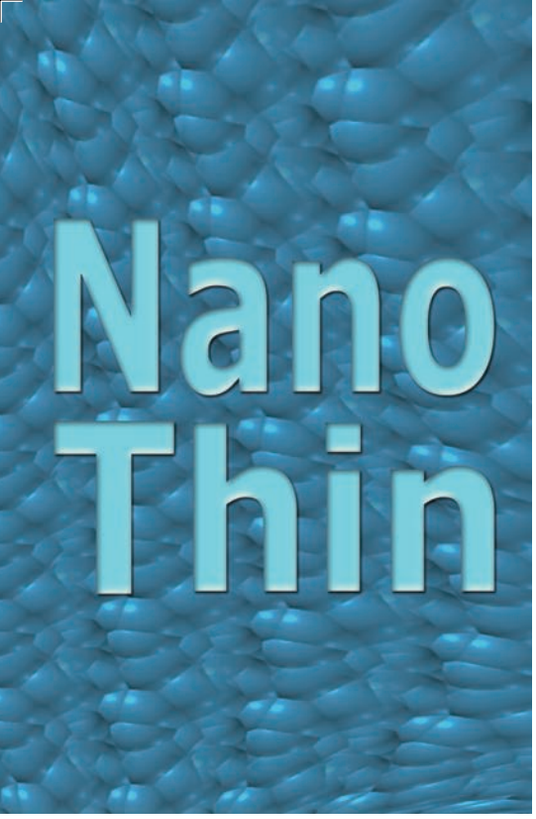

Biocompatible Ultra-Thin Polymer Films: A Mass Production Technology to Revolutionize the Medical Field

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Films used in industry today can be as thin as one micrometer, but in the near future, it is likely that these will be as thin as a few tens of nanometers. As such, at least one research center is already using web handling theory and roll-to-roll equipment to develop and utilize such films. Established to bring together up-and-coming researchers from a myriad of fields, the interdisciplinary Micro/Nano Technology Center (MNTC) at Japan's Tokai University is working to develop ultra-thin polymer films with thicknesses under 100 nm, as well as to search out potential applications. We spoke to Professor Rio Kita of the Department of Physics, School of Science; Associate Professor Yosuke Okamura of the Department of Applied Chemistry; and Tokai University Department of Mechanical Engineering Junior Associate Professor Yuta Sunami about their research in this field.

From Left, Junior Associate Professor Yuta Sunami, Professor Rio Kita, and Associate Professor Yosuke Okamura

Targeting Medical Applications

Consisting of eight campuses throughout Japan, Tokai University is one of the largest educational systems in the country. MNTC was established at the Shonan campus, located in Kanagawa prefecture, in January 2015. A comprehensive subsidy was provided by the Ministry of Education, Culture, Sports, Science and Technology (MEXT)—the MEXT-supported Program for the Strategic Research Foundation at Private Universities, a subsidy for supporting various research projects at private universities. MNTC covers a total floor area of 403.57 m^2 and is equipped with all of the advanced research facilities, including a clean room, a cell culture lab, a chemistry lab, and a constant temperature/humidity room.

Eight young researchers from the engineering, physics, and medical schools have come together to work at MNTC with the common goal of developing next-generation medical technologies using ultra-thin polymer films, a theme that allows each member to apply his or her individual field of specialty. Professor Rio Kita, Department of Physics, is an expert in polymers and leads the MNTC research team.

Under the concepts of “Create,” “Test,” and “Know,” the members have divided themselves into three sub-groups. Associate Professor Okamura of the Department of Applied Physics and Junior Associate Professor Sunami of the Department of Mechanical Engineering belong to the “Create” group. Dr. Okamura is in charge of design and production, and Junior Associate Professor Sunami is in charge of developing the roll-to-roll production process with an eye on eventual mass-production. Ultra-thin polymer film, in short, is any planar

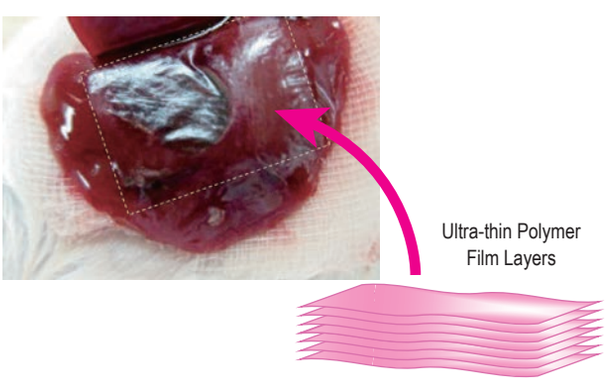
structure of under 100 nm in thickness that can stand without any support (free-standing). Such thin-films are often referred to as nano-sheets.

