Liposome-encapsulation increases the bioavailability of midazolam on oral administration

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Background

The oral administration of midazolam has often been used for sedation in pediatric patients. However, its bioavailability is low on oral administration because it is metabolized in both the intestine and liver at a high rate. Liposomes have been developed as vesicles encapsulating various kinds of drug to serve as a medical drug-delivery system (Fig.1). We developed liposome-encapsulated midazolam for oral administration (Ref. 1). The purpose of the present study was to evaluate the bioavailability of liposome-encapsulated midazolam after oral administration in rabbits.

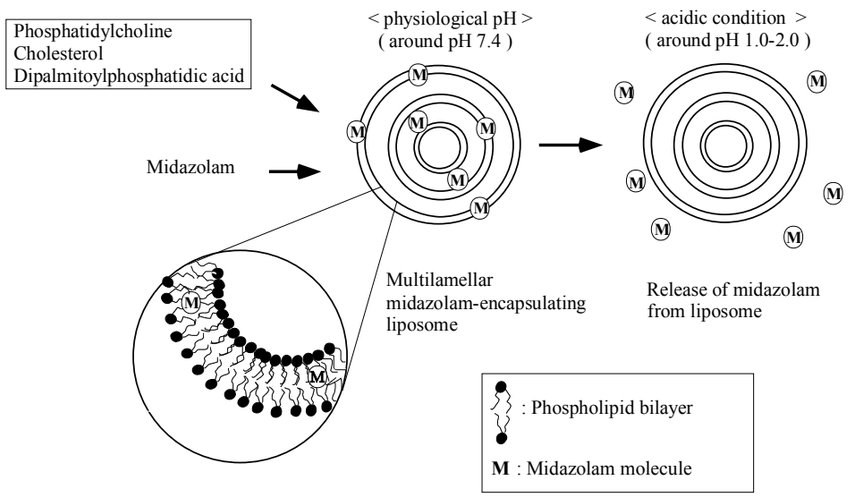

Fig.1 Liposome-encapsulated midazolam for oral administration

Materials and Methods

Liposome-encapsulated midazolam was produced from hydrogenated L-a-phosphatidylcholine, cholesterol, dipalmitoylphosphatidic acid, polyethylene glycol, and midazolam. A lipid film produced from the mixed materials was suspended and briefly sonicated in a water bath, resulting in the production of liposome-encapsulated midazolam (LE-midazolam) (Fig.2) . Furthermore, because smaller liposomes are expected to be efficiently absorbed from the intestine, we also produced miniaturized liposome-encapsulated midazolam (MLE-midazolam) using a sonic vibrator with ultrasonic waves (Fig. 3). After being approved by the Animal Care and Use Committee, we conducted experiments using 13 male New Zealand white rabbits (10–11 weeks old). LE-midazolam, MLE-midazolam, or midazolam solution was orally administered at the same dose of 2 mg/kg, and blood samples were collected until 4 hours after the administration. Blood midazolam concentrations of the samples were measured using HPLC, and analyzed using two-way ANOVA followed by Turkey's multiple comparisons test.

