



RAPHAS

DISSOLVABLE MICRONEEDLES: APPLICATIONS AND OPPORTUNITIES

Here, Jung Dong Kim, PhD, Chief Technology Officer, and Do Hyeon Jeong, PhD, Chief Executive Officer, both of Raphas, discuss dissolvable microneedle technology and its myriad uses. The authors go on to explain the potential dissolvable microneedles offer in the medical and pharma sectors, including opportunities to serve unmet needs.

INTRODUCTION

The microneedle was originally developed as a way to deliver active ingredients painlessly into the skin. At present, many companies are trying to develop drug-loaded dissolvable polymer microneedle products for the treatment or prevention of various diseases.¹⁻⁵

Dissolvable polymer microneedles are made by mixing active ingredients with dissolvable polymers to create a micron-sized needle shape that naturally dissolves away after skin insertion. These offer various advantages:

- First, the microneedle is a less painful way of delivering active ingredients compared with the syringe. This can potentially improve the quality of life for those who would otherwise need frequent injections.
- Second, the dissolvable microneedle is an environmentally friendly solution, leaving no dangerous or wasteful products behind, such as needles or glass, because microneedles dissolve into the skin after insertion.
- Third, cold-chain supply costs are reduced, because the solid state of the dissolvable microneedle enables greater stability during the distribution of various biopharmaceuticals without the need for refrigeration.⁶⁻¹¹

Many researchers are developing techniques used in the production of dissolvable microneedles, such as

micromoulding, drawing lithography, droplet-born air blowing (DAB) and centrifugal lithography.^{6,12-14} Micromoulding and DAB techniques are already applied in the manufacture of commercial products, such as the skincare patch. However, pharmaceutical dissolvable microneedle products have not yet been commercialised despite more than fifteen years of research and development.¹⁵⁻¹⁸

RAPHAS' DAB TECHNOLOGY

The DAB process was developed in 2013 to reduce the time required for microneedle fabrication and to allow for gentle fabrication conditions, without the use of UV irradiation or heat. The DAB microneedle array fabrication process occurs by dispensing viscous polymer solution by symmetric air blowing. This property of DAB makes it possible to fabricate microneedles in a few minutes, without loss of activity in ingredients which are sensitive to heat or UV light.

The main advantage of this technique is its simplicity, but there are many hidden

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Figure 1: (A) ISO 22716 certification for GMP relating to cosmetic biodegradable microneedle patches and (B) GMP certification for Raphas' medical device.

mechanical and rheological technologies that are utilised in the successful mass production of dissolvable microneedles.¹³ Additionally, DAB technology does not need to change any equipment to manufacture diverse patch patterns. Raphas has developed various microneedle patch designs using this advantage of DAB technology.

Raphas has registered a total of 24 DAB technology-related patents around the world, including in the US, Japan, China, and the EU. Raphas's DAB process has also received cosmetic GMP certifications from the ISO and medical device GMP from the Korean Ministry of Food and Drug Safety (MFDS) on microneedle patch products (Figure 1). Moreover, various Raphas products have been certified by the agencies of the EU, China, Brazil, the US and more.

SKINCARE APPLICATIONS

Raphas manufactures skincare microneedle patch products using hyaluronic acid as a matrix material. These skincare products contain various active ingredients with proven effectiveness. Raphas produces them to order from various brands in an “original development manufacturing” system. Most of these sales are for the overseas market, especially to the US and Japan. Sales of Raphas' dissolvable microneedle products totalled more than 12 million pouches (two patches per pouch) from 2013 to 2017.

Raphas continues to work closely with and support companies selling their own products with the selection of active ingredients, product design, testing and other new product development. In order

to better serve as a manufacturer, Raphas launched its own brand, Acropass, to prove the efficacy and improve the quality of new products.

In addition, these products are very safe for the skin because they do not contain any preservatives. There were no significant

side-effects after using Raphas' skincare products; this was tested by 25 clinical studies performed according to the good clinical practice guidelines of the Korean MFDS. Also, there were no significant side-effects reported from consumers after using Raphas products.