The major characteristic of these films is that they are planar (two-dimensional). This planar nature provides the films with excellent flexibility. They also have the ability to adhere easily to all types of uneven structures. In other words, they have contact adsorption and thus have the ability to adhere (anchor) extremely well to both flat and curved surfaces. As such, the films do not require any adhesives and can adhere to wet surfaces. As a member of Professor Shinji Takeoka's research team at Waseda University's School of Advanced Science and Engineering, Associate Professor Okamura developed unique nano-materials, which he has continued to develop under a different direction at MNTC. Currently, he is working to create an ultra-thin polymer film from highly biocompatible materials, with one major goal being to use these films inside the human body.

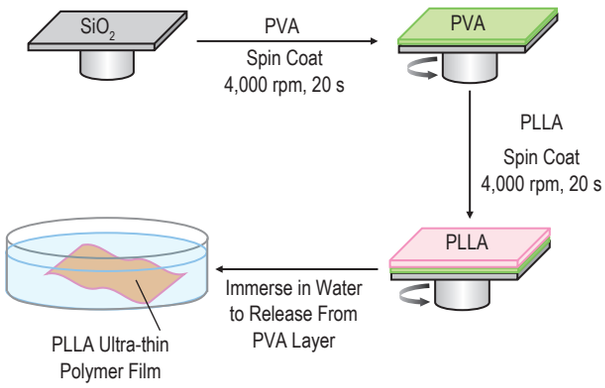
MICROGRAVURE Coating Method

One of the main applications of ultra-thin polymer films being developed at MNTC is wound dressing, in which the films are functionalized to close organ incisions after surgery for quick recovery. Associate Professor Okamura says that their most recent tests use ultra-thin polymer films of a few tens of nanometers in thickness and a few centimeters square in area. Tourniquet tests have been made where these films are used to stop bleeding from rat livers.

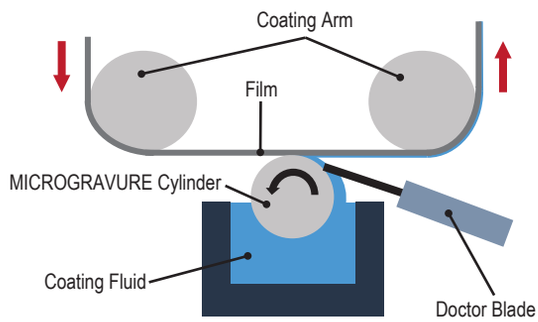
From such tests, Associate Professor Okamura has found that it is essential to use multiple layers of ultra-thin polymer films in these types of applications. Although layering the films is necessary to increase the strength when attached to an organ, the films themselves are not directly laminated. Instead,



Ultra-thin Polymer Film Being Tested for Its Ability to Stop Bleeding in a Rat Liver (provided by Professor Yutaka Inagaki of the Tokai University School of Medical)



Conventional Ultra-thin Polymer Film Forming Process

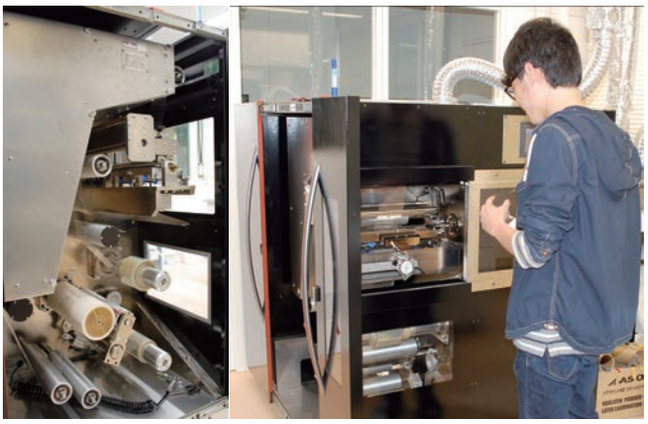


MICROGRAVURE Coating Method

as Associate Professor Okamura explains, mulitple layers of films are separated by spacers. The spacers are typically water-soluble. When the films become wet, the spacers slip out and water enters the area left behind. In this way, the structure looks like a mille-feuille pastry.

