Preparation of amorphous solid dispersions using VCM and evaluation of drug membrane permeability using μFLUX

Hiromasa Uchiyama, Pharm.D. Junior Associate Professor at Department of Formulation Design and Pharmaceutical Technology, Faculty of Pharmacy, Osaka Medical and Pharmaceutical University

Purpose

The amorphous solid dispersion can convert the drug to an amorphous state to improve its solubility. The vacuum compression molding (VCM) from MeltPrep GmbH (Austria) reduces the loss of powder used to prepare amorphous solid dispersions. In this study, we attempted to prepare amorphous solid dispersions with various water-soluble polymers using VCM. We further evaluated the membrane permeability of the model drug dissolved from the prepared powder using μFlux (Rainbow R6, AuPRO 7.0) from Pion Inc. (USA). μFlux is a device that can measure drug solubility and membrane permeability at the same time, which has so far been used to examine solid dispersions and nanoparticles. We examined the effect of the polymer used in the drug preparation on drug solubility and membrane permeability, and also examined the effect of the addition of surfactant and the amount of drug added to the donor side on drug solubility and membrane permeability.

Experiment

Carvedilol (CVD) was used as a model drug. Polyvinyl alcohol (PVA, Poval JP-05), Polyvinyl pyrrolidone K-30 (PVP), Hydroxypropyl methylcellulose E (HPMC), and Hydroxypropyl methylcellulose acetate succinate (HPMCAS) were used as the water-soluble polymers. Sucrose fatty acid ester L-1695 (SE) was used as the surfactant.

For preparing solid dispersions using VCM, approximately 500 mg of powder, which is a mixture of drug and polymer in a weight ratio of 1:3, was filled in VCM. Then, it was heated to a temperature of 180 °C, melted by heating for 10 minutes, and cooled at room temperature for 20 minutes. The resulting powder was then ground using a vibrating ball mill. In experiments using μFlux, we added a 100 or 300 μg/mL sample dispersed in phosphate buffer at pH 6.5 on the donor side, and measured the drug concentration on the donor side and the amount of drug permeated into the acceptor sink buffer at pH 7.4, at a measurement interval of 10 seconds under stirring conditions at 200 rpm.

Results

Figure 1 shows the powder X-ray diffraction measurement results of the powder prepared by VCM. All of the prepared powders showed a halo

pattern, and were in an amorphous state. In addition, the glass transition points evaluated by differential scanning calorimetry showed that all prepared powders exhibited single glass transition points.

Figure 2 shows the results of evaluation of solubility and membrane permeability of Carvedilol (CVD) from the prepared powder using μFlux, assuming that the amount of CVD added was 100 μg/mL. Table 1 shows the membrane permeation rate (Flux (μg/min/cm2)), which is calculated based on the results in Figure 2.

