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Imparting Superhydrophilicity to Diamond-Like Carbon by Plasma Surface Treatment Technique

Tatsuyuki Nakatani*, Keishi Okamoto,
Ikuo Omura[1] and Shuzou Yamashita[1]

Toyo Advanced Technologies Co., Ltd.,
5-3-38 Ujina-higashi, Minami-ku, Hiroshima 734-8501, Japan
[1]Japan Stent Technology Co., Ltd.,
5303 Haga, Okayama 701-1221, Japan

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The surfaces of medical materials are coated with polymer molecules or drugs in order to functionalize the surfaces in ways such as imparting biocompatibility. However, in the case where the medical materials are inorganic, there is the problem that they will have poor adhesiveness to polymers and be liable to peel. For coronary artery stents, the authors succeeded in developing a method of rendering a diamond-like carbon (DLC) film surface hydrophilic by using plasma surface treatment techniques, with the purpose of enhancing such a surface's adhesiveness to a stent base material of drug-containing polymer that enables imparting of functions such as biocompatibility. In this method, the DLC surface is first irradiated with acetylene (C_2H_2) plasma so as to cleave the carbon-carbon bonds and create reactive sites on the surface. Next, plasma that contains oxygen (O_2) is irradiated onto the surface, causing the reactive sites to react with the O_2. By this method, it becomes possible to introduce chemically stable superhydrophilic functional groups such as carboxyl groups or hydroxyl groups to the DLC surface, and to fix drug-containing bioabsorbable polymers evenly and firmly to the DLC surface.

1. Introduction

Myocardial infarction, a disorder arising from the occlusion or spasm of the coronary arteries, is one of the three major lifestyle-related diseases along with cancer and strokes. A technique for its treatment that has flourished in recent years is stent placement by means of a catheter, which is classified as a *specially controlled medical device*. As a minimally invasive medical technology that avoids highly invasive heart bypass

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*Corresponding author: e-mail: nakatani.t@toyo-at.co.jp surgery is advantageous for the patient's quality of life (QOL) and medical expenditure, and entails no surgical operations, this procedure is set to be one of the indispensable techniques for forming an aging society of healthy and long-lived people in the future. A coronary artery stent, which as Figs. 1 and 2 show consists of a metal tube made of meshes, is a medical device that is used to treat symptoms arising from the stenosis or occlusion of the coronary arteries. By being inserted into the affected part and left in place, it assures the flow of blood.

Medical devices for use in medical treatment, both on the inside and outside of the body, have been developed using a wide variety of forms and materials to suit diverse environments and purposes. Materials are selected in consideration of structurally required characteristics such as a desired shape or dynamical strength, as well as surface characteristics such as antithrombogenicity, biocompatibility and frictional wear. However, since the material on its own cannot easily assure the achievement of both the structurally required and surface function characteristics, modification of its surfaces via coating is being studied as a means of imparting surface functions. Concerning the stents available on the commercial market, a number of reports are currently being prepared by academic societies on the adhesion of drug coatings to metals, on the biocompatibility of the stent after the release of the drug is complete, and problems with the drug. Thus, it is now an urgent task to revise the surface functions of the stent base material.

Against this background, various coatings have been tested out on the metal surfaces in order to impart antithrombotic functions to the stent material.(1) Among these, particular attention is being focused on diamond-like carbon (DLC), a biocompatible and antithrombotic carbonaceous thin-film material.(2–8) As DLC is physically and biologically similar to pyrolitic carbon, which has a proven clinical track record in artificial heart valves and artificial blood vessels, it can easily be conjectured to have excellent properties for surface treatment for biocompatibility purposes.(9) However, for use in stents, major issues need to be resolved, including the fact that its low adhesion to the base material causes it to peel off, and that under stress during expansion, it is liable to crack.

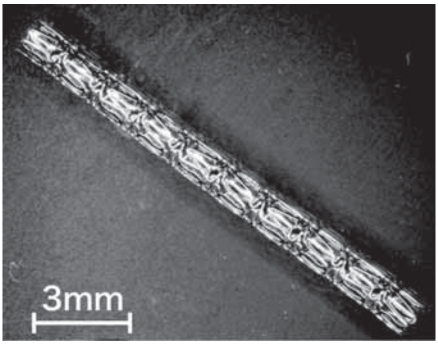


Fig. 1. Photograph of coronary artery stent's exterior. (Design: Japan Stent Technology. Laser cutting and electropolishing: Toyo Advanced Technologies.)