Wrinkle Treatment

Facial wrinkles are representative of skin ageing caused by reduction of skin elasticity and degradation of the extracellular matrix (ECM). Raphas has commercialised various wrinkle treatment microneedle patch products with a plethora of cosmetic companies. The matrix material of this microneedle is hyaluronic acid, which has been used as moisturising and filling agent for many cosmetic products. This hyaluronic acid based microneedle has wrinkle treatment efficacy by itself. Additionally, this product could be combined with a cream or essence type product for better wrinkle treatment efficacy.^{19,20}

Epidermal growth factor (EGF) loaded microneedles showed significant wrinkle treatment efficacy after applying every day for 10 days (Figure 2a). This product

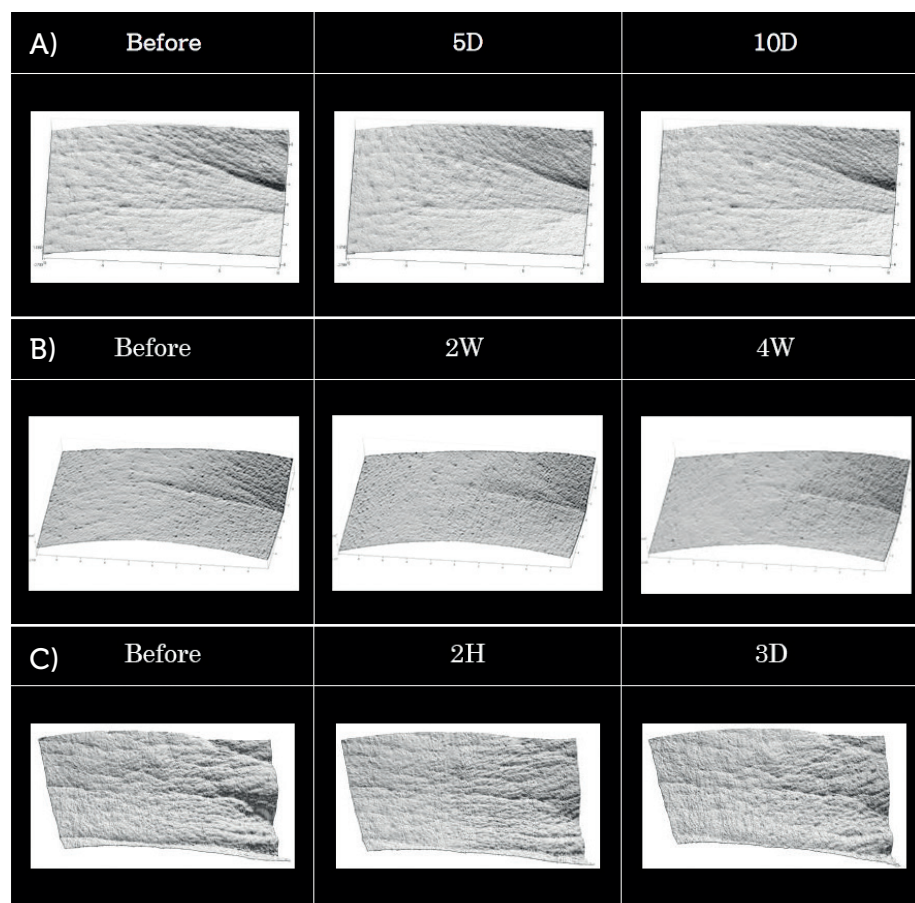


Figure 2: Clinical trial results for wrinkle care efficacy of EGF loaded microneedle patch, with (A) once daily application for 10 days and (B) twice weekly application for 4 weeks. (C) Clinical efficacy of new wrinkle care product after 2 hours of application.

also showed significant wrinkle treatment efficacy after applying twice a week for four weeks (Figure 2c).²¹

Recently, a new wrinkle care product has been prepared and finished clinical trials. This new product is composed of three major active ingredients. One of the major ingredients is acetyl octapeptide-3 which targets the inhibition of wrinkle formation and is very similar to botulinum toxin in terms of immediate efficacy. The other two ingredients, providing the long-term efficacy, are ascorbyl glucoside and sodium cyclic lysophosphatidic acid, which encourages the skin's natural rejuvenation process.

Figure 2c shows a clinical result which indicates wrinkle improvement efficacy after two hours of application; the peak of observed eye wrinkle was significantly decreased after 2 hours of using the product. These results indicate that this new product has fast-onset efficacy for wrinkle treatment.

