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Plasmonic Nanotags for On-Dose Authentication of Medical Tablets

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Plasmonic nanomaterials have attracted much attention to new anti-counterfeiting technology. Since one of current anticounterfeiting problems is fake medical tablets, on-dose authentication of the tablets is strongly required considering tiny area of tablets, biocompatibility, and long shelf life. Previously, Nanotags consisting of self-assemblies of colloidal gold nanoparticles with reporter molecules were proposed, which produce characteristic surface enhanced Raman scattering (SERS) activity. However, long-term stability is rarely discussed for SERS active nanostructures. This study deposits about 10 ng of the Nanotags on a very tiny area of the commercial tablets. Distinguishable SERS signals of reporting molecules are confirmed by 1s irradiation of 785 nm laser over the Nanotags, while Raman spectrum of the ingredients is observed on the tablet without the Nanotags. Rapid authentication of tablets stocked over 8 years is sufficiently carried out. In addition, the Nanotags on the tablets are almost invisible to the eye, in particular, if the tablet surface is uneven or colored. It is considered that the presence of discrete AuNP assemblies allows excellent performances of Nanotag.

1. Introduction

The counterfeit products are becoming more pronounced and widespread.[1–5] Counterfeit medicines[5,6] are significant problem for safety and quality from individual home to industry. To prevent these counterfeits, the development and introduction of taggant technology has been called for. "Microtaggants" are tracking additives that are incorporated into products to identify authentic products, such as radio frequency identification (RFID), deoxyribonucleic acid (DNA) inks,[7,8] special chemicals, and other unique identification substances[9–44] including plasmonic nanomaterials.[19–23,34–36,39–44] The plasmonic nanomaterials using surface-enhanced Raman scattering (SERS) spectra.[19–23,34–36,39–44] SERS is an effect in which the Raman scattering intensity of molecules trapped in voids is dramatically enhanced by the electric field enhancement effect created between noble metal surfaces such as gold or silver and nanovoids.[51–60]

Recently, the U.S. Food and Drug Administration (FDA) has established guidelines for the use of microtaggant technology as a physical chemical identifier and has recommended its use in the fight against counterfeit pharmaceuticals.[45,46] The prevalence of counterfeit medicines is a life-threatening problem whose societal impact is so great that a study by Rahman et al. found that from 1972 to 2017, 3604 people lost their lives to counterfeit medicines in publicly reported cases alone.[47] Therefore, microtaggant combined with physically unclonable functions (PUFs) have attracted much attention. The PUFs are originated from that the internal signal fluctuation of each device differs depending on the microfabrication accuracy of the semiconductor device.[61–64]

Thus, microtaggant using SERS is considered to meet the necessary requirements to be implemented in society because the goal is to prevent counterfeiting by point-attachment to the medicine tablet, but its long-term stability needs to be confirmed. Some long-term warranty period is necessary to eliminate counterfeit pharmaceuticals. On-dose authentication of the tablets is strongly required considering tiny area of tablets, biocompatibility, and long shelf life. However, long-term stability is rarely discussed for SERS active nanostructures.

Here, we have fabricated the self-assembly of gold nanoparticles (AuNPs) with Raman active reporting molecule (Nanotag),[19,20] deposited the solution of the Nanotag on the tiny area of tablets, and confirmed observation of SERS from Nanotag on the tablet bottle.[21] This paper reports the results of the evaluation of the long-term stability over 8 years of the

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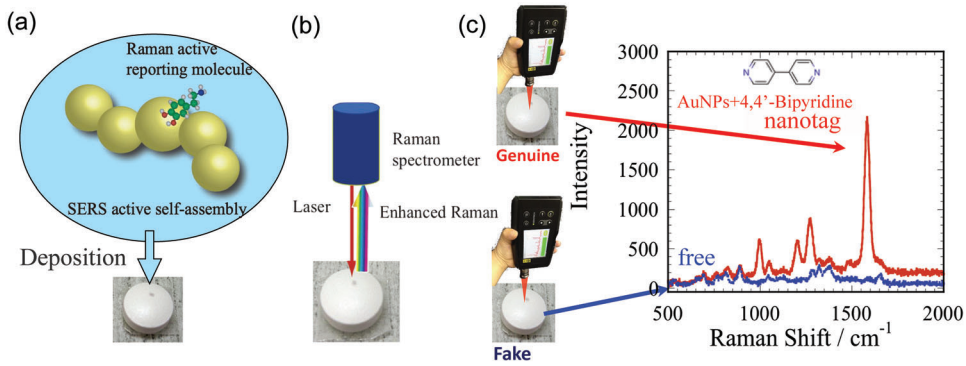

Figure 1. a) Schematic illustration of the surface-enhanced Raman scattering (SERS) active self-assembly consisting of Au nanoparticles (AuNPs) and reporting molecule. The SERS active self-assembly is work as a nanotag and is deposited onto a commercial tablet. b) Schematic illustration of the SERS measurement of the tablet which the nanotag was deposited. c) Comparison of SERS spectra of tablets with and without nanotag [AuNPs + 4, 4′-Bipyridine (4bpy)] deposits, with those with nanotag deposits as "Genuine" and those without nanotag deposits as "Fake."

fabricated Nanotags by attaching them to commercial tablets for the application to on dose authentication.