We have already developed a DLC thin-film formation + plasma irradiation + post-graft polymerization technique that solves the problem of the peeling of polymers from an inorganic base material (such as metals, ceramics and silicone), for use in the treatment of medical device surfaces to impart biocompatibility functions.(10,11) In addition, applying the physical control technology for DLC that had been built up during the development of a rotary engine,(12,13) we developed a high-elasticity concentration-gradient-type DLC film that can imitate the plastic deformation of the stent base material by adjusting the amount and concentration gradient of the Si added to the DLC. A report on such was issued.(14) In addition, we were able to establish original processing techniques and quality management systems (ISO13485) for the laser processing and polishing processing of stents made of Co-Cr, so as to further exploit the special attributes of DLC thin films.

Accordingly, in the present study we used a plasma surface treatment technique to impart superhydrophilicity to the surface of a high-elasticity DLC thin film used on coronary artery stents, and applied to stents a superhydrophilic DLC thin film with functionality further heightened relative to our earlier technology, with the purpose of enhancing to still higher levels the adhesion of biodegradable polymers to the surfaces of stents that undergo comparatively large distortion during expansion. Accounts of this are presented below.

2. Problems for Functionalization of DLC Surfaces

Stents are used for the clinical application of drugs such as antitumor agents (taxol) and immunosuppresants (rapamycin). Although it is evident that these drugs have a 6-month restenosis prevention effect, they have been cited as having many problems requiring amelioration, including the facts that when they are present, the stent surfaces do not become covered with endtherial cells over medium and long terms, and the mortality rate is comparable to that in the case where no drug is used with the stent.

Accordingly, we worked to develop a coronary artery drug-eluting Co-Cr alloy stent through the use of an antithrombotic agent that is in clinical use across the world and is expected to have the effect of preventing intimal thickening, and through a fusion of techniques for forming concentration gradient-type high-elasticity DLC films,(13) techniques for plasma surface treatment that introduces functional groups to DLC surfaces, and drug elution rate control employing biodegradable polymers.(14)

As regards imparting functionality to the surface of a DLC thin film, the surface of such a film that has been coated onto a stent of complex three-dimensional shape is irradiated with plasma so as to create reactive sites on the surface. Via such plasma irradiation, reactive sites containing radicals are created on the DLC surface, and it becomes possible to realize the graft polymerization of biocompatible polymers, using such introduced radicals as the starting point. Furthermore, through exposure to the atmosphere after the radicals are introduced, functional groups such as hydroxyl groups can be generated, and various modifications of the DLC thin-film surface can be carried out using the functional groups so generated. By thus modifying the DLC, it becomes possible to add various functions such as biocompatibility using polymers.(10,11) Figure 3

Fig. 2

Fig. 3

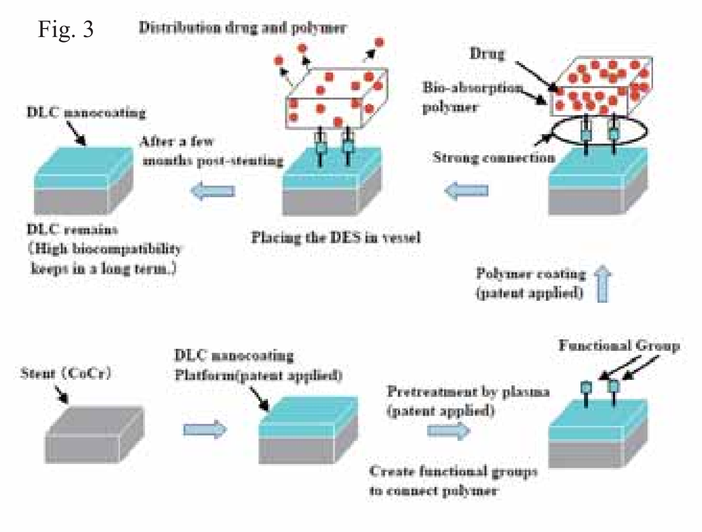


Fig. 4(a)