Trouble Cure

Trouble Cure is a product for restoring acne affected skin quickly without leaving scars (Figure 3a). This product can help people manage acne efficiently and hygienically. The microneedle contains antimicrobial and anti-inflammatory ingredients within the hyaluronic acid backbone structure. The length of the microstructure is around 500 μm so that the active ingredient can be

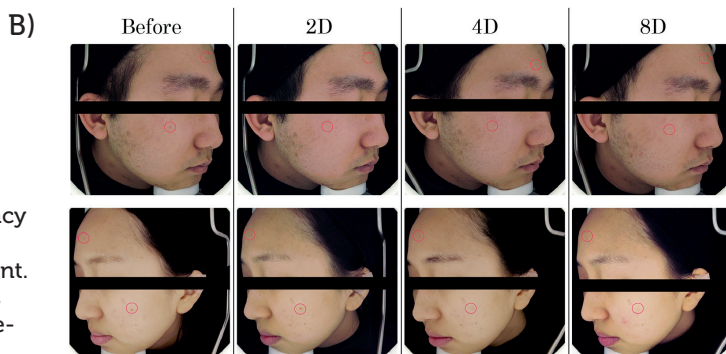
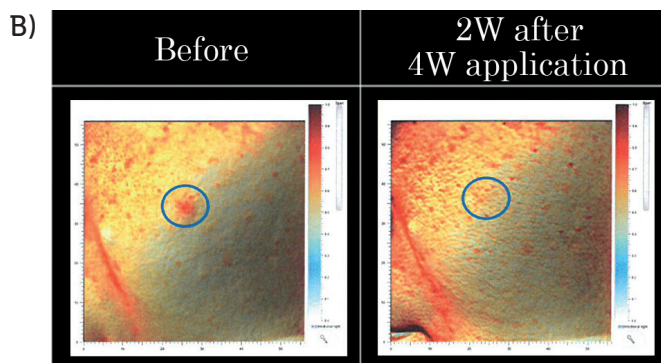
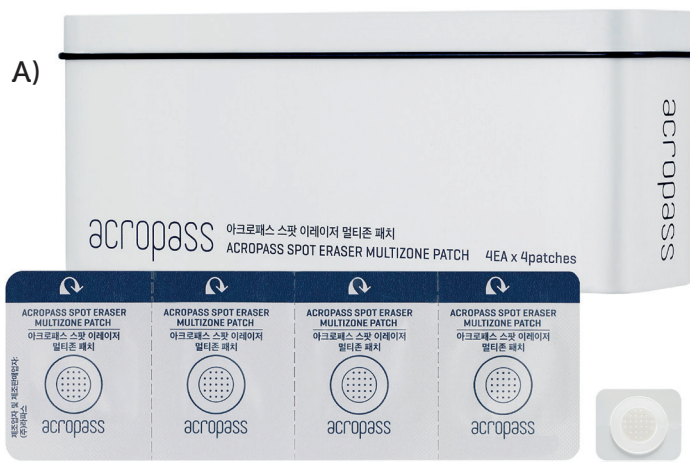


Figure 3:
(A) Trouble Cure product.
(B) Clinical efficacy of Trouble Cure for acne treatment. Red circle shows the Trouble Cure-treated area.

Figure 4:
(A) Spot Eraser product. (B) Clinical efficacy of Spot Eraser on the post-inflammatory hyperpigmentation two weeks on from the end of four weeks of application once every other day. Blue circle shows the Spot Eraser-treated area.



directly transferred to the hair follicle region where the bacterium causes the acne.

After application, an anti-inflammatory ingredient is delivered into the skin to suppress the inflammation of the acne, and an added antimicrobial ingredient helps to inhibit the activity of inflammation-causing bacteria. The antimicrobial ingredient is a peptide that is effective against antibiotic-resistant strains.

In general, the antimicrobial peptide is inactive at physiological salt concentrations and is rapidly degraded by proteolytic enzymes present in serum and the digestive tract.^{22,23} Therefore, it is difficult to show efficacy

at target area when used as ointment or cream formulation. However, Trouble Cure can deliver the antimicrobial peptide directly into the target region via the microneedle patch without loss of activity.

Clinical trial results showed that more than

90% of subjects had improved skin condition after four days from the first application of the product, which proved to be safe, without adverse skin reactions during the test (Figure 3b). In addition, this product is designed to be used hygienically with alcohol swabs and individual packaging to prevent secondary contamination occurring whilst managing the acne.

