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Measurement of Substance Diffusion on a Bio-body Surface Using Laser Plasma Spectroscopy

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생체 표면에서의 물질 확산 측정을 위한 레이저 플라즈마 분광법 적용

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ABSTRACT

The diffusion of the drug component of the inflammatory patch into the living tissue was analyzed by laser induced plasma spectroscopy (LIBS). Calcium element, which is a diffusion catalyst of the drug in the inflammatory analgesic patch, is transferred into the body through the diffusion process of the substance. The test pieces used in the experiment are pig skin tissues which are similar to human skin. As a result, the diffusion coefficient D of the calcium element was found to be average 8.24×10^{-2} ($\mu m^2/s$). Experimental results showed that the most influential factors on the diffusion of materials were temperature variables.

Keywords : LIBS(레이저 유도 플라즈마 분광분석), Medicated-patch(의료 약물 패치), Diffusion coefficient (확산계수), Pig skin(돼지 피부)

1. Introduction

As people's interest in exercise increases, the risk of injury is also on the rise. For minor bruises or muscle pain, medicated patches are mainly used. In the application of medicated patches, rapid diffusion of the drug in the patch is considered important for alleviating pain. Factors that affect the diffusion of drug in biological tissues include the type of medium, phase, temperature, time, and acidity (pH)[1-3]. For measuring the diffusion of matter, sample detection methods using sensors can be employed. The present study presents a new measuring method of in vivo diffusion using a laser.

Laser-Induced Breakdown Spectroscopy (LIBS) is an analysis method that identifies the elemental spectrum of material through spectroscopic analysis of the induced plasma generated by the interaction between the surface of the specimen and the laser. Plasma is generated by the ablation of material when laser is irradiated on material surface. This plasma exists in the excited state of the material

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elements, after which various elements and ions cool down and return to the ground state. In the plasma, element-specific atom and ion spectral lines are emitted, and the spectral data of each element can be obtained through the detectors of LIBS. The form and intensity of the spectral lines yield the information of the elements composing the material, and qualitative and quantitative analyses are possible. Through these analyses, the chemical and mechanical structure, and the characteristics, of the material can be determined[4,5].

The present study offers a method of quantifying the depth of drug diffusion by temperature, time, and medium by using the LIBS to measure the degree of diffusion of Indomethacin, which is the main component of the medicated patch, in the human body, and identify the major factors that affect the drug diffusion of the medicated patch. For the experiment, pig skin, which has similar thickness and subcutaneous tissue to that of humans, was used[6]. To trace the diffusion characteristics of Indomethacin, calcium (Ca), which is a diffusion catalyst included in the patch, was measured. Calcium showed different degrees of diffusion according to the type of medium, temperature, and time, and differences in diffusion distribution in biological tissues according to these variables were derived in diffusion coefficients (D) and used in quantitative analysis.

2. Background theory

The diffusion phenomenon of matter in the steady state in the medium can be expressed as a function related to the concentration of material particles and diffusion flux through Fick's first law of diffusion as shown in equation (1).

$$J = -D\frac{dC}{dx} \tag{1}$$

Here, J is diffusion flux, D is diffusion constant, C is concentration of particles, and x is diffusion depth. If the diffusion flux and concentration differences are determined, diffusion constant D (m^2/s) can be determined. Material diffusion according to time in nonstationary state can be expression through Fick's second law of diffusion as follows.

$$\frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{2}$$

The solution of equation (2) is as follows:

$$\frac{C(x,t)-C_0}{C_s-C_0} = 1 - erf\left(\frac{x}{2\sqrt{Dt}}\right) \tag{3}$$

Here, C_0 is the initial concentration, C_s is convergence concentration, and $C(x,t)$ is concentration at x depth after t seconds.

Using the equations above, the relative diffusion constant D of materials can be inferred by applying the LIBS signal peak of the target element in the depth direction.