2. Experimental Section

Aqueous colloidal dispersions of AuNPs capped with citric acid were prepared as previously reported.[65] Fabrication of self-assembled nanostructures was performed in the presence of 50×10^{-9} M of 4, 4′-bipyridine (4bpy) in aqueous media.[19,20] Nanostructures encapsulated or adsorbed with molecules as shown in schematic **Figure 1**a were considered to have been formed.[19,20,22,23] The resulting self-assembled AuNPs were dispersed in aqueous media and used as Nanotags. As shown in Figure 1a, 0.2 µL of Nanotags dispersion containing approximately 10 ng of AuNPs was carefully adhered to the surface of a commercial pharmaceutical tablet and allowed to dry at room temperature. Mucodyne (L-carbocysteine) and Loxonin ((RS)-2-{4-[(2-oxocyclopentyl)methyl]phenyl}propanoic acid) were used as model tablets. In these tablets, when the presence of Nanotags on the tablets is examined by Raman spectrometer as shown in Figure 1b,c, the Raman spectrum of 4bpy is detected in the tablets with Nanotags dotted. On the other hand, the Raman spectrum is not detected in tablets without Nanotags. The presence or absence of this Raman spectrum enables the authenticity of the tablets to be determined. In this experiment, the tablets with Nanotags-dotted tablets were stored at room temperature for up to about 8 years under atmospheric pressure. A portable Raman spectrometer RAM100S and RAMmini (Lambda Vision, Japan) were used and irradiated with a 785 nm laser. SERS measurements were performed by irradiating a 100 mW laser for 100 ms in out-of-focus mode. The measurements were averaged and recorded for 10 times. All experiments were performed at room temperature and under atmospheric pressure. Storage of the tablets was also performed at room temperature and under atmospheric conditions.

3. Results

Figure 2 shows the dynamic light scattering (DLS) measurement results of (a) prepared AuNP colloids before aggregation, (b) colloids after the conventional aggregation, and (c) controlled aggregation of AuNPs. In the case of conventional aggregation in Figure 2b, the aggregation size increased with time. On the other hand, the aggregates prepared by controlled aggregation are stable and keep their size for a long time. The absorbance spectra of AuNP and AuNP aggregates are plotted in Figure 2d. It can be seen that light absorption occurs over a wide range in AuNP aggregates. The SEM images of the AuNP and AuNP aggregates are shown in Figure 2e,f, respectively. The sizes of AuNPs and AuNP aggregates observed by SEM are in good agreement with DLS measurement results. It can be seen that irregularly shaped AuNP aggregates are randomly dispersed. Because of the irregular shape, it is impossible to determine which is the Nanotag encapsulating the molecule. By encapsulating molecules in these AuNP aggregates, the functionality as "Nanotag" is expressed. If they were in a periodic structure, they could be easily identified as Nanotag. This is why Nanotags are the chemical PUFs.[19,20]

As shown in the inset of **Figure 3**a, the dispersion of the prepared AuNP aggregates was dim brownish brown, while the AuNP colloids were transparent wine red. Figure 3a shows the results of the evaluation of the SERS activity of the prepared AuNPs using portable Raman RAM100S. There are three spectra in Figure 3a. One is the spectrum of aggregation of 50×10^{-9} M 4bpy added to the prepared AuNP colloid, depicted by red solid line, exhibiting the characteristic of 4bpy. In a solution of 4bpy dispersed in liquid without AuNPs (labeled by AuNP Free), clear Raman peak was not detectable even for 10×10^{-3} M 4bpy, depicted by the green dashed line. This suggests that a concentration of 10×10^{-3} M or higher of 4bpy is required for normal Raman detection without AuNPs. Here, the AuNP dispersion solution contains 50×10^{-9} M of 4bpy in the example in Figure 3a, and the deposited amount is 0.2 µL. Therefore, the amount of 4bpy is about 10 fmol. On the other hand, with the AuNP aggregates, essentially a 200 000-fold enhancement would have occurred. However, given that SERS allows detection at the single molecule level, the fact that a clear enhancement spectrum was obtained with as little as 10 fmol is not extreme. The AuNP colloid was found to be so ultrasensitive that even impurities in pure water were detected. The blue solid line denotes the back ground Raman spectrum of ultrapure liquid, labeled by "aq.". The background signal is attributed to reducing agent residuals of AuNPs

