Evaluation of Transdermal Dosing Volume for Biopolymer Drug Model by Sequential Ultrasound Irradiation

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1. Introduction

Biopolymer drugs are expected to have high efficacy and minimal side effects due to their specificity. Meanwhile, a minimally invasive method of administering these drugs is difficult to establish. As one of the attractive methods, sonophoresis is a minimally invasive method of transdermal drug delivery (TDD). Sonophoresis enables TDD using shock waves and microjets induced by the collapse of cavitation bubbles generated by low-frequency ultrasound (kHz band). Specifically, Shock waves destroy the stratum corneum on the skin surface preventing TDD. Microjets also facilitate the TDD of high molecular weight drugs[(1)] (Fig. 1(a)). However, the amount of drugs administered by conventional techniques is limited since the randomness of the microjets generated from cavitation bubbles makes stable TDD difficult. This is because the position of the bubble nucleus for generating cavitation bubbles is unstable and not directional.

Here, we propose a multiband ultrasound irradiation method to achieve efficient TDD of biopolymer drugs (Fig.1(b)). Significantly, this study quantitatively evaluated drug delivery in biopolymer drug models using calibration curves. This allowed for measurement of the administration at each ultrasound irradiation. Fluorescence-modified (Cyanine5 carboxylic acid) ovalbumin (biopolymer drug model) was used for drug administration. Porcine skin, similar to human skin in structure and thickness, was used.

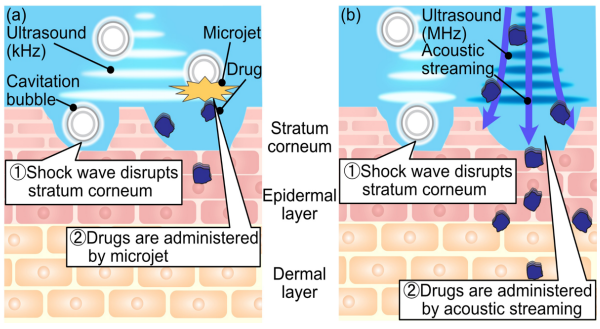

Fig. 1 Difference between (a) the conventional method of kHz band only and (b) the proposed method of sequential irradiation of kHz and MHz bands.

2. Material and Methods

2.1. Calibration curve for drug administration

A calibration curve was made to quantify the administered biopolymer drug model. After lysing porcine skin cut to the same diameter by biopsy trepanning, 3 µL, 6 µL, 9 µL, and 12 µL drops of the biopolymer drug model were added to the skin solution. No-drops were also prepared as a control. The calibration curve was made by measuring the fluorescence intensity of each solution with a fluorescence spectrophotometer.

2.2. Evaluation of sequential irradiation in the kHz and MHz bands

To evaluate the effect of sequential irradiation in the kHz and MHz bands on drug administration, 100 µL drops of a biopolymer drug model were placed on porcine skin and irradiated with ultrasound. Ultrasound was applied for 10 minutes, and the following conditions were examined: (i) kHz band only, (ii) MHz band only, (iii) kHz band (5 min) followed by MHz band (5 min), and (iv) MHz band (5 min) followed by kHz band (5 min). To compare,

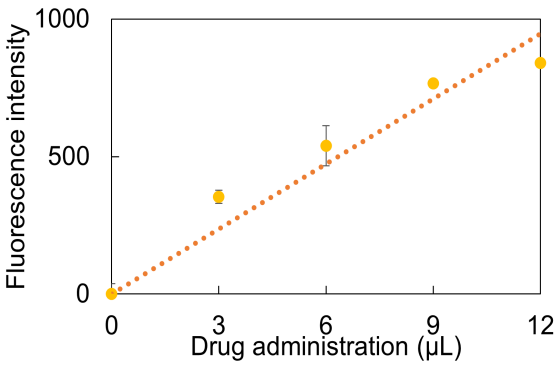

Fig. 2 Calibration curve showing the relationship between fluorescence intensity and drug administration.

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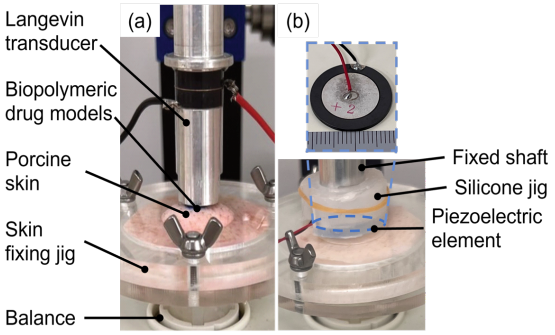

Fig. 3 Ultrasound irradiation devices with (a) kHz and (b) MHz band.

(v) application without ultrasound irradiation (10 min) was prepared. After the skin of each condition was lysed, a spectrofluorometer measured the fluorescence intensity of the skin solution. Using a calibration curve, the fluorescence intensity was converted to administration for quantitative evaluation of the biopolymer drug model.

3. Results

3.1. Calibration curve for drug administration

The calibration curve was prepared using the least squares method (Fig. 2). The coefficient of determination (R2 value) was calculated to examine the relationship between the obtained plots and the calibration curve. The result, R2 = 0.98, confirms that the calibration curve obtained is highly valid.

3.2. Evaluation of sequential irradiation in the kHz and MHz bands

The ultrasound irradiation device was constructed using two transducers. A Langevin transducer with a resonance frequency of 46 kHz was used for irradiation in the kHz band (Fig. 3(a)). A piezoelectric element with a resonance frequency of 2 MHz was used for irradiation in the MHz band (Fig. 3(b)). To equalize the pressure applied to the skin, ultrasound irradiation devices were adjusted to set the balance to zero. The results of drug administration (Table I) show that the highest drug administration was obtained under 5 min of irradiation in the kHz band followed by 5 min of irradiation in the MHz band. These results suggest that the sequential irradiation of the kHz and MHz bands proposed in this study is more effective than the conventional irradiation of the kHz band only. It was also shown that irradiating the MHz band first does not increase the administration efficiency.

Table I Fluorescence-modified ovalbumin administered by various ultrasound irradiation conditions. Relationship between drug administration and ultrasound irradiation method.

Frequency of ultrasound	kHz band	MHz band	kHz and MHz bands		MHz and kHz bands		Control
			kHz band	MHz band	MHz band	kHz band	
Irradiation time (min)	10	10	5	5	5	5	
Average of fluorescence intensity	568.5	102.4	758.2		414.4		62.6
Average of drug adminisitration (μL)	7.2	1.3	9.6		5.3		0.8

4. Conclusion

We established an ultrasound irradiation method for sonophoresis to achieve efficient TDD of biopolymer drugs. Specifically, the sequential ultrasound irradiation in the kHz and MHz bands improved drug administration efficiency compared to conventional and other ultrasound irradiation methods. In addition, the calibration curve enabled the quantification of the drug administration by ultrasound irradiation. These results suggest that adjusting the ultrasound irradiation time can enable the required drug administration.

Developing the kHz and MHz ultrasound irradiation method combining cavitation and acoustic streaming is promising for the research on biopolymer drugs.

Acknowledgment

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References

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