Q&A: SUCCESSFUL MASS PRODUCTION OF AN INNOVATIVE DRUG DELIVERY TECHNOLOGY

In this piece, Jung Dong Kim, PhD, Chief Technology Officer at Raphas Co, answers questions about the company, its capabilities, and the mass production of an innovative dissolving microstructure drug delivery technology.

Q: What is Raphas?

A: Raphas is a combination of the words "Rapha" (heal) and "Path". Technology originally developed in Yonsei University was transferred to this company, after which four years of research and investment led to the successful development of dissolving microstructure products. As the meaning behind the name Raphas suggests, the company is devoted to providing paths to healing in the medical services sector. A key mission of the company is to pioneer an affordable delivery system for vaccines and other drugs for efficient use in developing countries.

Q: What are dissolving microstructures?

A: Although the concept of microstructures was proposed in 1970, it was not until 1990 that it was first developed.[1] There are various application principles for microstructure-mediated transdermal drug delivery:

i) less painful than the typical shot from a needle, solid microstructures are effective in creating small punctures in the skin that are ideal for allowing the skin to absorb active ingredients

ii) later on, solid microstructures were coated in medicine or creams before insertion into the skin, thereby directly delivering the active ingredients into the skin. These coated microstructures are applied for a specified duration, allowing the skin to absorb the active ingredients, before being removed

iii) the next phase was the development of hollow microstructures that delivered medicine in a tiny needle and syringe combination form. However, the previously stated microstructures tips could be broken and left under the skin, which had the potential to cause undesirable side effects, so innovative solutions were found

iv) dissolving polymer substances were mixed with medicines and active ingredients to create microstructures that naturally dissolved away after delivering their active ingredients into the skin (see Figure 1).

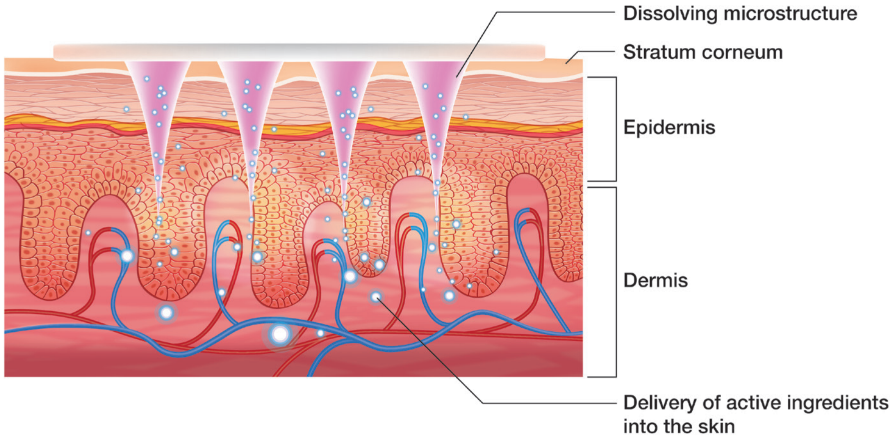
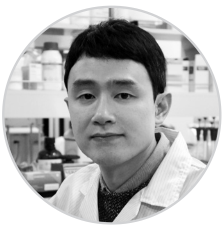


Figure 1: Diagram showing mechanism of action for dissolving microstructure delivery.



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The many phases of this research process led to the development of several different types of microstructures, all with their own characteristics and utilities. Although it is now well known that dissolving microstructures (Figure 2) are extremely safe, they are still not being used for the application of medicine or drugs. However, cosmetic products including sodium hyaluronate have recently been developed and marketed.

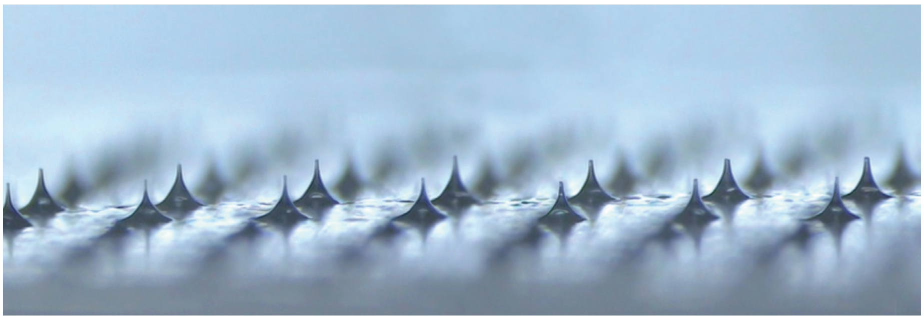

Figure 2: Microscope image showing the protrusions of a dissolving microstructure array.

