The Feasibility of Utilizing Space in Drug Discovery

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Mitsubishi Heavy Industries, Ltd. (MHI) has studied the possibility of a recoverable capsule type experiment system that will enable experiments with small animals in space with the goal of the industrialization of space since 2004. Some surveys have suggested that the pharmaceutical industry could use this system. Accordingly, as the groundwork for future business consortiums, the Space Drug Discovery Association was established, initiated by MHI, and consultants are now studying the possibility of using the space environment to develop new medicines for use on earth.

1. Introduction

In recent years, the prospects for the pharmaceutical industry have become less optimistic. For example, the patents on major medicines will expire in succession within a few years starting in 2010 and the process of developing new medicine using genomic drug discovery methods is very complex. In order to revitalize this industry, technical innovations for drug discovery are needed urgently. In addition, the major Japanese pharmaceutical companies are busy taking countermeasures against mergers and acquisitions, including their overseas subsidiaries. Nevertheless, the pharmaceutical industry has expressed interest in the concept of studying drugs in space. Accordingly, MHI is studying a recoverable capsule type experiment system as a way to realize drug discovery in space. This system enables biological experiments involving small animals from launch to recovery, at low cost and high frequency in a uniquely Japanese manner, by piggybacking it on the H-IIA Rocket, as shown in **Fig. 1**.

2. Space drug discovery concept

The concept of drug discovery in space considered by MHI is not to establish a pharmaceutical factory in space, but to contribute to the development of new medicine on the ground using biological data obtained from experimental animals in a microgravity environment, as shown in **Fig. 2**. Inbred lines of mice with a common genetic background are widely used in medical research because detailed analysis after an experiment is possible. We plan to utilize the changes that occur in these mice in a microgravity environment as a target search and link the results to the discovery of new compounds by observing changes in genes, proteins, and metabolism, and by compiling a database of the accumulated information. On observing the changes that occur in mice in a microgravity environment, researchers

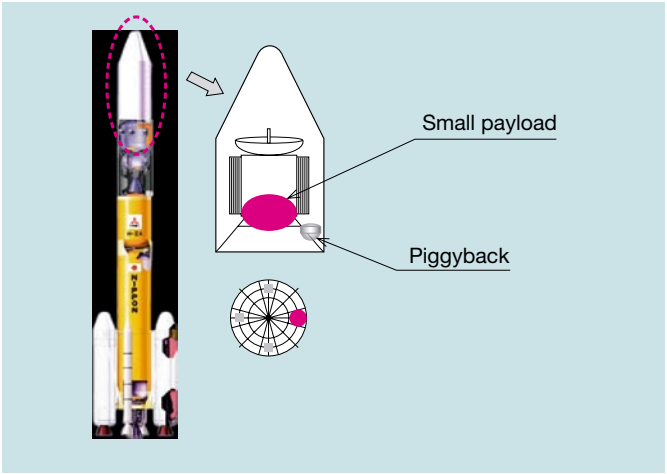

Fig. 1 System position layout

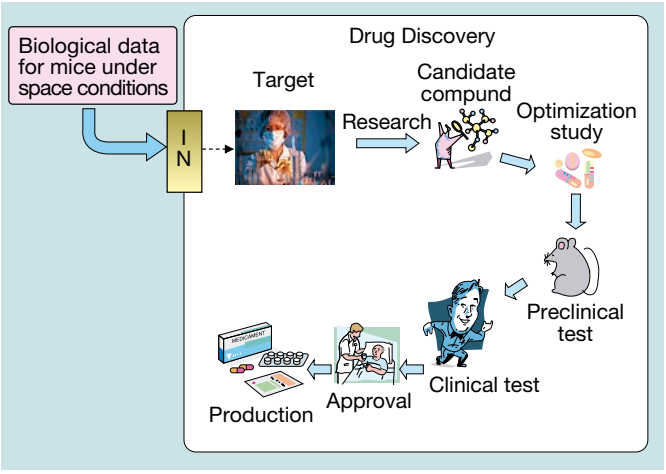

Fig. 2 Conceptual figure of drug discovery in space

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might consider the following hypotheses:

- The influence of microgravity on living animals could include effects on biological reactions involving bone, muscle, the cardiovascular, immune, and central nervous systems, and accelerated effects on aging.
- Astronauts develop a dowager's hump and amyotrophic change in muscles. In the amyotrophia that occurs in microgravity, the change of slow muscle to fast muscle is significant, and the clinical condition develops quickly. Therefore, studies conducted in space could be a useful approach for clarifying the mechanism of muscle attenuation disease (sarcopenia).
- Under a microgravity environment, intracellular insulin transport appears to decrease rapidly in the islets of Langerhans in the pancreas, which could be useful for clarifying the mechanism of the development of diabetes.