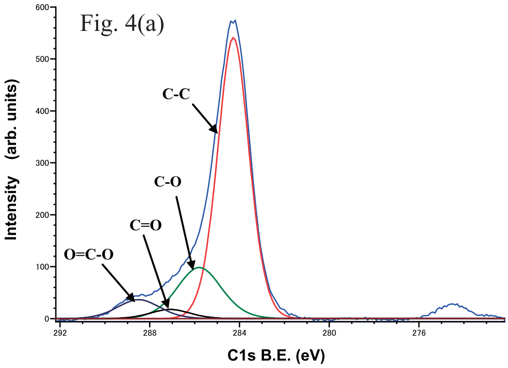


Fig. 4(b)

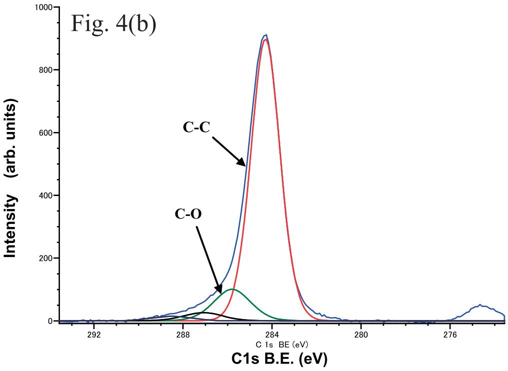


Fig. 4(c)

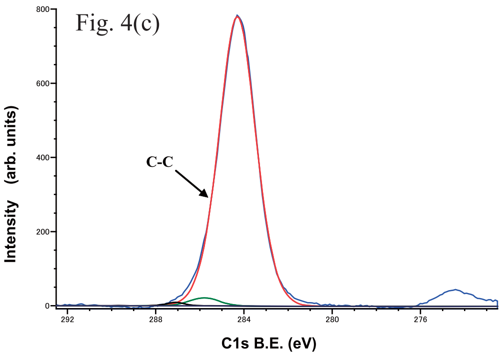


Fig. 4(d)

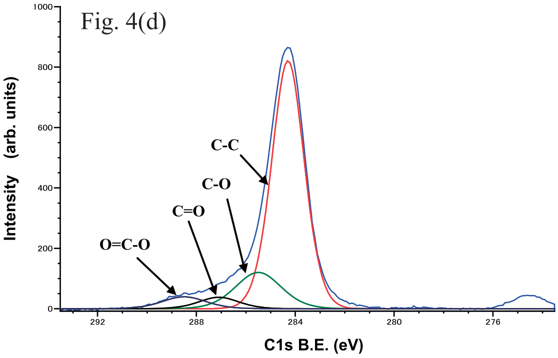


Fig. 2. Photograph of stent crimped into catheter. (Upper: before expansion. Lower: after expansion.)
Fig. 3. Schematic of technology for coating of drug-eluting stent.
Fig. 4. Results of XPS analysis of DLC film surfaces. (a) Results for DLC film that underwent C_2H_2 and O_2 plasma irradiations, (b) results for DLC film that did not undergo plasma irradiation, (c) results for DLC film that underwent C_2H_2 plasma irradiation, and (d) results for DLC film that underwent Ar and O_2 plasma irradiations.

shows schematically the coating process in the manufacture of a coronary artery drug-eluting stent that is able to prevent restenosis over a long term.(14)

However, it became clear that the existing DLC surface modification method developed by the authors suffered from several problems. In the existing method, plasma-irradiating the DLC that is coated onto the base material cleaves the DLC's carbon-carbon bonds, generating radicals, but the radicals thus generated are unstable and prone to disappear; furthermore, it is difficult to keep the quantity of the radicals at a constant level. Moreover, even when a DLC film with radicals introduced is exposed to the atmosphere so as to create hydrophilic functional groups such as hydrogen oxide groups in it, the reactions between the radicals and the hydrogen do not proceed adequately, and consequently, the DLC's hydrophilicity is not sufficiently enhanced. Also, even when it has been enhanced, the hydrophilicity deteriorates once more with the passage of time. Thus, there were numerous problems.