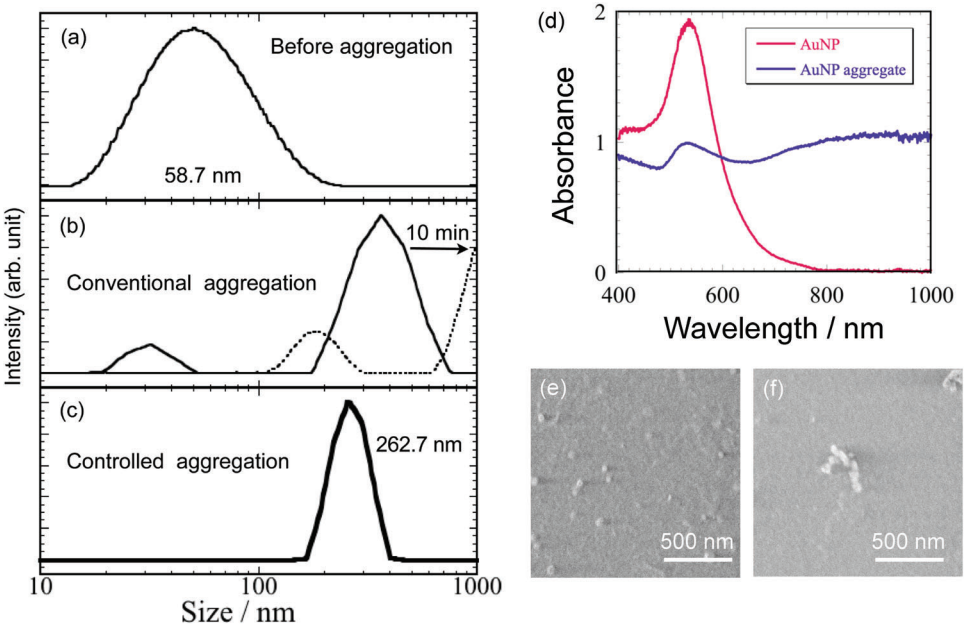

Figure 2. Dynamic light scattering (DLS) measurement results of a) prepared gold nanoparticles (AuNPs) before aggregation, b) conventional aggregation of AuNPs, and c) controlled aggregation of AuNPs. Absorbance spectra of AuNP (red solid line) and its aggregates (blue solid line). d) Absorbance spectra of AuNP (red solid line) and AuNP aggregate (blue solid line). SEM images of e) AuNPs and f) aggregates.

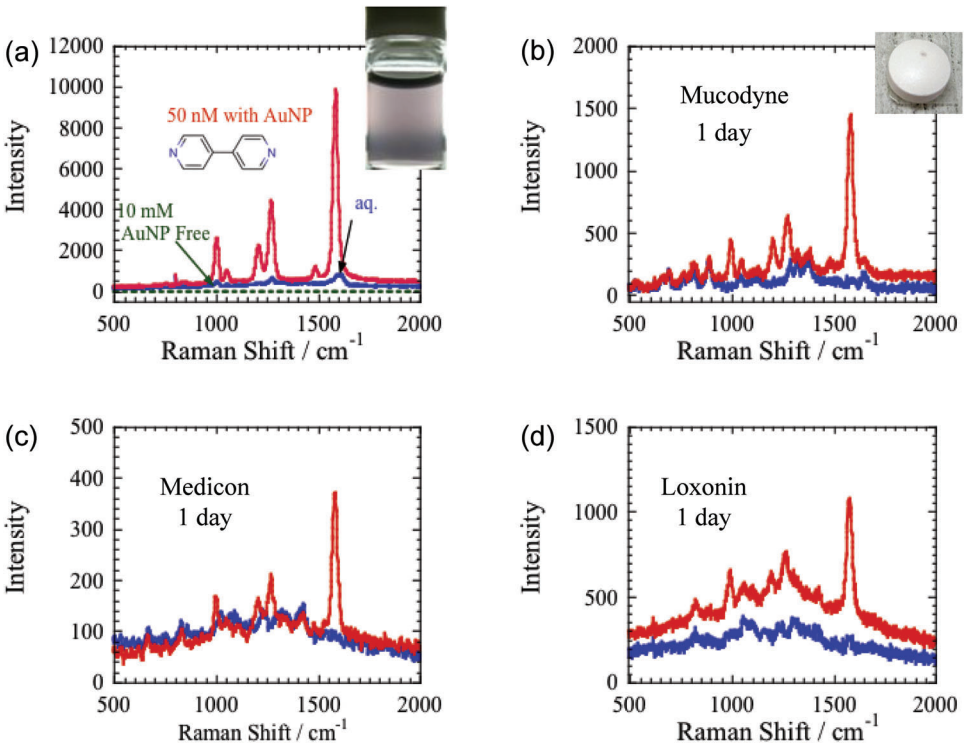

Figure 3. a) Raman spectra of 50×10^{-9} M 4bpy-containing nanotag (red solid line), solution of only gold nanoparticles (AuNPs) dispersed in ultrapure water (aq., blue solid line), and solution of 10×10^{-3} M 4bpy without AuNPs (AuNPs Free, green dashed line). Raman spectra of nanotag deposits on b) Mucodyne, c) Medicon, and (Loxonin), respectively, after 1 day of nanotag depositing. Red and blue solid lines denote the surface enhanced Raman scattering (SERS) spectrum from the nanotag and Raman spectrum from each tablet, respectively.

