent agents such as sodium bicarbonate, calcium carbonate, etc. Upon contact with gastric fluid, the capsule shell dissolves with subsequent swelling, forming a gelatinous barrier, which remains buoyant in the gastric juice for an extended period.

⑤ Mucoadhesive and bioadhesive system

A mucoadhesive and bioadhesive system uses its adhesive properties to target a drug to a specific region of the body for an extended period. For this, bioadhesive of mucoadhesive polymers are mainly used. Natural polymers such as sodium alginate, gelatin, guar gum, etc., and semisynthetic polymers such as HPMC, lectins, carbopol, and sodium carboxymethyl cellulose are widely used for mucoadhesions.

⑥ Swelling system

These system, when come in contact with gastric fluid, their size increases significantly than that of the pyloric sphincter and thus, after swelling, remain logged in the stomach. Controlled and sustained drug release is achieved using an appropriate excipient. The swelling ability of polymer mainly depends upon the degree of cross-linking of hydrophilic polymer network.

2. In vitro assessment

① Buoyancy lag time

It is the time taken for gastroretentive formulations to move onto the surface of the dissolution medium. It is determined using USP dissolution apparatus containing 900 mL of 0.1N HCl solution as a testing medium maintained at 37℃. The time required to flot different dosage forms noted as floating lag time.

② Floating time

This determines the buoyancy of dosage form. In this test, a specific dissolution apparatus is used depending upon the type of dosage form with 900 mL of dissolution medium kept at 37°C. The floating time or floating duration of the dosage form is determined by visual observation

③ Specific gravity/density

Specific gravity estimates are essential for both low-density and high-density GRDDS. Specific gravity is determined using the displacement method.

④ Swelling Index

Swelling index is determined by immersing the tablets in 0.1 N HCl at 37°C and their periodic removal at regular intervals.

3. Applications of Extended release systems

Gastroretentive dosage forms release the drug in a controlled manner to their specific site of action. These systems help increase the bioavailability of drugs

that get metabolized in the upper part of the gastrointestinal tract, such as riboflavin and levodopa, etc. For drugs that have a short half-life, gastroretentive dosage forms help reduce the dosing frequency and improve patient compliance by enhancing gastric residence time. Also, they provide a sustained and prolonged release of drugs in the stomach and intestine, which are helpful in local therapy.