Q: What advantages are there in using dissolving microstructures?

A: The biggest advantage of dissolving microstructures is that they are much less painful than the standard needle and syringe. When applied in the form of a patch, they are easy to use for any consumer, and provide much more comfort and convenience. As opposed to liquid substances needed for application by injection needles, microstructures make it possible to distribute medicine in a safer solid state. Lastly, the use of dissolving microstructures is an environmentally friendly solution that leaves no dangerous and wasteful medical products behind, such as sharp needles or glass.

Patch microstructure products overcome the disadvantages of existing transdermal drug delivery systems, while combining the effective aspects of needle and syringe delivery methods. For these reasons, dissolving microstructures are a promising technology that is both very safe and convenient to use.

One of the many advantages of dissolving microstructures, especially in their solid state, is their ability to maintain a high level of safety in the distribution of biomedical products. This will significantly help reduce costs in the cold chain needed in the distribution of such projects, and could bring on a major turning point in the treatment of illness and disease for all of mankind.

The cold chain is in reference to the constant refrigeration process and infrastructure needed in the distribution of certain foods such as meat and seafood or medical products such as vaccines, proteins, and other biomedical items. Aside from these, there are many other products that rely on a cold chain for distribution. Studies have shown that in the biopharmaceuticals industry alone, costs for cold chain distribution of products are almost US$1 billion (£0.68 billion) a year. Current cold-chain distribution methods make it so that most products are shipped by air, greatly increasing the cost of transport. Up to 66% of biomedical products are being distributed by air, while only 33% is being shipped by sea – which is half the cost of transporting by plane.[2]

Currently biopharmaceuticals for arthritis treatments, insulin shots for diabetes and other medical treatments have been developed into products. Thanks to advances in biotechnology, the mass production of biopharmaceuticals has been made easier, and this in itself has also contributed to increased research and development of the biopharmaceuticals industry. Therefore, the industry is also encroaching on the market share of synthesised drugs, which all leads to increased costs in refrigeration and storage of biopharmaceuticals. For example, vaccines are made up of various proteins that are often sensitive to heat and light, and therefore require refrigeration. The US$200-300 million annual cost of refrigerating vaccines may not be too much of a burden to bear for countries with an advanced medical industry, but less developed areas in Africa and Southeast Asia, and even countries like North Korea may not be able to afford these distribution costs. For these reasons, a large number of people around the world are not able to receive the vaccinations they need, and many are still dying from preventable diseases.[3]

In developing countries, **80% of the cost of vaccinations goes to the cold chain of distribution**, and therefore many efforts are being made throughout the world to reduce these costs.[4]

In order to solve these problems, international organisations such as the WHO and the International Society for Pharmaceutical Engineering (ISPE) have been putting out guidelines regarding cold chain management in order to help develop and propose methods to reduce costs as much as possible. However, viable cold chain methods differ between countries, so in order to reduce costs across the board, a truly ground-breaking method would have to be developed.

Microstructures are being researched by many institutions as an alternative solution to the high cost of cold-chain management, because if biopharmaceuticals can be delivered as a solid state in microstructures, its stability and effectiveness can be sustained for a long period of time. Furthermore, in the academic community there are many publications and presentations regarding stabilising agents for maximising desired effects in vaccines. In the near future, it should be possible to create microstructure vaccine patches that will greatly reduce the cost of storing and distributing vaccines.

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Q: What unique technology has Raphas developed for the production of microstructures?

A: There are many techniques used in the production of dissolving microstructures being developed around the world, such as micro-moulding, drawing lithography, and droplet-born air blowing. There are advantages and disadvantages to each, and they are constantly being improved to maximise their efficacy. Some are undergoing clinical trials and preclinical testing,