The objectives of the present research are to realize a method of modifying DLC surfaces that would enhance the hydrophilicity of DLC thin-film surfaces as well as—through the use of drug-supporting polymers—permit functions such as biocompatibility to be imparted to them stably and efficiently, and to apply such a method to a coronary artery drug-eluting stent proposed by the authors, in order to resolve such existing problems.

3. DLC Coating

3.1 *Coating conditions*

Various DLC plasma generation methods have been developed for coating, and the coating characteristics and properties often vary depending on the generation methods. Therefore, it is necessary to use a method that is suitable for the intended application and purpose. Methods often used for industrial applications include plasma-enhanced chemical vapor deposition (PECVD)(15) and ionized deposition.

In applying DLC to coronary artery stents, the authors employed a system that adds original improvements, enabling the coating of complex three-dimensional shapes, to a common type of ionized deposition. This innovative system enables the DLC coating of the entire outer and inner wall surfaces of a stent with nanolevel uniformity of film thickness. A basic ionized deposition system is one that introduces argon (Ar), which is the ion source, plus hydrocarbon gas such as benzene (C_6H_6) into a DC arc discharge plasma source installed inside a vacuum chamber, and causes the plasma thus generated to be bombarded onto a sample biased with a negative voltage, thereby forming a solid DLC coating on the sample. The advantage of this method is that since ionized hydrocarbons are accelerated by DC bias, hydrogen is expelled from the film, and consequently the film becomes compact. In the present research, DLC coating conditions for the coronary artery stent were as follows. Hydrocarbons including C_6H_6 and acetylene (C_2H_2), and gases including tetramethylsilane ($Si(CH_3)_4$) were used. The treatment temperature was 200°C or less. The bias voltage was 1.0 kV or more. The degree of vacuum in the chamber was approximately 0.1 Pa. Under such conditions, a coating rate of 1 μm/h was obtained.

3.2 *Physical control of DLC thin film used on a stent*

During the coating, the I_G/I_D ratios as determined by Raman spectroscopy were controlled so as to form a DLC coat with Si content that possessed a concentration gradient in which the area near the interface served as a low-Young's-modulus region (layer), in order to improve the adhesion of the DLC film to the stent base material. This was also carried out in order to avoid any abnormal interface formations between different materials and stress concentration arising from rapid changes in the materials, and furthermore to avoid the effects of local heat stress during expansion of the stent. The thickness of the DLC film on the coronary artery stent surfaces was 50 nm, and a film surface hardness of 29 GPa was obtained. As direct measurement of the hardness of the DLC thin film coated onto the stent surface was problematic, a hardness evaluation specimen (10-mm-square, 1-mm-thick pieces of Co-Cr alloy) was coated simultaneously by coating the stent and used to measure the hardness. The hardness measurement was carried out using a nanoindentation system equipped with high-sensitivity (0.0004 nm, 3 nN) sensors made by Hysitron Incorporated and using a 90° triangular pyramid diamond indenter. As regards the measurement conditions, the diamond indenter was pressed into the specimen while being controlled with a precision of 100 μN, and the hardness, elasticity modulus and other mechanical properties were quantified by analyzing the resulting load-displacement curves. The press-in duration for the indenter was set at 5 s, and the pull-out duration was also set at 5 s. The specific details of the physical control of the DLC film were as follows. By applying the technology for DLC coating in a rotary engine so as to make the Si content progressively decrease from the interface toward the film surface, it was possible, due to the relation between the Si content and the Young's modulus, to obtain a coating that was optimum in terms of elasticity and heat resistance. Such a decrease in Si content resulted in almost no silicon at the film surface, so that high hardness was obtained at the film surface. Also, the high Si content on the interface side produced a high-hardness film due to Si-C bonding. Moreover, owing to the high sp^2 orbital (in other words, the graphitization of the film) on the interface side, high elasticity was obtained, which enhanced the adhesion. These results led to the optimization of the coating conditions and the adoption of the concentration gradient-type DLC, by which there was obtained a DLC coating with superior elasticity for coronary artery drug-eluting stents.(12–14)

4. Introducing Functional Groups to the DLC Surface and Evaluating the Surface

4.1 *Conditions for plasma surface treatment*

We now explain the DLC modification methods in more detail. 10-mm-square, 1-mm-thick pieces of Co-Cr alloy were used as the samples for evaluating the DLC surface functionalization.