3. Experimental methods

Table 1 Experimental variable conditions

	Medium	Temperature(℃)	Time lapse(h)
Case 1	Skin	27 ~ 37	2
Case 2	Skin	37	2 ~ 6
Case 3	Muscle	27 ~ 37	2
Case 4	Muscle	37	2 ~ 6

Table 2 Experimental conditions

Laser and LIBS parameter	
Wavelength (nm)	1064
Energy per pulse (mJ)	7.2
Pulse duration (ns)	5
Spot diameter (μm)	100

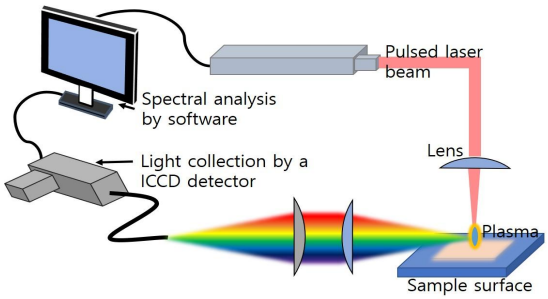


Fig. 1 Schematic of LIBS system and experimental setup

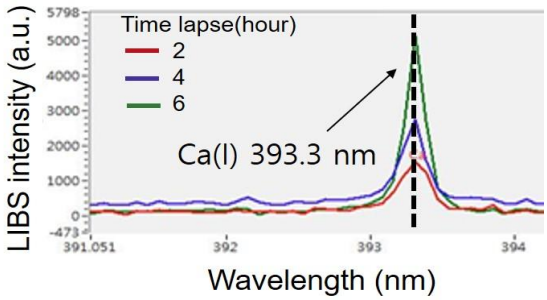


Fig. 2 Calsium atomic peak intensity by diffusing time lapse at LIBS spectrum

3.1 Variable conditions for medicated patches

Pig skin tissue, which is similar to human skin tissue, was chosen as diffusion substrate for medicated patches. After attaching the patch to pig skin and muscle tissue, oven temperature and time were set, and drug diffusion was induced at regular time intervals.

The experimental conditions to control the diffusion of the medicated patch materials are shown in Table 1. A total of four conditions were set up, with medium, temperature, and elapsed time as variables. The main component of the medicated patch used in the material diffusion experiment was Indomethacin ($C_{19}H_{16}ClNO_4$), and Ca element was a catalyst to promote diffusion in tissue. As controlled experimental conditions, surfaces and constituents of the patch and medium were assumed to be uniform, and the effect of attachment pressure of the patch was ignored.

3.2 Experimental setup

Table 2 shows the laser parameters of the LIBS system. The LIBS system setup is shown in Fig. 1. The Nd:YAG pulse laser used as the laser light source oscillated at a wavelength of 1064 nm and had 7.2 mJ per pulse with a 5-ns pulse width.

The focused laser beam spot diameter was 100 mm and was irradiated 100 times on the sample surface. The energy density per laser pulse (fluence) on the sample surface when the laser beam was irradiated was 91.7 J/cm^2. The induced plasma generated on the sample surface was analyzed using a 5-channel ICCD through the LIBS signal collector in the form of the spectral line data of LIBS elements. Afterward, spectra according to the depth were traced and analyzed, and the results are shown as LIBS elemental spectral lines. The measurements and trend observations of elemental spectral lines were performed using a series of laser pulse irradiation. When the surface is ablated by laser pulses, micro hole forming along with spectrum signal generation is performed simultaneously. Accordingly, hole forming from the surface in the inward direction of the sample and signal extraction can be performed by the irradiation of a series of laser pulse.