Several pharmaceutical enterprises are participating in the Space Drug Discovery Association, which started this fiscal year, and are studying the possibility of using the space environment as a new drug discovery research platform with the above-mentioned hypotheses as starting points. As a basis for evaluating the effectiveness of our system, a short microgravity experiment involving mice, using aircraft, showed clear differences in blood corticosterone levels and the development of genes that are an index of stress. This implies the usefulness of longer microgravity experiments.

3. Introducing the system

We have developed a recoverable capsule type experiment system as a means to realize drug discovery in space. During research on this system, we first studied a recoverable capsule that is piggybacked with the launch of other satellites. After examining the basic technical prospects, we studied a recoverable capsule with a small payload to enable long-term experiments.

3.1 Outline of the recoverable piggyback capsule

3.1.1 Outline of the system

Figure 3 shows an overview of the recoverable capsule for biological experiments. The capsule is conical, with a diameter of 0.65 m, height of 0.5 m, and mass of 110 kg. The shape and size must realize the lift-to-drag ratio (L/D) required for lifting flight for a piggybackable capsule. The system consists of multiple subsystems for propulsion, avionics, and the experiment unit, as shown in **Fig. 4**.

Figure 5 shows a conceptual figure of the experiment unit in this system. It weighs ca. 20 kg and measures 350 × 300 × 200 mm. In order to carry three mice, the unit consists of mice habitat, food and water supply units, a closed environment control system, and a biological data collection system (**Fig. 6**). The closed environment control system maintains the oxygen concentration, removes carbon dioxide, and controls humidity and temperature. Oxygen is supplied from a tank, and carbon dioxide, humidity, and temperature are controlled passively. An initial study showed that all of these could be controlled successfully. It should also be possible to control the temperature actively, after further study.

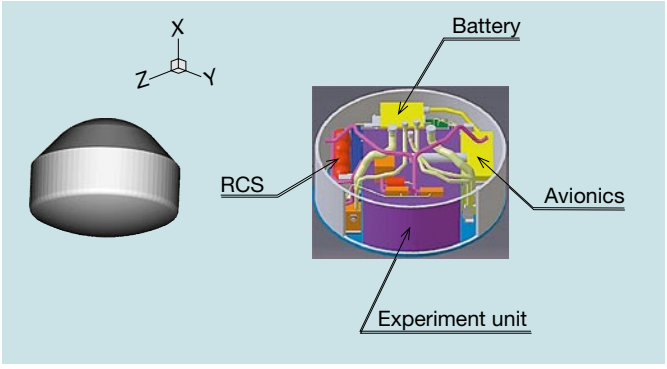

Fig. 3 Recoverable biological experiment capsule (piggyback size)

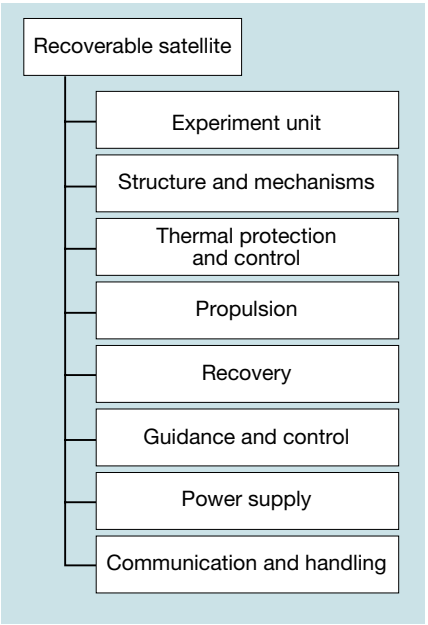

Fig. 4 Block diagram of constituent subsystems

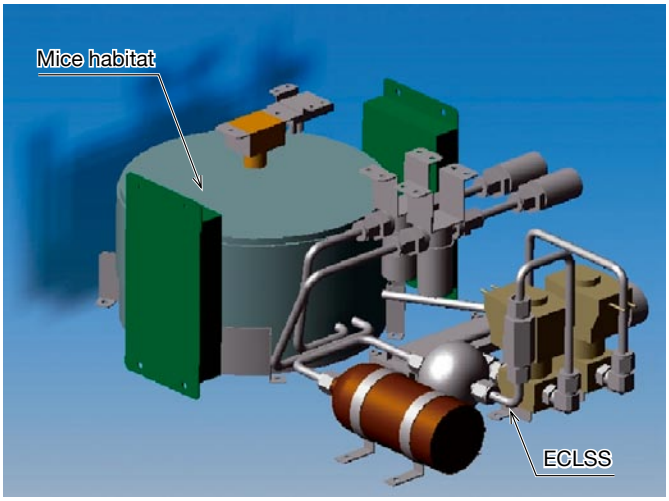

Fig. 5 Conceptual figure of experiment unit (piggyback size)