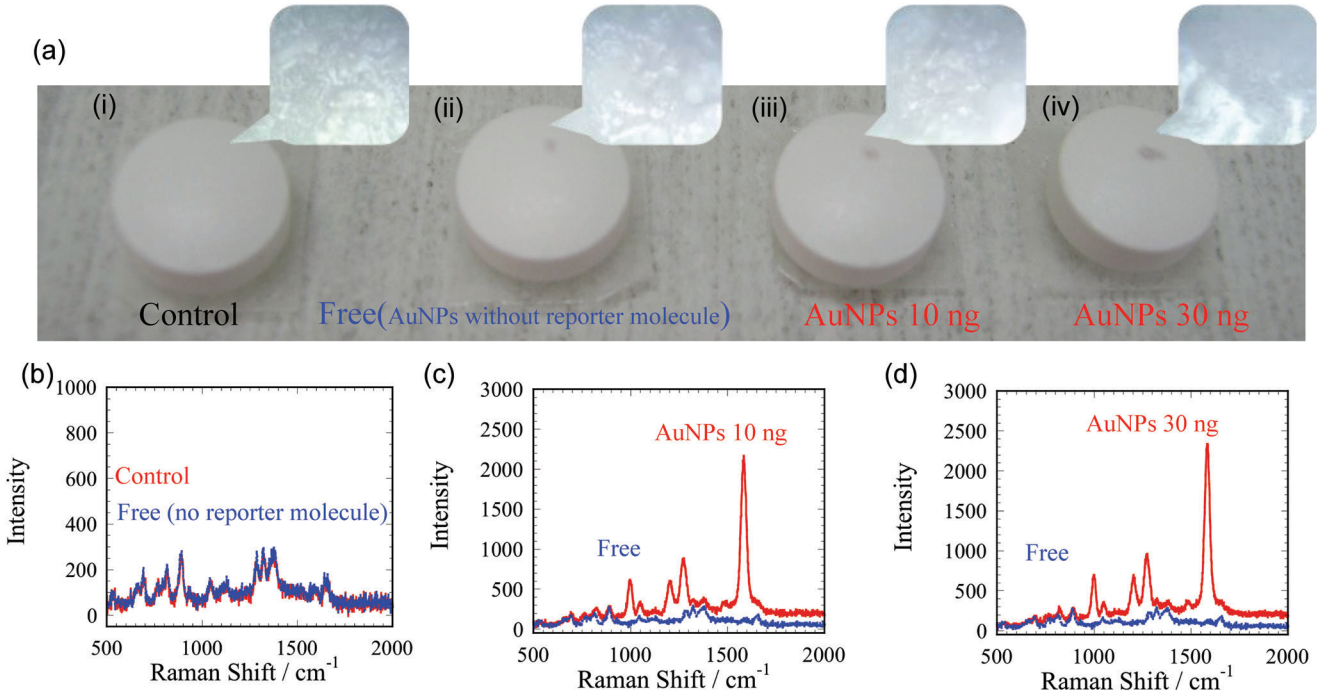

Figure 4. a) Photographs and surface optical micrographs of (i) tablet as it is (Control), (ii) tablet with only gold nanoparticles (AuNPs) without reporter molecule (Free), (iii) tablet with 10 ng of nanotag deposited (AuNPs 10 ng), and (iv) tablet with 30 ng of nanotag deposited (AuNPs 30 ng), respectively. b) Raman spectra of Control (red solid line) and Free (blue solid line). c) Raman spectra of AuNPs 10 ng (red solid line) and Free (blue solid line). d) Raman spectra of AuNPs 30 ng (red solid line) and Free (blue solid line).

synthesis and contamination results in experimental environment. Using this AuNPs, the adjusted Nanotags were deposited on Figure 3b Mucodyne, Figure 3c Medicon, and Figure 3d Loxonin tablets. Here, we dare to seal the stealthiness of the image, and we have devised the lighting so that it is easy to see the deposited area of Nanotags, so it is take in a visible manner. An example of invisible allocation will be shown in the later experiments. The stains of the deposited AuNP aggregates appeared pale gray. Although light and shadows are visible in the Figure 3b inset due to the lighting, the Nanotags based on 10 ng of AuNPs deposited on the tablet were difficult to see with the naked eye unless intentionally observed. Raman spectra were obtained by simply irradiating this tablet with a laser for 100 ms × 10 integrated averages (measurement time was about 1 s). When the Nanotag-attached tablets were irradiated by laser, we succeeded in observing characteristic 4bpy spectra [red lines in Figure 3a–c]. These 4bpy spectra were measured one day after the point attachment and had strong peaks at 995, 1200, 1270, and 1580 cm^{-1}, in close agreement with previous reports.[19,20,22,23,54–60,66] As shown by the red lines in Figure 3a–d, the signal-to-noise (S/N) ratio of the 4bpy peak is very high and identifiable in a 1 s measurement. Conversely, a completely different spectrum was observed for tablets without Nanotags. The Raman spectra themselves from the corresponding tablets are shown by the blue solid lines in Figure 3b–d. Mucodyne had peaks at 800, 880, 1035, 1275, 1315, and 1374 cm^{-1} with moderate intensities;[67] Loxonin had only weak peaks at 1100 cm^{-1} and around 1300 cm^{-1}; tablets labeled with AuNP aggregates without 4bpy also showed almost same spectra were observed. These spectra were presumed to be components in the tablets.