First of all, the sample surfaces coated with DLC film were irradiated with plasma to generate radicals. Then the DLC-coated samples were placed inside the chamber of an inductive-coupling-type plasma irradiation apparatus, and oxygen (O_2), Ar, C_2H_2 and other gases were passed into the chamber to render an interior pressure of 100 Pa. Following that, a plasma of the introduced gases was generated by applying radio-frequency power (50 W) to the electrodes using a radio-frequency power source (model AX-300, ADTEC Plasma Technology; high frequency, 13.56 MHz).

Next, the mixture of C_2H_2 and other gases inside the chamber was replaced with O_2 and radio-frequency power (50 W) was applied to the electrodes. As a result, O_2 plasma was generated inside the chamber, and the radicals generated by the earlier plasma irradiation reacted efficiently with the O_2, generating hydrophilic functional groups including carboxyl groups.

4.2 *Experimental results and discussion*

To evaluate the DLC surfaces, the functional groups generated on the surface of the DLC film were measured using X-ray photoelectron spectroscopy (XPS). The XPS measurements were performed using a JPS9010 X-ray photoelectron spectrometer made by JEOL, with unmonochromatized Al Kα rays (hv = 1486.3 eV) as the X-ray source, output at 187.5 W (12.5 kV, 15 mA). C1s spectrum measurement was performed via a series of 64 measurement passes with a pass energy of 10 eV and steps of 0.1 eV. The background was eliminated by the Shirley method,(16) after which they underwent curve fitting using a Gauss-Lorentz function.

Figure 4(a) shows the results of XPS measurements of DLC surfaces that underwent C_2H_2 plasma irradiation followed by irradiation with O_2, and were then exposed to the atmosphere for 2 min. The C1s orbital peak was measured at close to 288.5 eV. This is a peak based on the O=C–O bonding of the carboxyl groups. In the DLC film that did not undergo plasma irradiation, on the other hand, no peak was observed at close to 288.5 eV, as shown in Fig. 4(b). From this, it is evident that as a result of performing a second irradiation with plasma containing O_2, the radicals generated on the DLC surface by the first plasma irradiation react with the O_2 and carboxyl groups are generated. Figure 4(c) shows the results of XPS measurements of DLC surfaces that underwent a single irradiation with O_2 plasma, followed by exposure to the atmosphere for 2 min. Here too, almost no peak due to carboxyl groups is observed. In Fig. 4(a), we can also observe a peak close to 287.1 eV, which is scarcely observable in Figs. 4(b) and 4(c). This is a peak based on the C=O bonding of the hydroxyl groups, which demonstrates that hydrophilic hydroxyl groups are generated in addition to the carboxyl groups.

It was also determined through the XPS analysis results shown in Fig. 4(d) that when Ar is used for the first plasma and O_2 for the second, carboxyl and hydroxyl groups will be introduced to the DLC surface. This may be assumed to be because the Ar plasma cleaves the carbon-carbon bonds, generating radicals on the surface, and then functional groups are introduced by the succeeding O_2 plasma.

However, although it is certain, from the fact that functional group bonding takes place, that carbon-carbon, carbon-hydrogen and other bonds are cleaved by the first plasma in the ascending order of their binding energy, it cannot be determined which bonds are cleaved. In the future, we hope to elucidate such mechanisms of the surface modification.

Next, the wettability of the DLC surfaces after undergoing the second plasma irradiation was measured using a contact angle measurer. The contact angles were measured by placing 1 μL water droplets onto the surface of the medical material, using a DM300 automatic contact angle measurer made by Kyowa Interface Science. Each measurement value was averaged from 10 measurements.