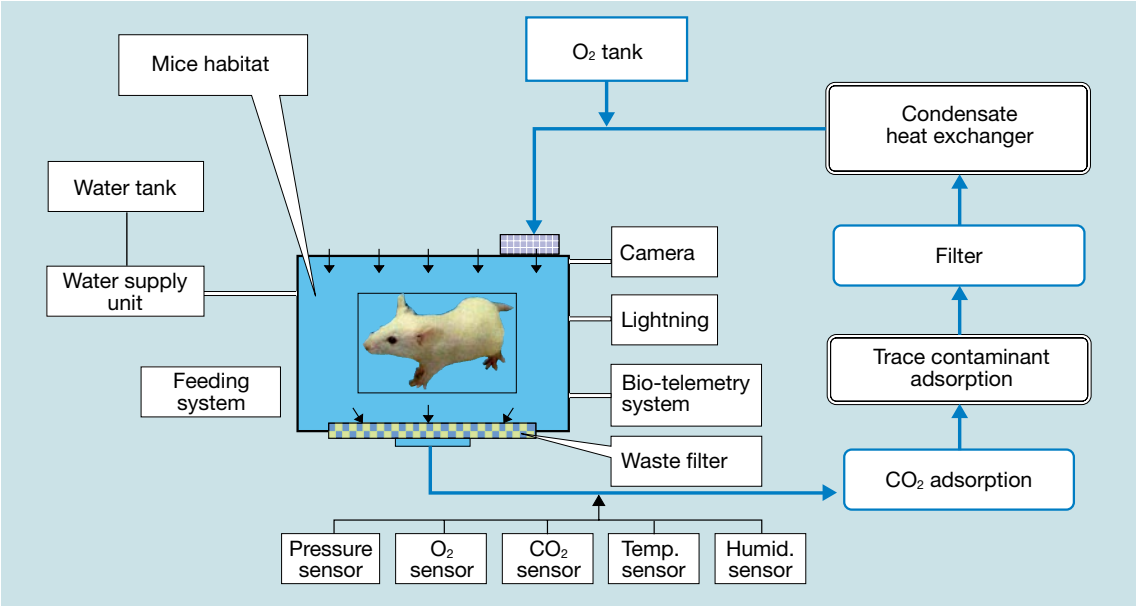

Fig. 6 Block diagram of constituent systems and components

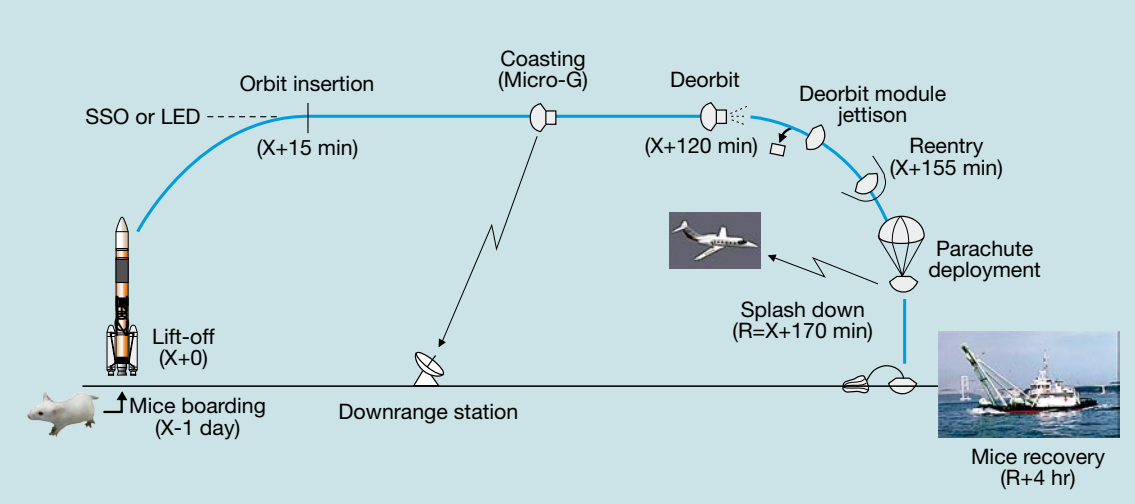

Fig. 7 Mission profile

The biological data collection system collects blood pressure and pulse data for the mice using biotelemetry, takes moving images of mice behavior using a charge-coupled device (CCD) camera and light-emitting diode (LED) lighting, and collects urine and feces.