Next, the results of the study on the amount of Nanotags dots are shown in **Figure 4**. Here, Mucodyne tablets were used. The following four samples were prepared: 1) a tablet without any treatment for comparison, 2) a tablet with only gold nanoparticles without reporter molecule encapsulation, 3) a tablet with 10 ng of Nanotag, and 4) a tablet with 30 ng of Nanotag. Optical and microscopic magnified images of each are shown in the insets of Figure 4a (i)–(iv). These results show that almost no differences are visible, especially when AuNPs or Nanotags are dotted on the tablets. Since it is for testing purpose, the experiment was conducted by preparing a medicine that was adjusted to have a relative high concentration so that the spotted site could be recognized by reflection. Furthermore, since the laser was irradiated by many times, it is easy to recognized with the naked eye after burning due to the laser irradiation. If the concentration is reduced or if it is kneaded into a tablet, it becomes impossible to recognize whether there is a Nanotag or not. Next, the results of Raman spectra measurements are shown in Figure 4b–d. In Figure 4b, the red line is the Raman spectrum of the untreated tablet only, and the blue line is the Raman spectrum of the tablet with the gold colloid without the reporter molecule encapsulated. Comparing the two, it can be seen that the Raman spectra are in agreement, indicating that the Raman spectra reflect the drug component of Mucodyne. Next, in the tablet with 10 ng of Nanotag deposited on it, shown in Figure 4c, the Raman spectrum, indicated by the red line, is clearly detected. Here, the blue line is the Raman spectrum of the tablet in which only gold colloidal particles, which do not encapsulate the reporter molecule, are deposited. From the results in Figure 4c, when Nanotags are spotted, a clear SERS signal is detected, and it is immediately apparent