RESEARCH TOPICS- Ⅳ

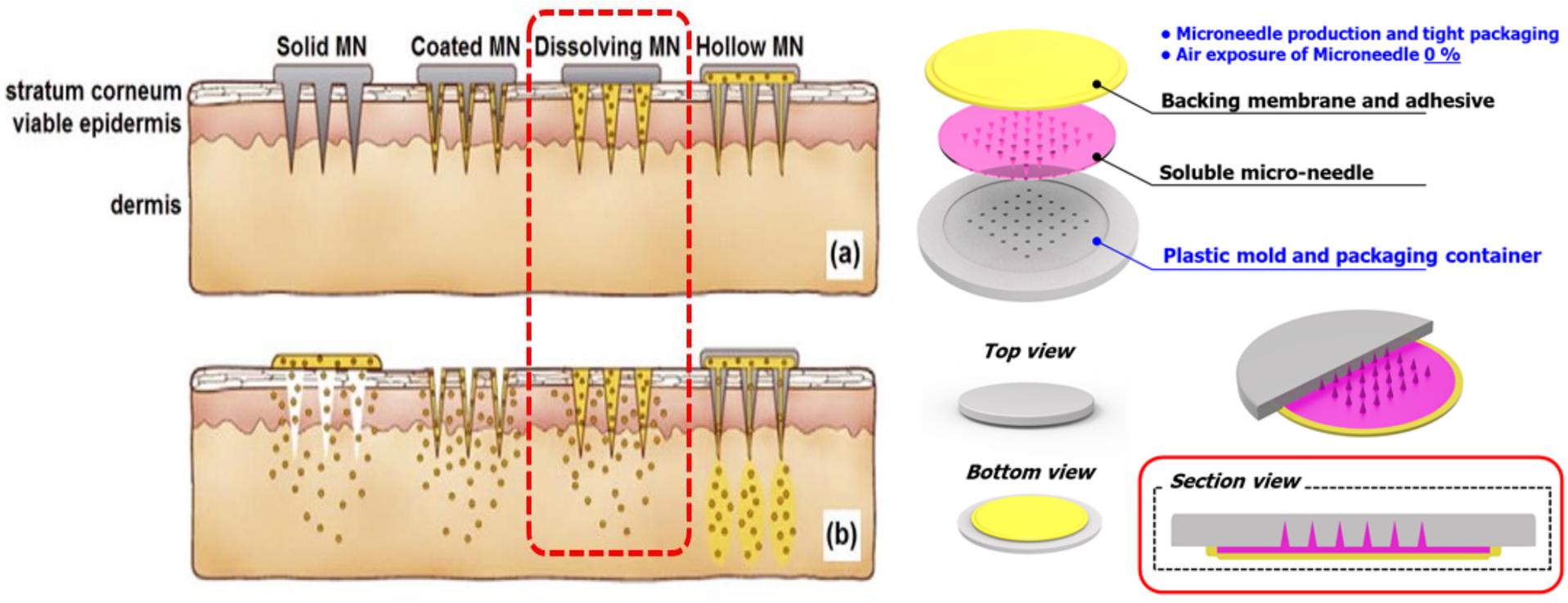
Platform Technology Development for Microneedle Technology

1. Objectives:

Differentiated-Dissolving Microneedles Technology

2. Probable Approaches to Achieve Objectives:

Among various types of microneedles, soluble microneedles are made of biodegradable polymers and are applied to the skin and then dissolved in interstitial fluid to deliver drugs [Figure 1].



[Figure. 1] Types of microneedles and soluble microneedles

Daewoong Pharmaceutical is equipped with these soluble microneedles including semaglutide (indication: type 2 diabetes and weight loss), teriparatide (indication: treatment of osteoporosis in postmenopausal women), which are peptide drugs that can be administered by subcutaneous injection. We are developing a new needle formulation product.

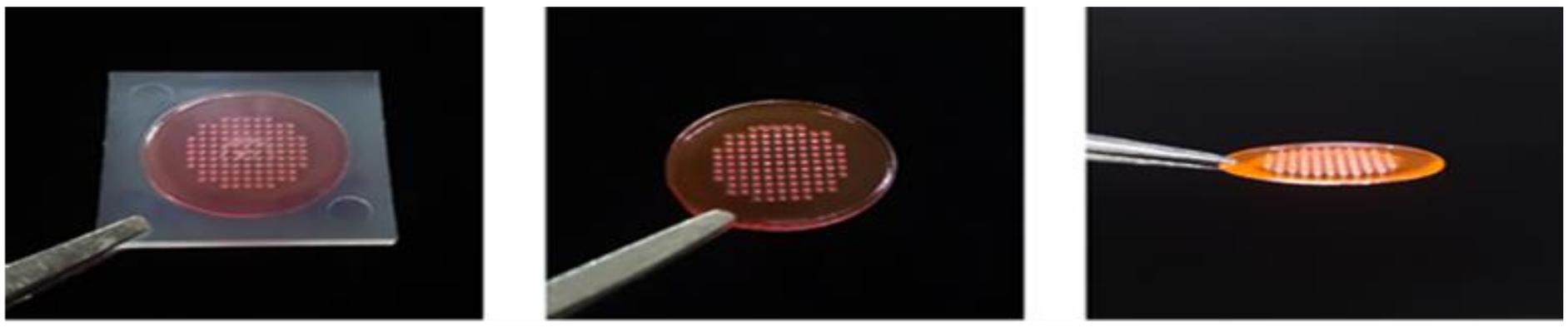
The development target product is expected to be in great demand in the market as it can significantly improve administration convenience while lowering manufacturing costs compared to existing pen formulations.