3.1.2 Flight plan

Figure 7 shows the mission profile.

(1) The day before launch, the unit containing living mice is loaded on a rocket.

(2) It is launched in a piggyback configuration. After it reaches orbit, the microgravity experiment starts. The experiment lasts for approximately 2 hours while the capsule orbits the earth once. Then, it deorbits. The system separates from the rocket before deorbiting, which reduces the amount of self-contained resources required in the experimental system while orbiting, such as a battery and propellant, to realize the piggyback size.

(3) The acceleration of the system during re-entry into the aerosphere is reduced to less than 4 G from approximately 10 G during ballistic flight, by making use of lifting flight. We consider it necessary to reduce the load as much as possible to avoid affecting the mice after completing the microgravity experiment.

(4) The system is recovered at sea and the mice are returned alive. The recovery location depends on the injection orbit; we plan to use a location near South America for sun-synchronous orbits (SSO) and the North Pacific Ocean near Japan for low earth orbits (LEO). **Figure 8** shows the flight route for an SSO mission.

3.1.3 Design and prototype test

(1) Shape design

Packaging is one of the most important factors for

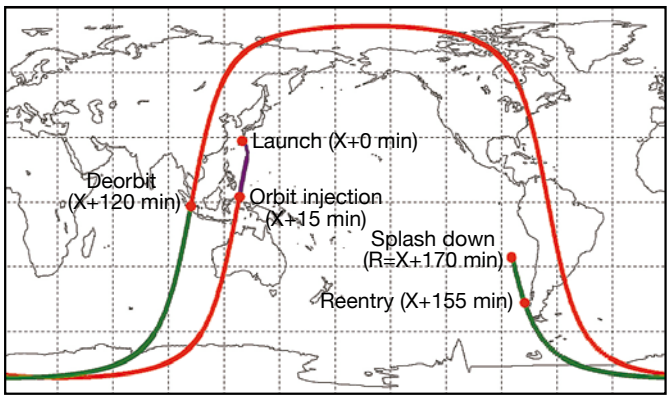

Fig. 8 Flight route (sun-synchronous orbits)

a recoverable capsule type experiment system. Unlike ordinary piggyback satellites, the experimental and recovery units require a large volume. Furthermore, a shape with a lift-drag ratio (L/D) that realizes an acceleration of 4 G during atmospheric re-entry is indispensable. **Table 1** shows the shape designed to meet the constraints allowed for the piggyback satellite.

Table 1 Results of reviewing shape designs

Type	Current	Apollo CM	Soyuz DM
Shape	Main spacecraft / Fairing / Satellite adapter	Main spacecraft / Fairing / Satellite adapter	Main spacecraft / Fairing / Satellite adapter
Size (D x H) (m)	0.66 x 0.51	0.66 x 0.38	0.49 x 0.51
Volume (m^3)	0.120	0.075	0.080
L/D@ AOA=25 deg	0.30	0.37	0.31

In comparison with the shapes of Apollo and Soyuz capsules, an additional volume of approximately 1.5 times was assured, after obtaining the required L/D.

(2) Prototype test

Important parameters such as control of a closed environment are imposed on this system, in addition to those for the flight environment. We conducted many prototype tests in order to solve these issues. Here, we present a verification test of the enclosed environment control system. This test verified that normal oxygen and carbon dioxide concentrations and humidity were maintained in the closed environment. We conducted a mouse breeding test with an experimental unit of the size specified for flight, as shown in **Fig. 9**. All three parameters were regulated within the respective limits. The system could maintain a closed environment for about 34 hours, which would cover the estimated time from launch to recovery.