Spot Eraser

Skin whitening and brightening products are used for various hyperpigmentary disorders. Skin whitening ingredients usually act as tyrosinase inhibition to block the synthesis of melanin from melanocyte.^{24,25}

Raphas has developed a novel concept for a topical whitening product by the name of Spot Eraser (Figure 4a). This product can treat topical hyperpigmented spots by inhibiting the multi-pathway of hyperpigmentation using tranexamic acid, niacinamide, ascorbic acid and arbutin. Tranexamic acid can inhibit melanogenesis

“The efficacy of topical steroids could be enhanced via a microneedle patch by physically penetrating the thickened skin.”

through the activation of autophagy in a melanoma cell line. Niacinamide reduces cutaneous pigmentation by inhibiting melanosome transfer. Ascorbic acid is a strong antioxidant that can inhibit melanin oxidation to keep the melanin in a relatively brighter colour form. Arbutin is a glycosylated hydroquinone which can inhibit tyrosinase activity.

Clinical results for Spot Eraser showed significant efficacy in terms of post-inflammatory hyperpigmentation after a single application every two days for four weeks, and observing for an additional two weeks without further applications (Figure 4b). Clinical results also showed a significant decrease in melasma area and severity index (MASI). These results indicate the Spot Eraser could be a good solution for the topical treatment of hyperpigmentation.

MEDICAL DEVICE APPLICATIONS

Drug Absorption Enhancer

Therapass is a dissolvable microneedle product composed of hyaluronic acid (Figure 5a). This product does not contain any active ingredients. It enhances skin absorption of ointment, such as topical steroids, when applied to the skin after ointment application (Figure 5b).

Although topical steroids have been used as a general treatment for a variety of skin diseases, some patients, such as *prurigo nodularis* patients, do not sufficiently respond to the strong steroids, possibly due to the thickened skin leading to a low drug penetration rate. However, the efficacy of topical steroids could be enhanced via a microneedle patch by physically penetrating the thickened skin. Dermatologists have performed clinical trials using this product for two kinds of skin diseases, psoriasis and *prurigo nodularis*.

Prurigo nodularis is a skin disease characterised by itchy nodules which are distributed in symmetric and bilateral manner.²⁶ Patients often scratch these nodules and it causes permanent changes to the skin, including hyperkeratosis, hyperpigmentation and skin thickening. A topical steroid, with moderate to high potency, is the standard therapeutic agent, and it is the most widely practiced treatment method. However, the efficacy of topical steroids can be dependent upon the thickness of the lesion. Microneedle based therapy can help to overcome this problem. In the clinical study, microneedle-assisted delivery showed significantly enhanced efficacy of



Figure 5: (A) Therapass: Dissolvable microneedle based medical device. (B) Mechanism of Therapass as an enhancer of ointment absorption.

“Dissolvable microneedle based pharmaceutical products are yet to be commercialised. However, many dissolvable microneedle companies, including Raphas, are developing various pharmaceutical products for various diseases.”

the topical steroid, decreasing the area and height of nodules ($p < 0.05$) compared with topical steroid alone.

Psoriasis is a chronic, inflammatory skin disease, which decreases quality of life, and affects roughly 2-4% of the population.²⁷ There is no cure for psoriasis, however, treatments such as topical steroids can help control the symptoms. In a clinical study in psoriasis patients, the median decrease of modified Psoriasis Area Severity Index (mPASI; range 0 to 12), which is a sum of scores for plaque thickness, scaliness and redness, was 60% after one week's application of the microneedle patch.²⁸ This result shows that use of the microneedle patch significantly enhances the therapeutic effects of topical steroids and shows fast onset for the topical psoriasis treatment compared with conventional application of topical steroids on the region ($p < 0.001$).

Diagnosis

The microneedle can be used in diagnostics as a minimally invasive patient monitoring tool. Previous studies have focused on hollow microneedle based blood or interstitial fluid

extraction for glucose sensing or disease marker diagnosis.²⁹⁻³² However, hydrogel microneedle-based *in vivo* diagnosis showed the possibility for a user friendly and comfortable disposable microneedle patch sensor.^{33,34} Although research has shown the potential for a microneedle-based diagnostic application, no such product has yet been commercialised.

Raphas has begun researching disposable microneedle patch sensors using DAB technology with other partners, looking to overcome the obstacles to commercialisation, including manufacturing cost and sensitivity.

PHARMACEUTICAL APPLICATIONS

Dissolvable microneedle based pharmaceutical products are yet to be commercialised. However, many dissolvable microneedle companies, including Raphas, are developing various pharmaceutical products for various diseases. Raphas is currently developing products for Alzheimer's disease, osteoporosis, immunotherapy and others.