Figure 5 shows the change in the contact angles over time, following plasma irradiation. The contact angle of the DLC that did not undergo irradiation and is indicated by "▲" in Fig. 5 was almost constant in the range of 70 to 80°. By contrast, the contact angle of the DLC film that underwent a first irradiation with C_2H_2 plasma and a second irradiation with O_2 plasma and is indicated by "●" was almost constant at 0 to 3°, from which it can be seen that its hydrophilicity was greatly increased by the second plasma irradiation, so that it became what is called a superhydrophilic surface. Figure 6 shows photographs of water droplets during the contact angle measurement. Figure 6(a) shows a DLC film that did not undergo plasma irradiation, and Fig. 6(b) a DLC film that underwent surface treatment with C_2H_2 and O_2 plasmas. Then again, in the case where only a single plasma irradiation with C_2H_2 was carried out, which is indicated by "■" in Fig. 5, the initial contact angle was 120°, larger than that of the DLC that did not undergo plasma irradiation. Moreover, in this case, the contact angle decreased with time, so that ultimately it had a value only slightly larger than that of the DLC that did not undergo plasma irradiation. This indicates that the radicals formed by the first (C_2H_2) plasma irradiation react with the O_2 in the atmosphere extremely slowly, and that only a portion of such radicals so react. The results for the case where a single plasma irradiation was performed using O_2 instead of C_2H_2 is indicated by "♦". With a single irradiation with O_2 plasma, the generation of the radicals and their reaction with the O_2 proceed simultaneously, which may render the DLC surface hydrophilic. In the present case however, although the contact angle was low initially, it subsequently showed a rising trend with the passage of time. The reason for such behavior is not clear, but it is thought that during the single O_2 plasma irradiation, insufficient reactions took place between the radicals formed in the DLC and the O_2. The mechanism whereby the DLC surface is rendered superhydrophilic when 2-stage irradiation is carried out is not evident, but it would seem to be that the reactive sites formed by the first plasma irradiation are made to react efficiently by the second, O_2-including plasma irradiation, so that hydrophilic functional groups such as carboxyl groups are produced. We believe

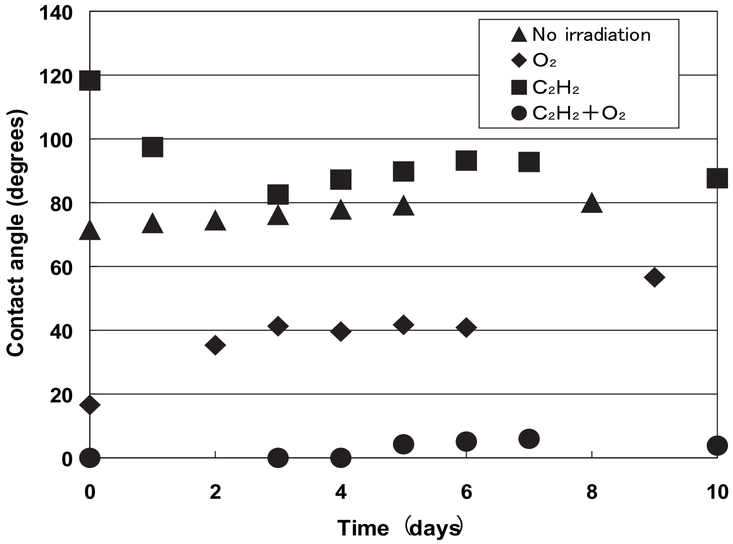


Fig. 5. Change over time in water contact angle (wettability) of DLC films.

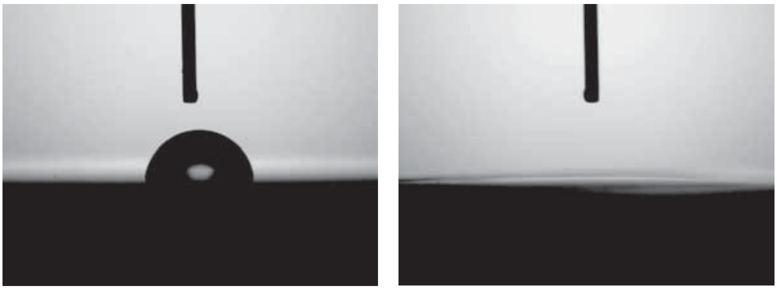

(a) (b)

Fig. 6. Photographs of water droplet situations during contact angle measurement. (a) Wettability evaluation of DLC thin film surface that did not undergo plasma irradiation (contact angle 73°). (b) Wettability evaluation of DLC thin film surface that underwent surface treatment with C_2H_2 and O_2 plasmas (contact angle 0°).