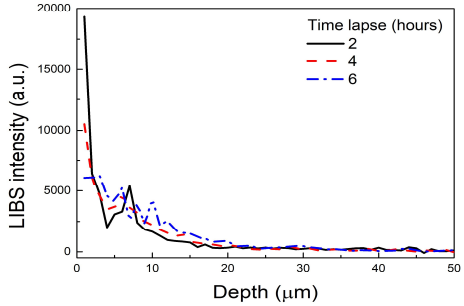
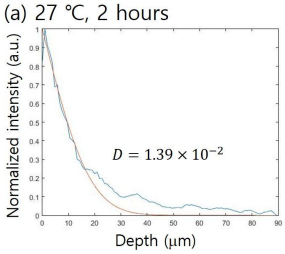
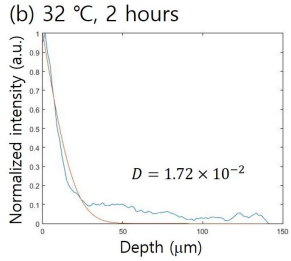
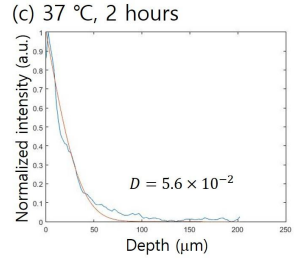
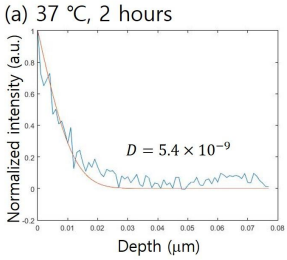
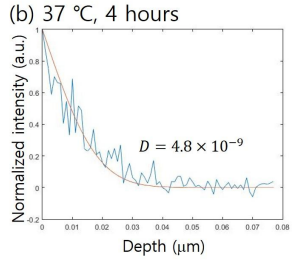
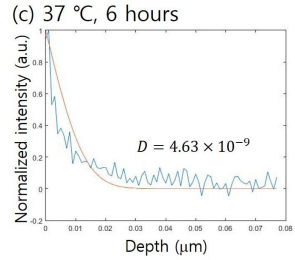
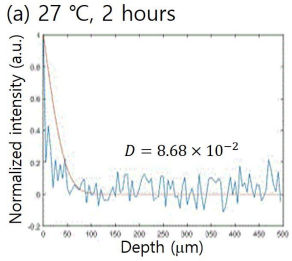
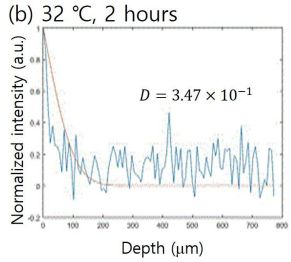
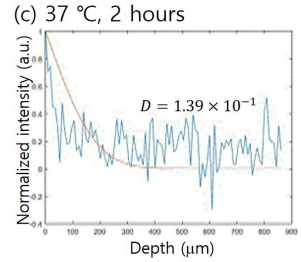
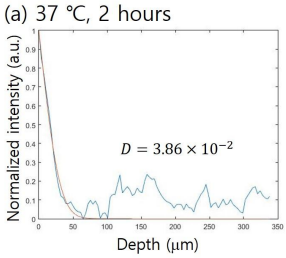
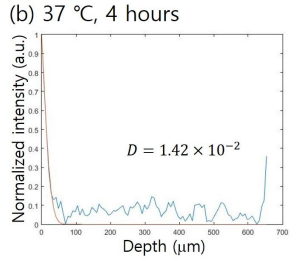
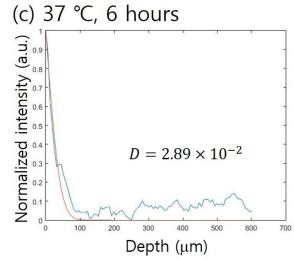


Fig. 3 LIBS intensity vs. distance from the surface (Depth) about time lapse

Table 3 Diffusion coefficient results by experimental conditions(nomarlized LIBS intensity vs. distance from the surface (Depth))

Case 1	(a) 27 ℃, 2 hours	(b) 32 ℃, 2 hours	(c) 37 ℃, 2 hours
			
Case 2	(a) 37 ℃, 2 hours	(b) 37 ℃, 4 hours	(c) 37 ℃, 6 hours
			
Case 3	(a) 27 ℃, 2 hours	(b) 32 ℃, 2 hours	(c) 37 ℃, 2 hours
			
Case 4	(a) 37 ℃, 2 hours	(b) 37 ℃, 4 hours	(c) 37 ℃, 6 hours
			

Using this principle, qualitative and quantitative analyses of diffusion concentration in the sample can be conducted temporally and spatially.

The elemental spectral line for diffusion measurement is interpreted by dividing it into atomic peak and ionic peak according to the passage of time (from femtosecond to millisecond) during the creation and decay of plasma. Analysis was performed using the signal of calcium as shown in Fig. 2 (Ca(I): 393.3 nm), which is the diffusion catalyst in the patch, among the elements that compose the drug in the patch, excluding the elements in the catalyst and the atmosphere including C, H, O, and N.