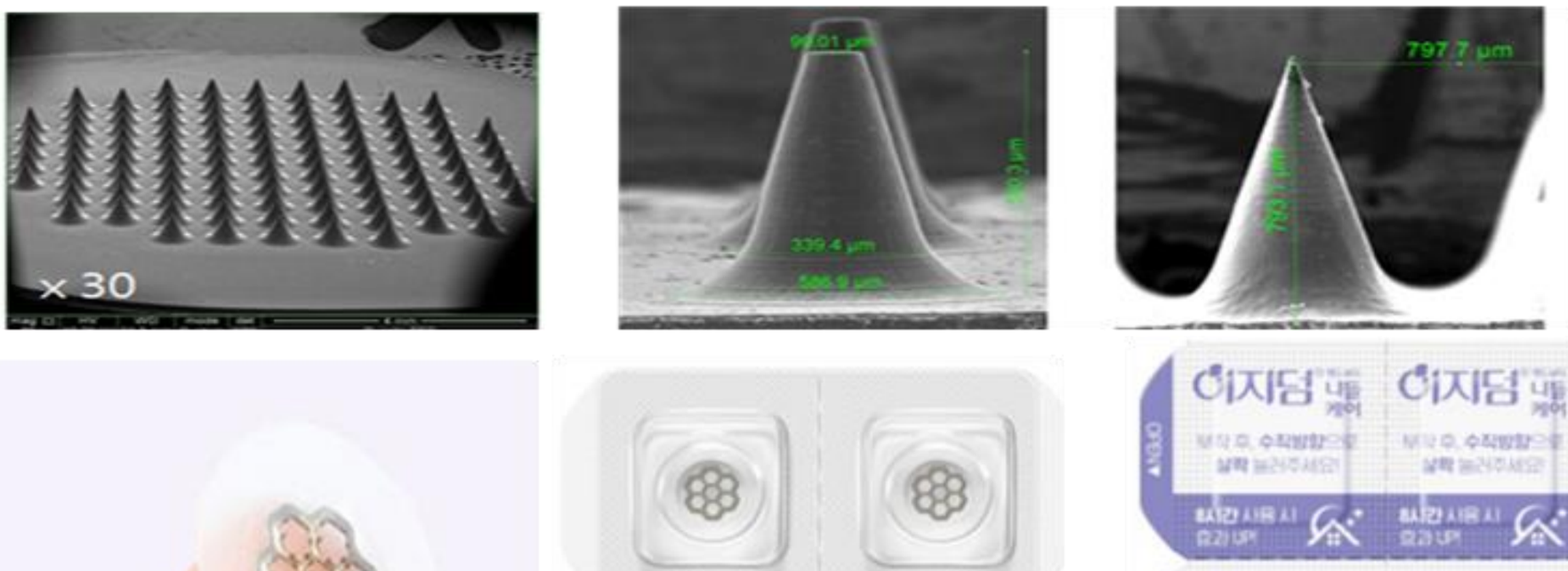
3. Applications of Microneedle systems

① **Peptide medicines** (indications: type 2 diabetes and weight loss)

② Microneedle technology that **changes the administration route of injections**

③ **Development of a wide range of products from pharmaceuticals to cosmetics**





Easyderm microneedle
** quasi-drugs*

[Figure. 2] Examples of Daewoong products

RESEARCH TOPICS- V

Platform Technology Development for Platform Technologies Applicable to Bio-Pharmaceuticals

1. Objectives:

The aim is to collaboration is talents within emerging pharmaceutical technologies. These areas include Platform Technologies Applicable to Bio-pharmaceuticals.