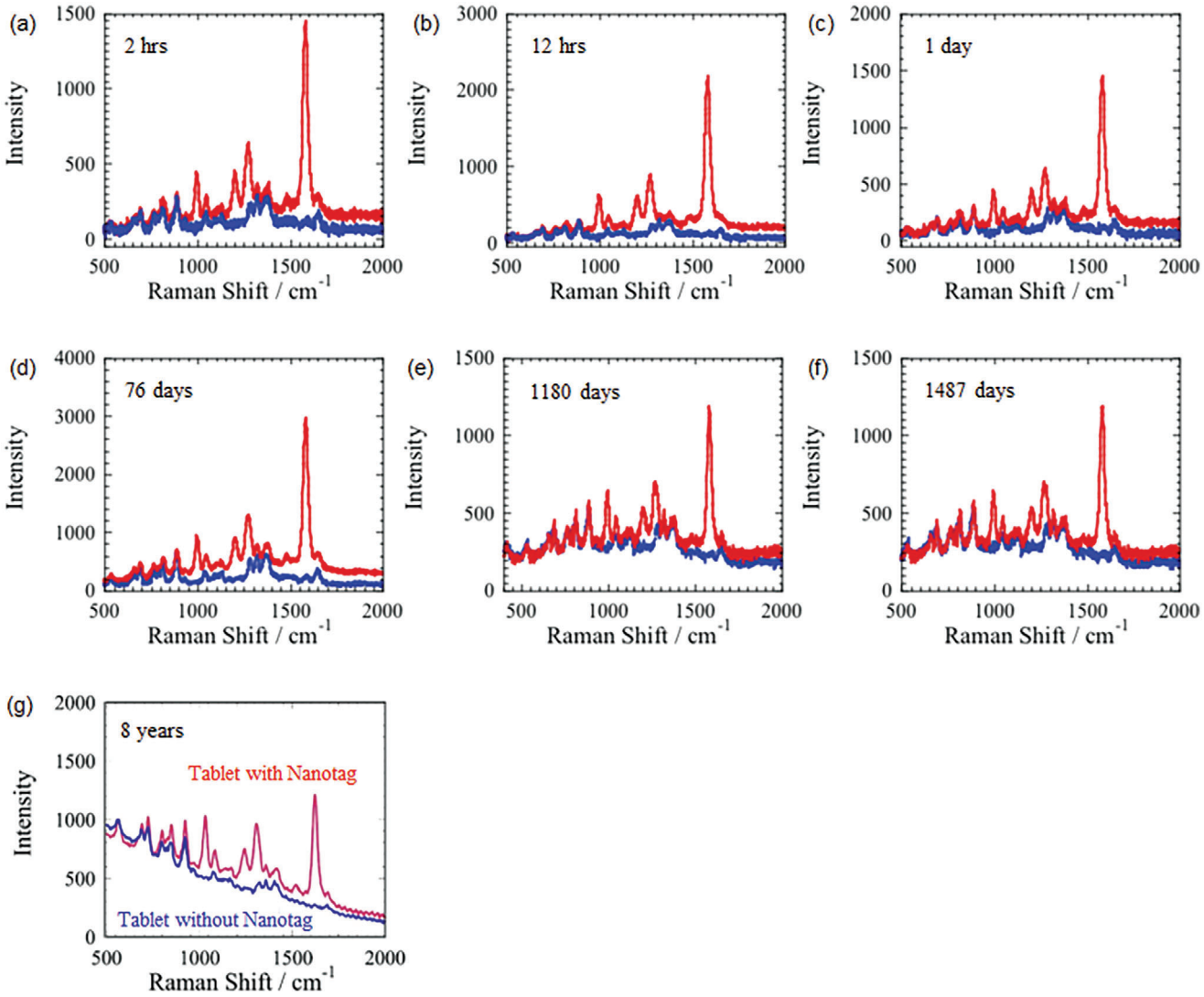

Figure 5. Raman spectrum monitoring results to confirm long-term stability of Nanotag. Raman spectra of a) 2 h, b) 12 h, c) 1 day, d) 76 days, e) 1180 days, f) 1487 days, and g) 8 years, respectively. Red and blue solid lines denote the surface enhanced Raman scattering (SERS) spectra from Nanotag deposited and nondeposited area (Mucodyne tablet itself), respectively. The Raman spectra of (a)–(f) were obtained by the Raman spectrometer, RAM100S malfunctioned. The Raman spectra of g) were measured by another Raman spectrometer, RAMmini/785.

that the tablet is a Nanotag-deposited tablet. Next, Figure 4d shows the results when the amount of Nanotags spotted was set to 30 ng. This result is almost the same as the result in Figure 4b, where Nanotag was 10 ng. This suggests that the amount 10 ng of Nanotags is sufficient for distinguishing the genuine and fake. These results suggest that it may be possible to achieve the low amount of Nanotags and low cost required for anticounterfeiting.

Next, to examine long-term stability, the time course was tracked from 2 h to 1487 days after the Nanotags were deposited on Mucodyne tablets, and the results are shown in Figure **5**. Mucodyne tablets were stored indoors in air at room temperature. The Raman spectra indicated by the red lines are those derived from the Nanotags, and the blue lines are the Raman spectra from the tablets themselves without the Nanotags dotted. The basic spectra remained unchanged from 2 h to 1487 days after the deposition, indicating that not only the tablets but also the Nanotags are stable over the long term in Figure 5a–f. To further confirm its stability over a long period of time, we measured the spectrum after 8 years, and the results are shown in Figure 5g. These Raman spectra were measured by the RAMmini. 8 years later, we could still detect a spectrum similar to the results as shown in Figure 5a–f. This result suggests that Nanotag functions are stable over a very long period of time. According to our previous studies,[19,20,22,23] the stability of the Nanotags depends on the physical properties of the tablet surface. It has been found that the Nanotags exhibit high stability on hydroxypropyl methylcellulose (HPMC) coat, a commonly used film-coating substrate that is believed to coat the surface of Mucodyne tablets.[23] The mechanism for this stability is not fully understood, but it is believed that the embedding of gold nanoparticles within the HPMC film restricts the particle motion, and the moisture-resistant nature