Fig. 9 Prototype experimental unit

3.2 Outline of a recoverable capsule with a small payload

3.2.1 Outline of the system

In order to meet the needs of long-term experiments, we studied a recoverable capsule with a small payload, as shown in **Fig. 10**, as a next-generation system for a recoverable

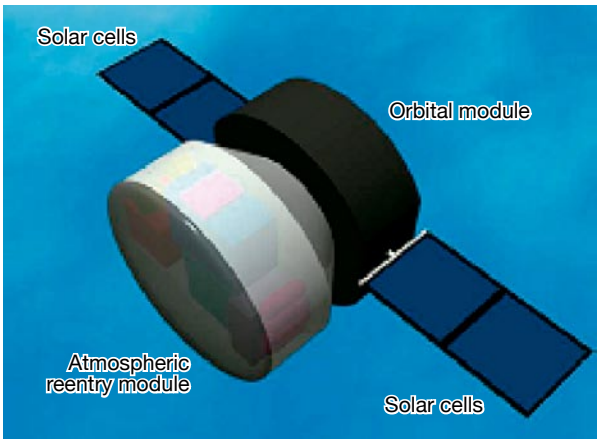

Fig. 10 Recoverable capsule type experiment system

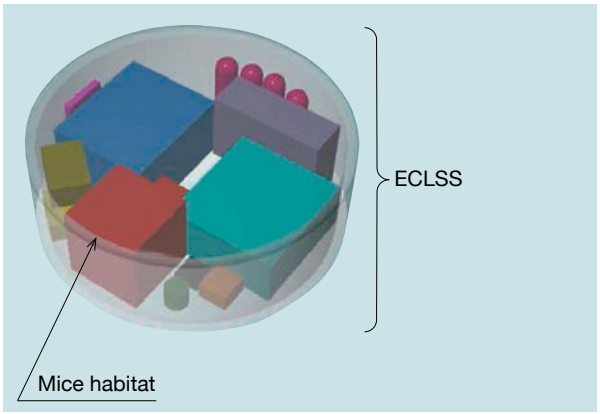

Fig. 11 Conceptual figure of experiment unit (recoverable capsule size)

piggyback capsule. This system would be used to realize space experiments lasting two weeks with five mice. The focus is on keeping the mice alive, which is critical from a technical perspective. **Figure 11** shows a conceptual figure of the experiment unit. It weighs about 40 kg, and measures ca. ϕ 1200 mm × 400 mm (height). While the temperature and humidity are controlled passively in the recoverable capsule, the system adopts a method of active control, while reducing the amount of relevant consumable materials required (especially for adjusting the humidity). To treat unwanted gases, such as carbon dioxide and harmful trace gases, we adopted a system that uses consumable absorbent materials suitable for an experiment lasting as long as 2 weeks. We are now studying a reusable system for treating unwanted gases for yet longer future experiments.

3.2.2 Design outline and prototype test

In comparison with the short-term experiments discussed above, a unit for long-term experiments must be able to store the resources required for breeding animals (especially water and food) in a limited space, supply food and water to the mice on an ongoing basis, remove urine and feces from the habitat, and control the concentrations of trace gases (especially ammonia), among other functions. Accordingly, we manufactured the prototype model of the experiment unit shown in **Fig. 12**, which meets these requirements, and conducted a closed breeding test for 2 weeks.

The system successfully controlled the ammonia, oxygen, and carbon dioxide concentrations, as well as temperature and humidity within the respective required ranges for 2 weeks, while supplying food and water, to enable closed breeding.

4. Conclusion

We are continuing with technology development and expect to launch this system in 2012. In order to meet the demands of pharmaceutical researchers, we are now studying the specifications required for actual full-scale missions, involving longer stays in orbit with more mice on board.

Finally, to discover drugs based on studies conducted in space, it is necessary to meet the requirements of the end users. We would like to accelerate the development of the recoverable capsule type experiment system that MHI is now developing because many researchers understand the effectiveness of developing new medicines through utilization of the space environment, and have contributed to the activities of the Space Drug Discovery Association to this end.

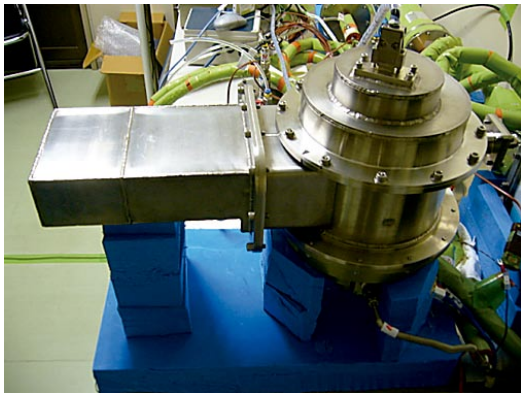

Fig. 12 Prototype model of experiment unit (cage)


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