Although monolayer films adhere well to the incision, the pressure of the blood during bleeding may break the films. As an alternative, thicker films can be used, but this results in poor adhesiveness. Hence layering of individual layers was chosen, which ensures both strength and adhesion. Associate Professor Okamura intentionally chose the liver for these tests because the high blood flow would help verify the performance of the film. For example, they found that five layers of film were sufficient to stop bleeding from rat livers. Despite these results, a mass-production technology is still essential in moving towards practical application.

Junior Associate Professor Sunami, who works under Professor Hiromu Hashimoto, an internationally recognized leader in web handling theory and professor at the Tokai University Department of Mechanical Engineering, is in charge of mass-production of ultra-thin polymer films using a wet coating roll-to-roll process. Using MICROGRAVURE, a coating method patented by Yasui Seiki Co., Ltd., Junior Associate Professor



MICROGRAVURE Coating Machine at MNTC

Sunami first applies a layer of water-soluble polyvinyl alcohol (PVA) onto a 100 μm thick PET film. Then, L-type polylactic acide (PLLA) is coated onto the PVA layer, dried in hot air, and rewound. Finally, the PVA layer is dissolved in water to produce fairly large amounts of free-standing ultra-thin PLLA films.

MICROGRAVURE, already used widely to produce ultra-thin film coatings in industry, works like standard gravure. The small-diameter gravure cylinder spins counter to the substrate travel direction and picks up the coating fluid from a fluid supply pan, after which a doctor blade scrapes the excess coating fluid from the cylinder. An extremely small, stable bead forms between the spinning cylinder and substrate, providing the resulting film with excellent thickness uniformity.

According to Junior Associate Professor Sunami, the maximum coating width of the PLLA fluid at this point is 100 mm and the coating speed is 5 m/min. A coating fluid PLLA concentration of 1% will form a wet film of 6 μm in thickness and a dry film of about 60 nm in thickness. By adjusting parameters such as gravure cylinder rotational speed and coating fluid concentration, Junior Associate Professor Sunami has achieved a thickness precision in the width direction of ±10%. The influence of hot air convection currents on the film is controlled using their know-how acquired through previous web handling research.

The Freedom to Research

MNTC originated from the Tokai University Micro/Nano Study Group, an interdisciplinary, self-initiated research association made up of young researchers that got its start in the summer of 2013. The impetus behind the group's formation was a meeting held around that time on campus at which Professor Kita and the current members had an opportunity to meet each for the first time. Junior Associate Professor Sunami says that none of the members had spoken before then, and at best they knew each other's names and had a vague idea about their research. Despite their lack of prior history, the members immediately hit it off and decided to meet again with the intension of working together on some project. Junior Associate Professor Sunami was not in attendance during the original meeting, but met up with the group later at the invitation of Professor Tsuchiya.

The group spent an entire weekend debating the topic of research. As a result, they decided to focus on Associate Professor Okamura's ultra-thin polymer film given its originally, future outlook, and the potential for all members to utilize their strengths. Professor Hashimoto and other veteran professors at Tokai University responded to this initiative by the younger researchers with support for the study group's activities. From there, their idea suddenly took-off and led to the establishment of MNTC.

Class 1000 Clean Room

Cell Culture Room Is Equipped With All the Necessary Equipment for Research

Despite there only being eight members, Professor Kita says the group is far from closed. Rather, he says they want MNTC to evolve into a location for communication between different groups, including students and professors of Tokai University, outside researchers, and private companies. For this reason, MNTC began its CORE TIME COFFEE, an open brainstorming session held every Monday, Wednesday, and Friday afternoon at 3 pm that anyone can attend. A comment by Professor Tsuchiya sums up the atmosphere of the MNTC. He says that every member of the group chooses to be here, and they are doing exactly what they want.