2. Introduction:

The broad theme of the research is "Platform Technologies Applicable to Bio-pharmaceuticals" with specific areas of focus including (1) technologies for changing the administration route (Subcutaneous) of Bio-pharmaceuticals using Hyaluronidase, and (2) technologies for increasing stability of Bio-Drug Delivery Systems (DDS) such as Lipid Nanoparticles (LNP), among other possibilities.

The exploration of items with strong applicability holds significant importance for the development of 'Biopharmaceutical-based Platform Technology.' By creating platform technologies that effectively address unmet medical needs, the potential to generate substantial additional value becomes feasible. Especially within the realm of biopharmaceuticals, which have a relatively brief development history, notable unmet demands are anticipated. This forms a primary rationale for our concentrated efforts in developing 'Biopharmaceutical-based Platform Technology'.
By developing these platform technologies, we hope to meet the unmet needs of patients, improve patient convenience, lead the advancement of medical/pharmaceutical industry in Indonesia.

RESEARCH SUPPORT
In INDONESIA

Daewoong has research centers in the bio and chemical fields in Indonesia.

1. Bio research field

① Location :
- University of Indonesia(UI) in Depok

② Title :
- Bio Tech. R&D Center Daewoong
- Bioanalysis Laboratory UI–Daewoong

③ Research facility :
Support for analysis of raw material products and bio products is available, and support for culturing and purification research and stability testing of bio medicines is available.

Laboratory Testing for HCD

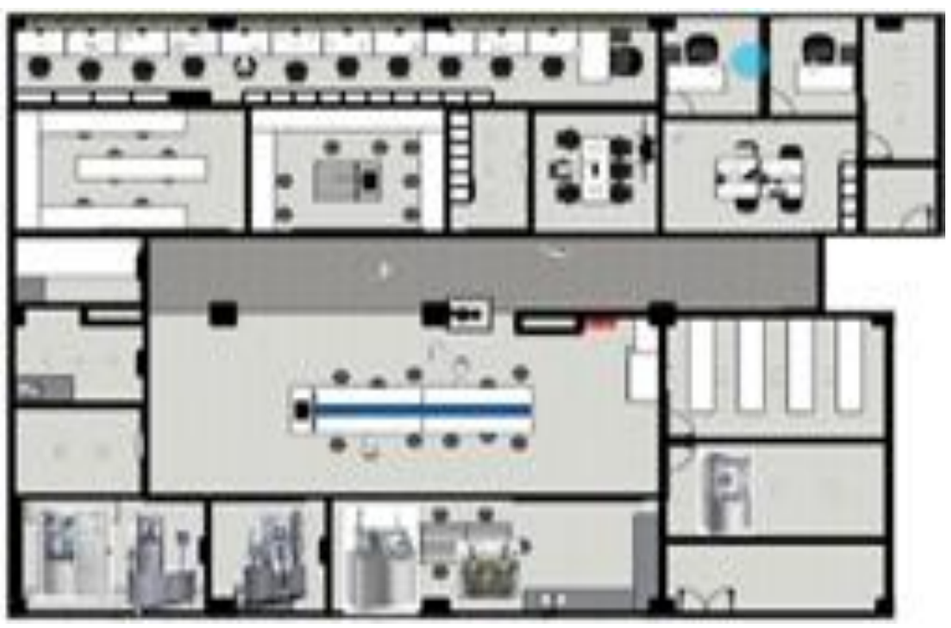
View of Education Laboratory

2. Chemical research field

① Location :
- Bandung Institute of Technology(ITB) in Bandung
  (Scheduled to open in the second quarter of 2024)

② Title :
- Drug Delivery System Research Institute ITB-Daewoong
  (DDS RI ITB-DW)

③ Research facility



In order to research composite/sustained-release technology, we are building equipment to apply sustained-release and composite technology, as well as essential analysis equipment for pre-processing through a multi-well press, and multi-coating/pellet manufacturing facilities.