Alzheimer's Disease

Alzheimer's disease is a chronic neurodegenerative disease which causes difficulty in remembering recent events. Donepezil tablets are a widely used oral administration for Alzheimer's disease, and clinical studies have shown modest benefits in cognition and/or behaviour.³⁵

However, there is an unmet need for a new administration route of donepezil because of adverse effects in the gastrointestinal (GI) tract and patients with dysphagia.³⁶ Raphas and its partners have been co-developing a donepezil-loaded microneedle patch to overcome the problems inherent to the current dosage form. An IND application will be submitted to the Korean MFDS for the clinical study of this product during the first half of this year.

Osteoporosis

Many elderly people suffer from osteoporosis, a disease which causes chronic bone weakness. Parathyroid hormone injection is the only US FDA approved bone building medication for the treatment of advanced osteoporosis, requiring a once daily injection, which can adversely affect quality of life. Therefore, various companies such as Zosano Pharma, Corium and 3M are developing parathyroid hormone-loaded microneedles. Raphas has been developing this formulation with the support of the Korean government for the past two years, and an IND application will be submitted this June.

Immunotherapy

Allergen-specific immunotherapy (SIT) is an effective treatment for allergy-related symptoms, such as atopic dermatitis (AD). However, frequent clinical visits over a three-year period, as well as looming adverse events, tend to discourage patient compliance.

Raphas has been developing a house dust mite (HDM) allergen-loaded microneedle patch for HDM-SIT of AD, and this microneedle patch showed a similar efficacy to a ten times higher dosage delivered via subcutaneous injection.³⁷

RAPHAS' FUTURE PLANS

Raphas plans to expand its business area beyond the cosmetic market to include medical devices and pharmaceuticals. Recently, Raphas started research into vaccine-loaded microneedle patch development with a multinational vaccine company and constructed a new building to setup GMP facilities for clinical studies.

ABOUT THE AUTHORS

Dr Jung Dong Kim holds BS and PhD degrees in biotechnology from Yonsei University (Seoul, South Korea). Dr Kim joined Raphas in 2010 for the industrialisation of microneedles using droplet-born air blowing technology. He was a co-operative researcher with the Institute of Industrial Science, University of Tokyo, from 2014 to 2017. He was also on the steering committee of the 2016 International Conference on Microneedles. He received the IR52 Jang Young Sil Award twice from the Minister of Science, ICT and Future Planning in 2016 and Minister of Science and ICT in 2017. His research is focused on the commercialisation of dissolvable microneedle technology in the cosmetic and medical markets.

Dr Do Hyeon Jeong received a Master of Engineering degree from Yonsei University in 1993. In 2004, Dr Jeong received his PhD in Biotechnology from Yonsei University. Since 2009 he has worked as CEO and Co-Founder of Raphas. He also worked as a professor at Osan University in South Korea. He has been a member of the steering committee of the International Conference on Microneedles from 2017. He received a prize from the President of South Korea at the end of 2017 for his achievements in the commercialisation of dissolvable microneedles.

Additionally, Raphas is continuing to develop various medical products, such as a dementia treatment patch, hormonal therapy patch, and immunotherapy patch, using DAB technology.

The foundation of Raphas is closely connected with the aspirations of professional researchers into drug delivery systems. Raphas believes that this remarkable method for enjoying "a healthier life, without pain" is the future of drug delivery systems. Raphas will open up the road to this treatment for everyone in the world.

ABOUT THE COMPANY

Raphas started as a microneedle business from 2009 and its DAB technology has since drawn worldwide attention. The corporate name, Raphas is a compound of two words: Rapha, which means "heal", and Path. This represents the objective of Raphas to become a path towards healing for all of humankind. Raphas is continuously conducting innovative research towards the evolution of various technologies and products.

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Raphas developed Droplet-born Air Blowing(DAB) technology for the most effective transdermal drug delivery. The corporate name, Raphas is a compound of two words: Rapha, which means 'heal', and Path. This represents the objective of Raphas which is to become a path towards healing for all mankind. Raphas continue to conduct innovative research for the evolution of products and technologies. DAB technology has already been developed into microneedle patch products for the beauty industry, and received high praise for its strong results. Raphas is also continuing the challenge for the development of medical application of DAB technology to provide healthier lives and future happiness of all mankind. Based on this belief of universal value, Raphas will become the world's best creative and leading technology company.

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