In addition, Junior Associate Professor Sunami says that his research also focuses on the anisotropy of the mechanical strength of the ultra-thin films. This is a capability specifically based on their understanding of web handling theory and will be important in producing wider films when there is a demand for higher productivity in the future.

From Webs to Platelets

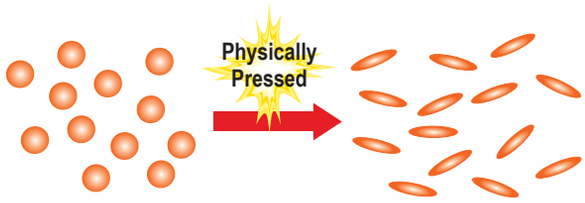
In addition to producing long sheets of ultra-thin polymer films in a roll-to-roll process, the team is also working on smaller disk shaped ultra-thin polymer films. This was one of Associate Professor Okamura's research themes prior to arriving at Tokai University.

Associate Professor Okamura says that some 10 years ago he was part of a team focused on functionalizing platelets in the blood with nano-particles. Typically, platelets in the blood will gather near damage in a blood vessel to close any openings. Cancer patients receiving anti-cancer drug treatments, however, have drastically low platelet counts and there are many people whose platelets do not function properly to begin with. As such, he felt it would be extremely beneficial if it were possible to artificially create a replacement for platelets.

The research team Associate Professor Okamura was part of at the time developed a nanoparticle in which the surface was modified with a special molecule that could recognize damaged parts of blood vessels. They confirmed that the nanoparticles had the potential to stop bleeding when injected into the blood, but they also recognized that flat, disk shaped particles would be more effective than the spherical particles they were using. They also saw the potential to use the nanoparticles as the carrier in drug delivery systems.

During this stage, around 2010, their work required a fairly complex process that combined UV photolithography and self-organizing monomolecular film technologies to produce disk shaped objects with thicknesses on the nano-scale. After transferring to Tokai University, however, Associate Professor Okamura continued with his research and succeeded in developing an extremely simple generation process for the disks.

The approach uses alginic acid, a compound found in seaweed (brown algae) that instantly gels when mixed with calcium. Tiny polymer particles are dispersed into this gel, which is then physically pressed and the gel chemically removed to extract the disk-shaped ultra-thin polymer films. Particles with a diameter of 1 μm, for example, will produce disks with a diameter of 1.6 μm and a thickness of 100-200 nm. Currently, they are working with polystyrene polymers, but PLLA is also an option.



Process for Forming Micro-particles Into Disk Shapes

The surfaces of the disk-shaped ultra-thin polymer films can be modified so that the nano-disks dissolve blood clots when injected into the blood. In addition, Associate Professor Okamura is focused on the development of a vascular disease model to speed up this research.

A Flood of Original Ideas

Although this ultra-thin polymer film has the potential to change the future of medicine, the team must first investigate the viability and safety of the films, as well as conduct countless tests from different perspectives. This work is handled by the young, energetic researchers in the "Test" and "Know" groups. Members of the Test group include Professor Kazuyoshi Tsuchiya of the Department of Precision Engineering; Assistant Professor Asako Otomo of the Department of Molecular Life Sciences, Basic Medical Science and Molecular Medicine, Tokai University School of Medicine; and Associate Professor Hiroshi Kimura of the Department of Mechanical Engineering.

Professor Tsuchiya is a pioneer in developing the world's finest painless hypodermic needles. His focus is on combining the technology of painless needles and ultra-thin polymer films to fabricate a novel sensing device designed to measure blood pH and glucose levels. Assistant Professor Otomo is in charge of developing medical applications for cell culture and cytopathology. She is an expert in the field of cell culture, including differentiating nerve cells from ES and iPS cells, and is involved in growing biological cells for clinical testing. Associate professor Kimura is in charge of developing devices using these films for specific medical applications. For example, he has developed micro-fluid devices closely modeled on internal structures, such as the blood vessels that connect the liver, small intestine, and cancer cells found in the lungs. These devices allow for research that simulates how metabolic products (substances absorbed by the small intestine and metabolized in the liver) affect cancer cells. This technology is essential to testing the viability of disk-shaped ultra-thin polymer films.