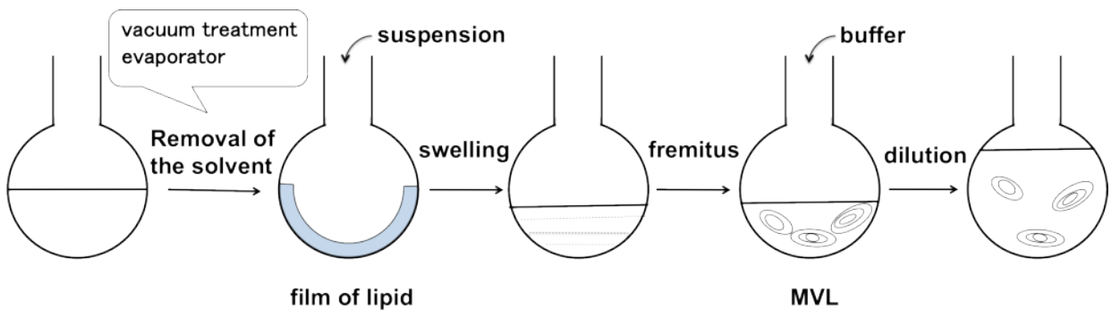

Fig. 2 Production of midazolam-encapsulating liposomes

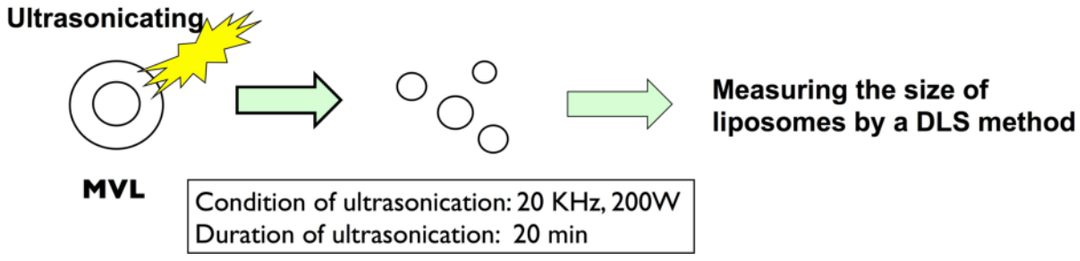

Fig. 3 Miniaturization of the midazolam-encapsulating liposomes

Results and Discussion

Blood midazolam concentrations in rabbits administered LE-midazolam and MLE-midazolam solutions were significantly higher than that in rabbits administered midazolam solution (Fig. 4). It is possible that the encapsulating liposomes inhibited the metabolism of midazolam and/or increased its absorption in the intestine.

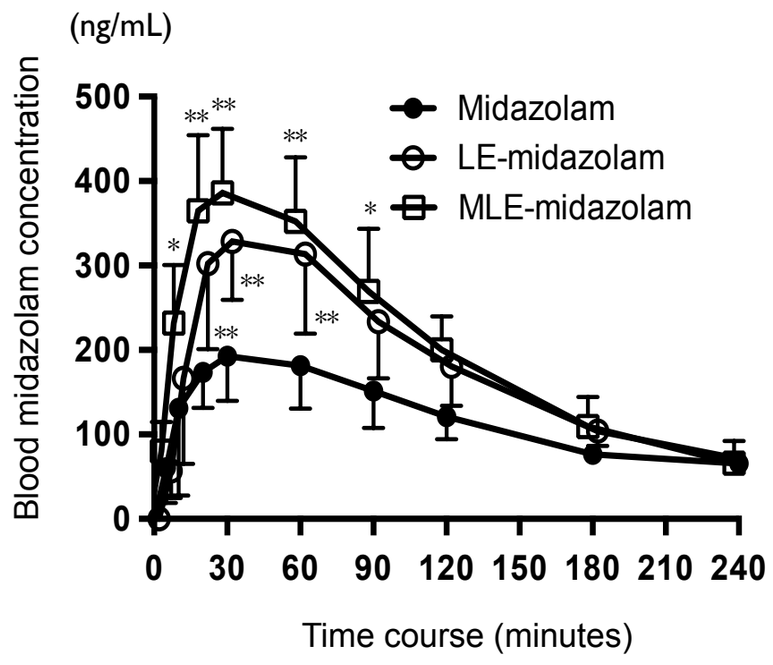

Fig. 4 Blood midazolam concentration after oral administration
LE-midazolam: liposome-encapsulated midazolam solution
MLE-midazolam: miniaturized liposome-encapsulated midazolam solution
*P<0.05, **P<0.01 vs. midazolam

Conclusion

The results of the present study indicate that liposome-encapsulation increases the bioavailability of midazolam on oral administration.

Reference 1:
Tomoyasu, Y., Yasuda, T., Maeda, S., Higuchi, H. and Miyawaki, T.: Liposome-encapsulated midazolam for oral administration. *J. Liposome Res.*, **21**, 166-172, 2011.

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