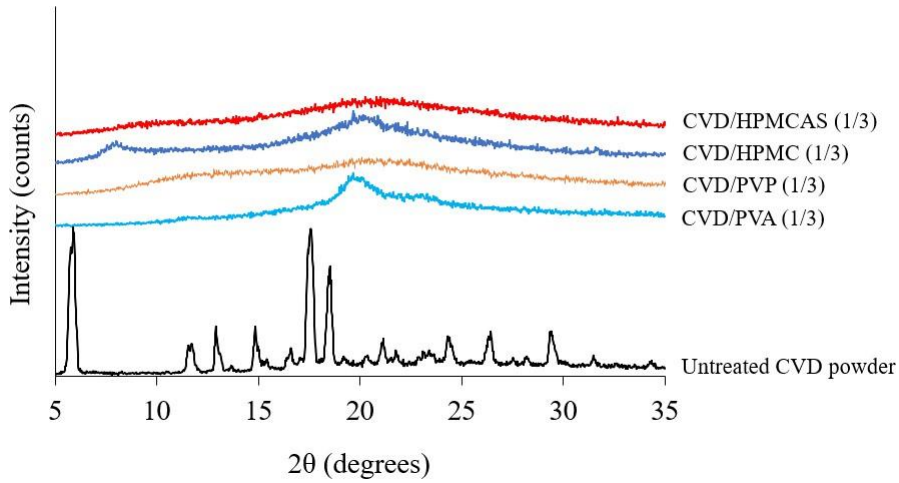


Figure 1 Powder X-ray diffraction measurement of powder prepared using VCM

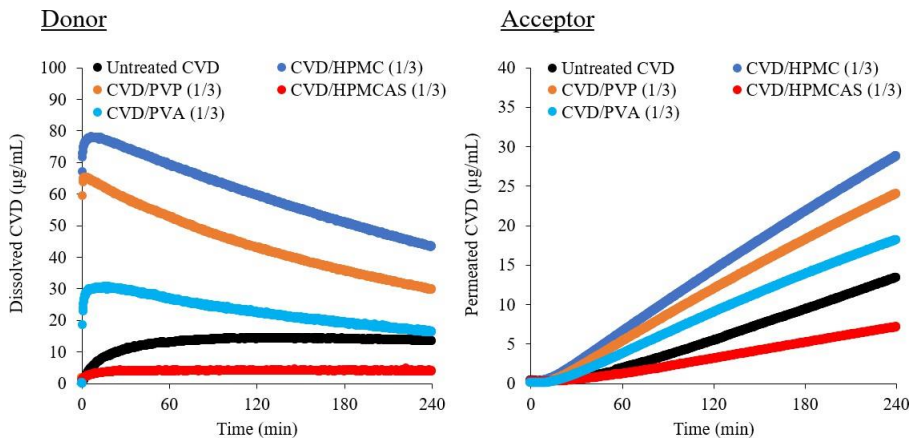


Figure 2 Evaluation of solubility and membrane permeability of CVD from amorphous solid dispersions (Amount of CVD added: 100 μg / mL, temperature: 37° C, stirring speed: 200 rpm, measurement interval: 10 seconds)

Table 1 Membrane permeation rate of CVD from amorphous solid dispersion (FLUX)

	Untreated CVD	CVD/HPMC (1/3)	CVD/PVP (1/3)	CVD/HPMCAS (1/3)	CVD/PVA (1/3)
Flux (μg/min/cm^2)	0.567	1.263	1.077	0.322	0.850

Among the water-soluble polymers used in this experiment, CVD showed the highest solubility and membrane permeability when using hydroxypropylmethylcellulose E (HPMC).
They showed lower solubility and membrane permeability when using hydroxypropylmethylcellulose acetate succinate (HPMCAS) than when using the bulk powder of CVD This may be attributed to the formation of ionic interactions between CVD as a basic drug and HPMCAS, which reduced the release of CVD from the prepared particles. Figure 3 shows the evaluation by μFlux of the powder prepared using VCM with surfactant SE physically mixed by half with respect to the amount of CVD.
The amount of CVD added was 100 μg/mL. Table 2 shows the results of Flux (μg/min/cm2), which is calculated based on the results in Figure 3. The addition of surfactant increased the concentration and membrane permeability of CVD on the donor side. The SE-added CVD/PVP (1/3) formulation had an approximately 1.3-fold

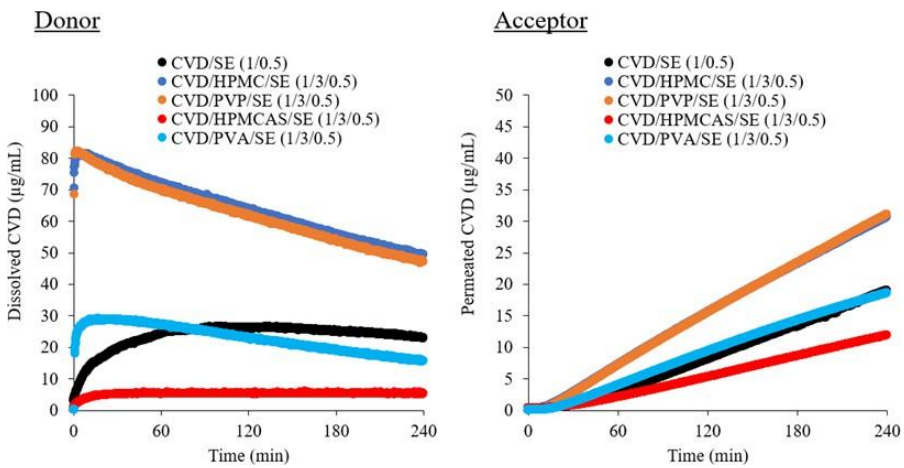


Figure 3 Effect of addition of surfactant to amorphous solid dispersion on the solubility and membrane permeability of CVD

(Amount of CVD added: 100 μg / mL, temperature: 37° C, stirring speed: 200 rpm, measurement interval: 10 seconds)

Table 2 Effect of addition of surfactant to amorphous solid dispersions on membrane permeation rate of CVD (FLUX)

	CVD/SE (1/0.5)	CVD/HPMC/SE (1/3/0.5)	CVD/PVP/SE (1/3/0.5)	CVD/HPMCAS/SE (1/3/0.5)	CVD/PVA/SE (1/3/0.5)
Flux (μg/min/cm^2)	0.852	1.349	1.354	0.418	0.875

higher CVD membrane permeation rate than the SE-free formulation.