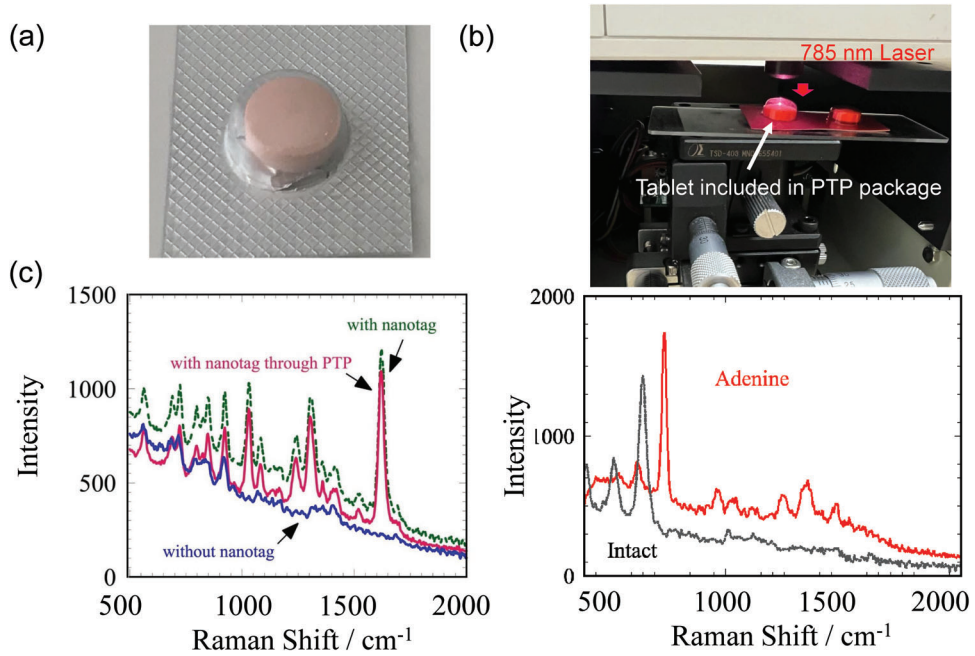

Figure 6. a) Photograph of hydroxypropyl methylcellulose (HPMC) coated commercial tablets dotted with Nanotag, sealed in a press-through package (PTP). Tablets stored for 8 years after depositing were applied and stocked at room temperature. Surface enhanced Raman scattering (SERS) spectra of Nanotags deposited on fexofenadine tablets through the PTP. b) 785 nm laser irradiation for the tablet included in PTP package using the RAMmini. On-dose authentication results of the tablets dotted with Nanotags including c) 4bpy and d) adenine through the PTP. The green dashed, red solid, and blue solid lines in (c) correspond to the Raman spectra from Nanotag including 4bpy, tablet with Nanotag through PTP, and tablet itself without Nanotag, respectively. The red and black solid lines in (d) denote the Raman spectra from the tablet with Nanotag including adenine and tablet without Nanotag, respectively.

of the HPMC film has a positive impact on the stability of the Nanotags.

In this study, we have shown that Nanotag is very stable, but we need to consider its toxicity to organisms. There are a lot of studies on the toxicity of AuNP.[68–73] In many cases, cells and other organisms have been exposed to the far larger amount of AuNP than that of AuNP used in this study. Those studies have reported that the aggregates larger than 100 nm used in SERS do not invade cells.[68–74] These evidences can provide very positive support for the application of Nanotags in medicine. In other words, because of their noncell-invasive size and very small amounts used in medicine, Nanotags are likely to cause very little or rare health harm when taken. However, since no actual biological toxicity tests have been conducted, it would actually be necessary to test the Nanotags according to international standards to prove that they are nontoxic if they are to be used. This toxicity testing will be done as a future study.

Until now, SERS measurements have been performed by storing tablets in the open air, but assuming that they will actually be used, it is necessary to perform authenticity determination while sealed in a press-through package (PTP) or the like. Therefore, we conducted an experiment in which Nanotags were attached to the same tablet that was shown in Figure 5 to see if they could be detected through the PTP. The Nanotags used in this study were prepared with 4bpy as a reporter molecule. **Figure 6**a shows the tablet with point attachment. From this photograph shown in Figure 6a, it is completely unrecognizable where the Nanotag was dotted. Figure 6b shows photograph of Raman measuring moment for HPMC-coated commercial tablets dotted with Nanotag, sealed in a red colored PTP. Figure 6c shows the Raman spectra of tablet with Nanotag measured through the PTP, tablet with Nanotag directly measured, and tablet without Nanotag. The blue solid line is the Raman spectrum from the tablet without Nanotags, and the red solid line is the Raman spectrum from the tablet with Nanotags dotted, detected in 1 s through the PTP. The green dashed line denotes the Raman signal derived from the Nanotags without the PTP. Nanotags with adenine as a reporter molecule were also deposited on fexofenadine tablets and SERS detected through the PTP. The presence of the Nanotag is also not easily visible on the colored tablets. The on-dose authentication of the tablet using the Nanotag with adenine can be also clearly achieved as shown in Figure 6d. It was found that the Raman signal from Nanotags can be detected regardless of the presence or absence of PTP. In other words, Nanotag can be used to make measurements even through PTP. The Nanotags enable us to attach the items or things themselves, so there is no risk of the Nanotags being removed. This result indicates that Nanotags can be also used to determine authenticity even through the PTP. Therefore, the Nanotags pointing and coating process can be introduced into the tablet manufacturing process and controlled even if the tablets are converted to PTP. It is also expected to be used for manufacturing and distribution management, as well as for tablet management as schematically illustrated in **Figure 7**.

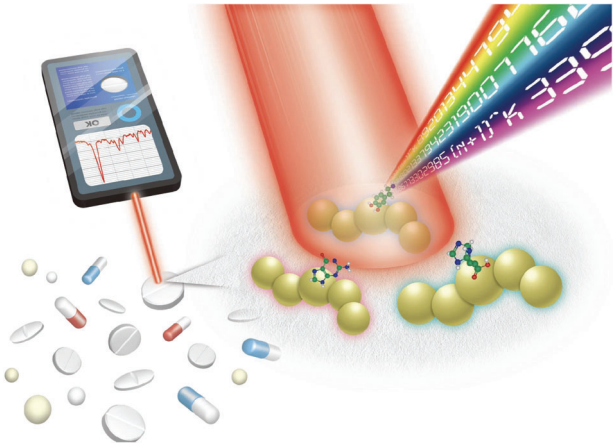

Figure 7. Schematic illustration of nanotag application to tablets: authenticity, manufacturing information, active ingredient information, distribution information, dosing and administration information, etc., or links to access this information.