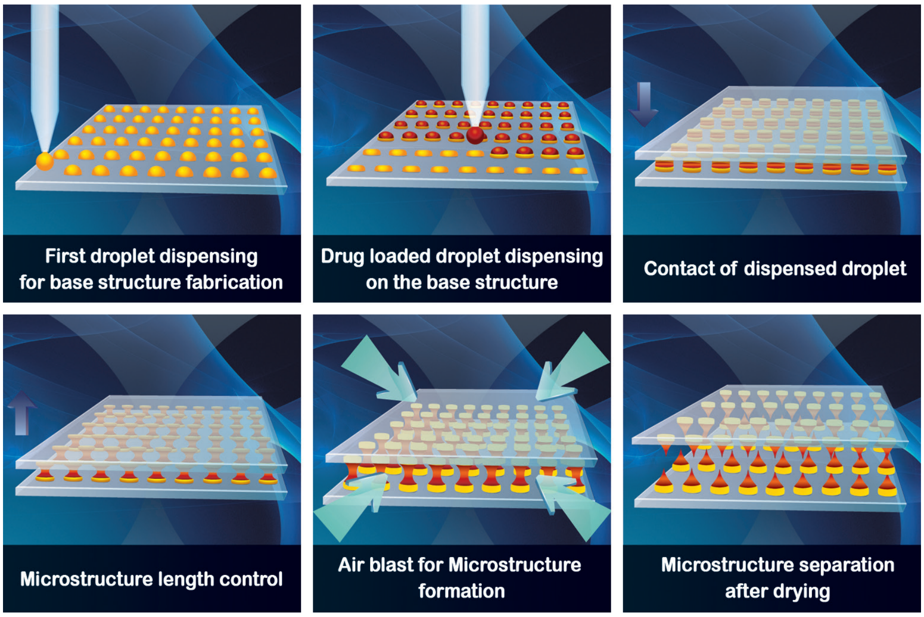

Figure 3: Steps in the Droplet-born Air Blowing (DAB) microstructure manufacturing technique employed by Raphas.

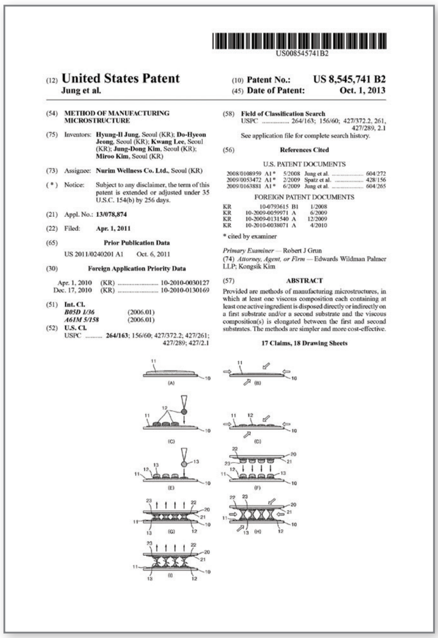

Figure 4: The key US Patent Application covering the DAB manufacturing process.

while others are in use for products currently on the market.[5]

The first dissolving microstructures were created using photolithography, which was commonly used for a semiconductor fabrication process. To create dissolving microstructures using photolithography, first various etching methods are used to create master moulds. Then, polydimethylsiloxane (PDMS) is poured to make PDMS moulds from which dissolving microstructure replicates are formed. A dissolving solution is poured into the PDMS mould, and is set using heat or UV light. Once the needles are taken out of the cast, they are just about complete.

This step, called micro-moulding, is a process used at most microstructure manufacturers. It is the process used to make the very first dissolving microstructures, and its big advantage is that access to the mould and the related equipment makes it possible to mass-produce dissolving microstructures.

However, micromoulding requires strong negative pressure using centrifuge and vacuum pumps to fill in the microscale mould with dissolving polymer solution. Furthermore, the dissolving polymers applied in this manner can be dried by carefully applying heat or UV light which has the potential to cause denaturation of sensitive proteins.

In 2010, Professor Jung Hyeong-il's research team at Yonsei University (Seoul, Korea), developed a technique called drawing lithography. In this technique, dissolving substances are coated onto a surface and heat is applied to make them stick. At the same time, microstructures are formed by pulling the surface vertically. The convenience of this technique, and its flexibility in adjusting the length and breadth of the needles made it very popular, and was featured on the inner cover of Advanced Materials and as a research highlight in Nature Phototonics. However, this process still needs the application of heat, and the coating process caused the loss of active ingredients, so the technique is not yet widely adopted for use.[6]

The technique currently being used at Raphas is called Droplet-born Air Blowing (DAB) (see Figure 3). This process was developed to reduce the microstructure fabrication time allowing for gentle fabrication conditions without the use of UV irradiation or heat. The main advantage of this technique is the ability to apply the desired amount of polymer drop in the desired location to form a single droplet into a single microstructure using a controlled air blowing. This makes it possible to fabricate microstructure in a few minutes without loss of active ingredients which are sensitive to heat or UV light.[7]

Figure 5: Raphas' beauty patch product, Acropass.

"In the biopharmaceuticals industry alone, costs for cold chain distribution of products are almost US$1 billion a year"

Figure 6: Raphas extended two production lines in 2014 to enhance its manufacturing capabilities.

Q: What types of intellectual property rights or certifications does Raphas have in relation to their techniques?