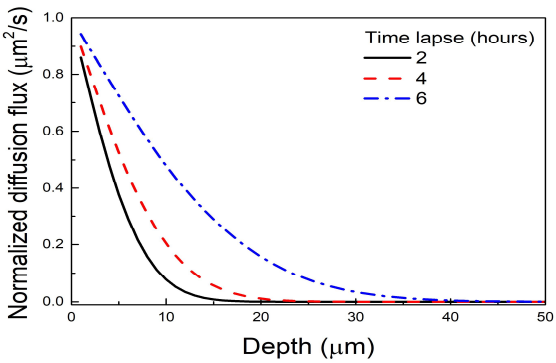


Fig. 4 Diffusion flux of calculated value vs. distance from the surface (depth)

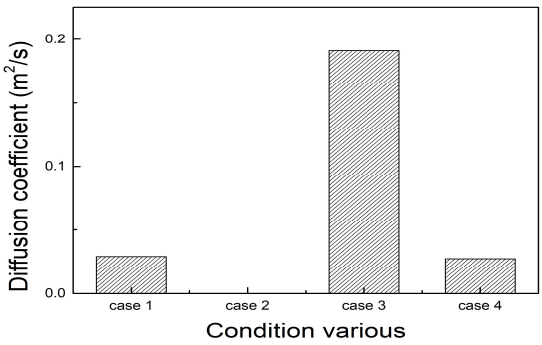


Fig. 5 Effect of conditions on diffusion coefficient (Critical factor; case 1, 3: temperature, case 2, 4: time)

4. Results

Diffusion analysis through LIBS was performed up to 900 μm deep from the sample surface. Changes in LIBS spectral line intensity of Ca according to the depth was calculated using Fick's first law of diffusion to derive the diffusion coefficient, D. Intensity changes in the Ca elemental spectral line in pig skin according to depth at room temperature are presented in Fig. 3. The graph shows measurements at time lapses of 2, 4, and 6 hours. The spectral line intensity of the surface signal was the highest after 2 h. Internal diffusion concentration, however, was found to increase as more time passed after attaching the patch. Fig. 4 shows the calculated diffusion concentration with respect to a distance from the surface to verify the reliability of the experimental values. Since the comparison of Figs. 3 and 4 shows a similar trend, this experiment was inferred to be valid.

Table 3 shows the results of diffusion for the experimental conditions from Case 1 to Case 4 in Table 1. The results of Case 1 showed that the diffusion coefficient in the skin increased from 1.39 × 10^{-2} ($\mu m^2/s$) to 5.6 × 10^{-2} ($\mu m^2/s$) with increasing temperature. In Case 2, the diffusion coefficient was found to decrease through time after attaching the patch at 37 ℃, but the trend of diffusion coefficient cannot be determined because it was considerably different from other cases due to the overall shallow depth of diffusion. Case 3 shows the changes in the diffusion coefficients with increasing temperature in pig muscular tissue. Similar to Case 1, the diffusion coefficient was found to increase with increasing temperature. The diffusion coefficient was higher than that of Case 1, which indicates that drug diffuses better in muscle than skin tissue. Case 4 shows the diffusion coefficient of Ca over time in muscle substrate at 37 ℃. Identifying trends in the results over time appears to be difficult. Considering that the drug effect of medicated patches lasts up to 24 h, it can be inferred that either time conditions in the experiments were too short to observe trends or that the diffusion model was working at the stationary state.

Fig. 5 shows the degree of the influence of experimental variables on the diffusion coefficient. The experimental results show that temperature had the largest influence on the diffusion coefficient, followed by diffusion substrate and then time. In the case of diffusion substrate, the diffusion of Ca element was greater in muscle than skin tissue. No obvious trend was found in the changes in diffusion coefficients according to the time passed after the attachment of the patch.

5. Conclusions

A method of measuring drug diffusion coefficients in biological tissues using LIBS was presented and investigated. Analysis was performed on the spectral line intensity of Ca, which is a diffusion catalyst for Indomethacin in medicated patches. In medicated patches, the diffusion of Ca element into the skin and muscle tissue of pigs showed different trends according to the medium, temperature, and time. The average diffusion coefficient, D, across the experimental conditions was 8.24×10^{-2} ($\mu m^2/s$), and the degree of diffusion increased with increasing temperature, given that the temperature is not high enough to modify the protein. The maximum diffusion coefficient, D, 1.39×10^{-1} ($\mu m^2/s$), was obtained when the temperature was 37 ℃. In the case of diffusion substrate, the degree of diffusion in muscle was about eight times that in skin tissue. These findings indicate that the delivery of drug from anti-inflammatory and analgesic patches is relatively greater through muscle tissue at a temperature similar to body temperature. Using LIBS analysis, it was possible to directly extract internal signals when measuring material diffusion in biological tissues by drilling micro-holes in the sample.

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