4. Discussions

SERS is an analytical technique that is so fast and sensitive that it can detect a single level of molecules within 1 s.[45–50] In addition, the enhanced Raman spectra contain much information about the target molecule. In other words, different spectra are generated by SERS active molecules. SERS using a near-infrared laser enables highly sensitive near-infrared spectroscopy because near-infrared light is invisible to the naked eye. Aggregates of small AuNPs were inherently sufficient to produce enhanced Raman if the nanostructure was well designed. These properties of SERS make it suitable for unclonable and high-throughput authentication. The amount of 4bpy encapsulated in the AuNPs used in this study was 10 fmol, indicating that only a very small amount of reporter molecules is required. 10 fmol is well within the detection range, as SERS ultimately allows for single-molecule detection. The 10 fmol mark can be dotted on a tablet and measured for about 1 s to distinguish between marked and unmarked tablets, suggesting that there is sufficient potential for social implementation.

Many nanoparticle printing techniques use organic solvents and polymers, but organic solvents and polymers tend to adsorb onto the active surface of AuNPs, inhibiting the adsorption of reporting molecules and consequently severely impairing the SERS activity of the AuNP assembly. Therefore, we chose a mild precipitation method using aqueous dispersions of self-assembled AuNPs.[19,20] The aqueous precipitation method does not require vacuum conditions or heating. It is also flexible for marking not only tablets but also hydrophilic surfaces such as glass and paper.

However, this convenient aqueous deposition method has also presented some problems. Previous studies have confirmed quantitative SERS intensity dependent on the amount of 4bpy molecules using AuNP aggregates.[54–60] However, in the case of AuNP aggregates deposited on the tablet surface, the SERS intensity was found to be almost independent of the amount of deposited AuNPs and 4bpy as shown in Figure 6, and the reproducibility of the SERS intensity measurement was poor. These may be attributed to the fact that the dispersion of AuNP aggregates was randomly expanded due to the rough surface of the tablets, and the staining and thickness of the deposited Nanotags, i.e., the distribution of AuNP aggregates on the surface, varied.

Despite these defects, as shown in Figure 4, the presence of the stealth Nanotags on the tablet produced a clearly characteristic SERS spectrum that distinguished the reporting molecule within 1 s. In the absence of Nanotags, no critical spectra were observed. Notably, the SERS activity of Nanotags is preserved for at least 8 years on tablets stored at room temperature as shown in Figure 5g. The spectrum in Figure 5a was measured from a tablet immediately after the end of deposition; Figure 5d shows the spectrum of the tablet in Figure 5a obtained after 76 days when the Nanotags was deposited on the tablet. The spectrum in Figure 5d was measured from the same tablet as Figure 5a and shows almost the same peak pattern, although the intensities are not identical. Of course, the similar spectral patterns can still be detected as demonstrated in Figure 6. Thus, the SERS intensity varies somewhat depending on the measurement conditions at the time, etc., but the pattern of the SERS spectrum remains unchanged. In other words, the use of Stealth Nanotags as a physical chemical identifier is considered to have a sufficient lifetime for authentication in the distribution of commercial products. Furthermore, as clued in Figure 6, we have shown that SERS discrimination via PTP is also possible, and we have successfully created Adenine-containing Nanotags other than 4bpy.[23] Thus, Nanotags showing various SERS patterns can be created by changing the reporter molecule.

Considering the above points, as shown in Figure 7, by combining multiple Nanotags on a tablet, it is possible to embed information such as drug manufacturing information and ingredients. Furthermore, the combination with a terminal for reading suggests the possibility of deployment not only for tablet distribution management but also for patient dose management. The biggest difference between the Nanotag and the conventional microtaggant is that the amount of the dots is so small that it cannot be discerned by the naked eye, so the numbering can be done for each drug tablet, not for drug bottles, and the management and tracking can be done. Another major advantage is that it is possible to create and implement a social authentication system that meets the needs of users by flexibly responding to management costs and user requirements.[75]

5. Conclusion

Self-assembled AuNPs with Raman-active reporting molecules were applied to stealth Nanotags to develop a novel anticounterfeiting technology. Commercially available tablets were coated with trace amounts of AuNPs containing 10 fmol of reporter molecules. As a result, the SERS signal of the stealth Nanotag was monitored to enable highly sensitive authentication of commercial tablets by a portable Raman spectrometer. Its long-term stability was monitored, and it was confirmed that the SERS pattern remained unchanged for 8 years, indicating that the long-term stability was sufficiently assured. Furthermore, by changing the molecules contained, a new type of stealth Nanotag was successfully created, and it was shown that the SERS spectrum can be measured and determined via the PTP package of tablets. From the above points, we showed that it is also possible to control and authenticate each tablet.

Once the Nanotag is developed, it can be applied to pharmaceutical managements, such as manufacturing, distribution, and patient adherence.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Keywords

anticounterfeit technology, fake medicine, gold nanoparticle, self-assembly, SERS

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