The "Know" group consists of Assistant Professor So Nakagawa of the Department of Molecular Life Sciences, Basic Medical Science and Molecular Medicine, Tokai University School of Medicine; Associate Professor Kazuya Kabayama of the School of Science, Graduate School of Science, Osa-

ka University (formerly of the Institute of Glycoscience, Tokai University); and Professor Kita. With the goal of establishing a method to evaluate the interaction between thin films and cells, Assistant Professor Nakagawa analyzes this interaction at the genetic level using genome analysis technology. Associate Professor Kabayama, one of the founding members of MNTC, is specialized in observing living cells (live cell imaging), and works on application to cell and drug screening. Professor Kita analyzes the ultra-thin polymer film structure and function using molecular property analysis and rheology analysis.

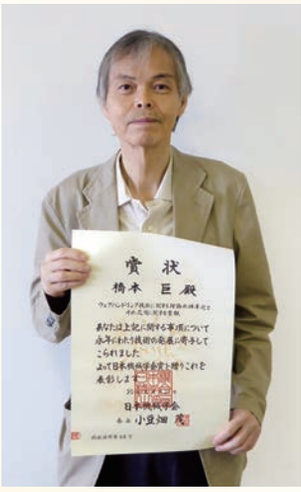
To achieve the ultimate goal of applying ultra-thin polymer films to the human body, the team must still overcome many hurdles on their path. As such, the research also considers applications more focused on the near future. Additionally, Professor Kita comments that the main strength of the MNTC members is that they are all young researchers, which means they constantly bring new ideas for various applications. All the team members are also extremely dedicated to both research and education.

Instead of using large films, the new concept proposed by Professor Kita is to use fine, fragmented films to modify all kinds of surfaces such as microfluidic channels and the inner surfaces of the needle. A homogenizer is used to fragment the macroscopic films into microscopic pieces. The surface of any object dipped into the solution of microscopic pieces will become covered with tiny pieces. As a result, the functionality of the ultra-thin polymer film surfaces is transferred to the surface of the object. This approach also works to completely cover microscopic surface unevenness. At present, this technology is utilized to modify the inside surface of the painless microneedle developed by Professor Tsuchiya, which has gained positive attention as a means of developing novel sensing devices.

Professor Kita goes on to say that they also assume these films will be used in operating rooms. Although produced in a standard environment today, it will thus be necessary to produce these films on roll-to-roll equipment in a contaminant-free, clean environment. The films will also be cut into the desired shape and packaged in a clean room, only being opened again in the operating room immediately before use. Given these criteria, Professor Kita says it will be necessary to go beyond the bounds of their research institute and cooperate with private businesses. As such, he looks forward to working with companies that are interested in their research.

Dr. Hashimoto of Tokai University Wins JSME Award for Technological Achievement

Established nearly 60 years ago, the Japan Society of Mechanical Engineers (JSME) has held its JSME Awards annually since 1958. In addition to the three JSME awards for "Academic Papers," "Technology," and "Technological Achievement," JSME also offers honorable mentions (research, technology) that celebrate young JSME members, as well as the JSME Education Award to highlight educational activities in mechanical engineering and other industrial fields.



Dr. Hashimoto Holds the JSME Award Certificate for Technological Achievement

From Left, JSME Award for Technology, Technological Achievement, and Academic Papers

In recognition of his contributions to systematizing and applying web handling theory over the past 30 years, JSME bestowed the 2015 Technological Achievement Award on Professor Hiromu Hashimoto of Tokai University. In 1990 Professor Hashimoto received the Academic Paper Award for his research in the field of tribology and in 2010 received the Technology Award for his work in web handling. Professor Hashimoto is one of the few, if only, people to have received all three awards.

In this way, his monumental work and continued research activities with a constant focus on actual manufacturing processes have placed him in a position that publishing cutting-edge academic papers and contributing to new commercial product development alone could not have done alone.