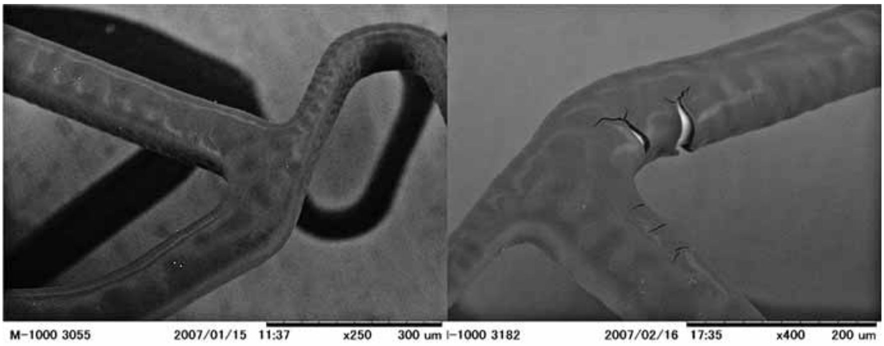
that here the functional groups introduced to the DLC surface serve as sites that attract water molecules, and that due to hydrogen bonding, an adsorption phenomenon occurs whereby the moisture concentration at the DLC surface-air interface is higher than the moisture concentration in the atmosphere. In other words, this can be considered to be the working of moisture-absorbing effects in the DLC thin-film surface that are due to the hydrophilicity produced by the carboxyl groups introduced into such a surface.

The hydrophilic functional groups introduced into the DLC are chemically stable and hence are able to sustain superhydrophilicity over extended time periods. Moreover, the functional groups introduced can readily be activated and are amenable to the graft polymerization of polymers. We believe that it will also be possible to use the functional groups as binding sites that bind polymers, enabling the various functions possessed by polymers to be imparted with ease to the DLC, and that this may effectively permit the creation of new materials.

5. Instance of Application of Superhydrophilic DLC Film to Stents that Release Coronary Artery Drugs(16)

First, the Co-Cr alloy stent was coated with a concentration-gradient-type DLC film. Then its surfaces were irradiated using a radio-frequency plasma reactor, so as to bond superhydrophilic functional groups to the surfaces. The next process was to fix biodegradable polymers containing a drug with a mild pharmacological action (the antithrombotic agent in this case) onto the surfaces. As the polymer coating method for this, a solution containing the polymers and the drug was sprayed onto the surfaces at a rate of 0.02 ml/min over a period of 8 min, while the stent was rotated at 120 rpm. This method enabled us to firmly fix the polymers and superhydrophilic functional groups introduced onto the DLC surfaces. As a result, we realized a stent whose polymer layer will not crack or peel away from the DLC surface when the stent is expanded with a balloon catheter.

Figure 7(a) shows a reflected electron image of the surfaces of a stent coated via the process shown in Fig. 3 that was expanded with a balloon catheter. A Hitachi High-Tech Science Systems Corporation (TM-1000) desktop microscope was used for the reflected electron imaging. For comparison, Fig. 7(b) shows a reflected electron image, taken after expansion, of a stent that was coated with the polymers directly, without a DLC nanocoating being applied to the stent base material. In this image, the white portions that are visible through the splits in the polymer layer correspond to the stent base material. It can be seen from this figure that DLC coating plus plasma modification improves the adhesion between the polymers and the base material, so that even under the deformation produced by stent expansion, no cracking or peeling of the polymer layer will occur.



(a) (b)

Fig. 7. SEM images of polymer coatings. (a) DLC + plasma irradiation. (b) No DLC.

6. Conclusion

We developed a DLC film modification method that by enhancing the hydrophilicity of the DLC film permits functions such as biocompatibility to be imparted to it efficiently. In such a method, the DLC surface is first irradiated with a plasma of Ar, C_2H_2 or the like so as to cleave the carbon-carbon bonds and create reactive sites on the surface. Next, a second plasma containing O_2 is irradiated onto the surface, causing the reactive sites to react with the O_2. By this method, it becomes possible to introduce chemically stable hydrophilic functional groups such as carboxyl groups, and to fix bioabsorbable polymers evenly and firmly onto the DLC surface.

As a result, we succeeded in producing a coronary artery drug-eluting stent whose polymer layer will not crack or peel away from the DLC surface when the stent is expanded with a balloon catheter.

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