It has been reported that phase separation occurs when the drug concentration in the solution exceeds the amorphous solubility. Using the probe attached to μFlux, approximately 170 μg/mL was calculated as the concentration at which CVD phase separation occurs, due to turbidity change. To confirm the effect of the phase-separated phase on CVD membrane permeability, CVD solubility and membrane permeability were evaluated by μFlux using a formulation of an amorphous solid dispersion of CVD / HPMC (1/3) (see Table 3 and Figure 4). A quantity of either 100 or 300 μg/mL of CVD was added. When adding 300 μg/mL, we separated it into two components for making an evaluation, a component dissolved on the donor side and a component phase-separated. When adding 300 μg/mL, we confirmed that the same level of amorphous solubility was maintained on the donor side and that the membrane permeability was improved within the tested time. This may be due to the re-dissolution of the dissolved CVD from the phase-separated phases when it permeated the membrane.

Conclusion

In the study using both VCM and μFlux, we were able to easily perform tests on polymer selection in solid dispersion formulations. Also, we could evaluate the solubility and membrane permeability of the drug when the surfactant was added. In addition, it was possible to perform the evaluation of CVD after separating it into two components, a component dissolved on the donor side and a component phase-separated when an amount exceeding the amorphous solubility was added, as well as to evaluate the contribution of the phase-separated phase to the membrane permeability.

Table 3 Effect of added amount of CVD on membrane permeation rate of CVD (FLUX) (Formulation: CVD/HPMC (1/3))

Added CVD amount in donor side (μg/mL)	100	300
Flux (μg/min/cm^2)	1.23	1.73

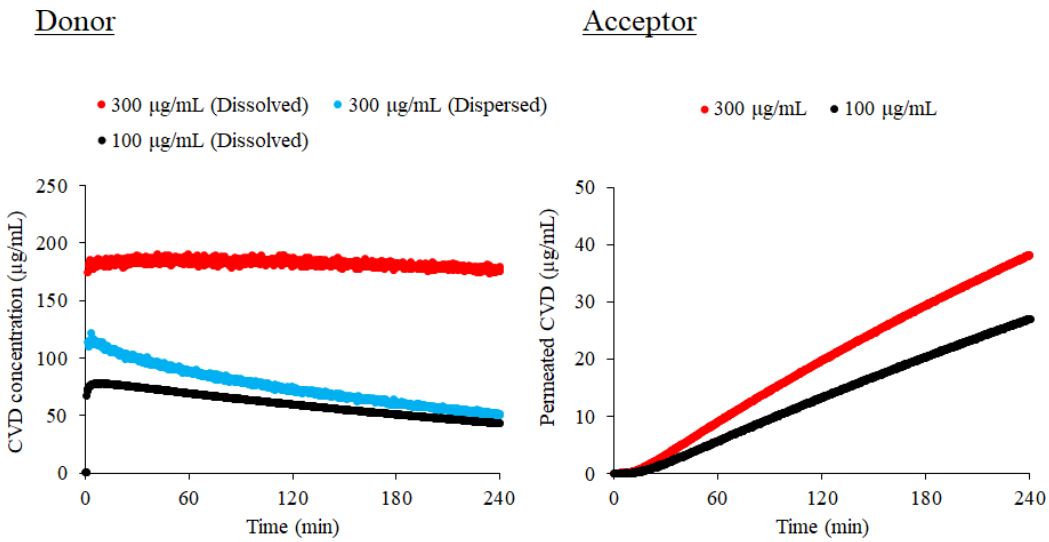
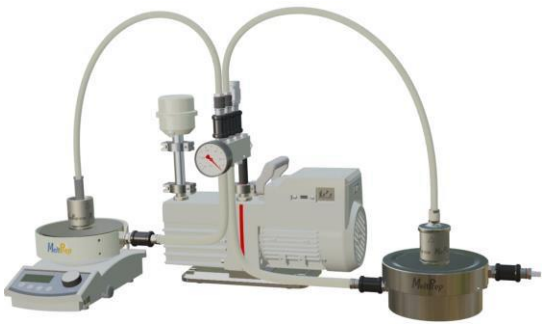
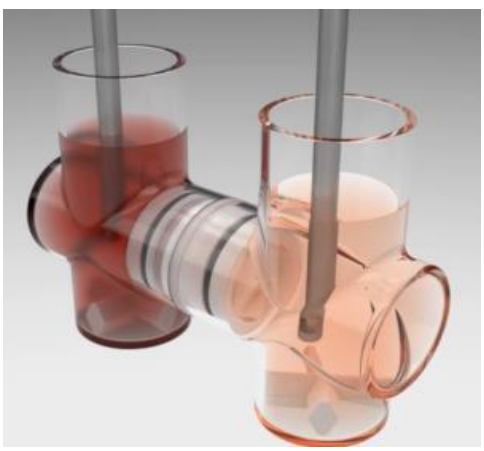


Figure 4 Effect of difference in added amount of CVD on solubility and membrane permeability of CVD (Formulation: CVD/HPMC (1/3), amount of CVD added: 100 or 300 μg/mL, temperature: 37° C, stirring speed: 200 rpm, measurement interval: 10 seconds)

Equipment for preparing amorphous solid dispersion
VCM



Equipment for evaluating the absorbency of API scale
μFlux



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