A: Raphas, using technology and rights transferred from Yonsei University, continuously works to strengthen its patent portfolio and other intellectual property. The company has registered a total of 12 patents, with its key patent DAB technique also registered in the US (Figure 5). Raphas is currently in the process of registering its patents in other countries around the world in order to strengthen its IP position further.

In addition to registration as IP, Raphas' DAB technology has received many certifications and awards in Korea and abroad. One of Raphas' many accreditations was for its microstructure skin care patch manufacturing technology, which was selected as a New Excellent Technology by the Korean Ministry of Trade, Industry and Energy in 2012. This served as a successful opportunity for Raphas' innovative industry technology to be recognised by the market and eventually led to mass distribution of its product.

In 2014, Raphas' beauty patch product Acropass (Figure 5) was approved by the Chinese CFDA, and was once again lauded for its safety and high quality. Also, Raphas' production facilities has a Class 10,000 clean room for the manufacturing of microstructure beauty patches, and has received ISO 22716 certification, ensuring consistent quality management of its products and facilities.

Q. What is the current status and future sales strategy for Raphas products?

A: Raphas product sales are primarily business to business (B2B). The company manufactures microstructure products containing a variety of raw materials with proven effectiveness, and sells them as ordered from various brands in an Original Development Manufacturing system. Most of its sales are for the overseas market, and products exported to the US and Japan make up the biggest shares of our sales. Raphas continuously works closely with companies selling their products for the selection of active ingredients, product design, testing, and other product development.

In order to serve in its role as a manufacturer better, Raphas extended two production lines in 2014 (Figure 6). Continual improvement of its processes and development of new products has pushed the company to expand to the manufacturing capacity of one million patches per month. During 2015, Raphas plans to expand its manufacturing ability by three times.

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Raphas is also looking into ways it can operate as a Contract Manufacturing Organisation in the pharmaceuticals sector by co-operating on research with raw material medicine corporations and developing new products for these companies to sell. In this system, Raphas will use its technology to create drug delivery platforms for a wide variety of medicines, which will help further the company's scope of business.

As the focus of Raphas has been on development and manufacturing, close mutual co-operation with key companies has been essential to its business. Instead of simply partnering with anyone willing to sell its products, Raphas carefully seeks out partners that understand its products the best. This in itself was a process that was full of much trial and error. But through experience, Raphas found that no matter how much a large corporation was willing to mass distribute their product, a long-sustained relationship can only be possible if the seller had a deep understanding of Raphas's products and technology.

Q. What are some difficulties that Raphas has faced?

A: Raphas is the first to be using the technology that it employs, and has had to put together all of the necessary research and manufacturing equipment on its own, which came together which present challenges, naturally. In the beginning, there was much to be fixed and a lot of instability in the manufacturing. Thanks to years of hard work, Raphas now proudly maintains a consistently high-quality manufacturing system.

Also, the initial reaction of the market to Raphas's technology and products was difficult to influence. The dissolving microstructure patches that were developed took the industry time to get used to – even for those familiar with solid microstructure products. In order to overcome this, Raphas representatives travelled to every corner of the world where their products were being sold, to meet people directly and give detailed explanations of the advantages behind the technology and products. Sometimes new business was secured, and at other times Raphas was unsuccessful. However, overall there is now much more knowledge and interest in Raphas's microstructure patch products.

Q: What are the future plans for the company?

A: Up until now, the focus has been on the commercialisation of this new technology and developing the manufacture of its related products. Now that Raphas has a solid foundation in this, we are able to produce a wide variety of beauty products. Raphas will continue to add new lines of products using microstructure technology, which will have a wide variety of features and effects. Raphas is also looking into developing new products that can be created in combination with existing cosmetic products.

In addition to this, Raphas hopes to put new efforts into the development of medical products. The current microtechnology being used can be effectively applied for use with a wide variety of drugs, especially as a platform for delivery of biopharmaceuticals.

Just as Raphas did in the beauty and skincare industry, the company plans on creating close partnerships with pharmaceutical and other companies to move quickly into this new market. By doing this, not only will Raphas contribute to the growth of Korea's pharmaceuticals industry, it will also move closer to becoming the "Path to Healing" that its name means.

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ABOUT THE AUTHOR

Dr Jung Dong Kim became Director of the Raphas R&D Center in March 2014, and is now the company's Chief Technology Officer. He has also been a Co-operative Researcher at the University of Tokyo since May 2014. From September 2006 until February 2014, he completed a PhD in Biotechnology at Yonsei University, Seoul, Korea.

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