NVT Application Notes 11-MF

August, 2022

Evaluation using µFlux of solubility and membrane permeability of two kinds of drugs from an amorphous complex

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

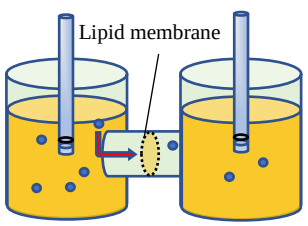
Purpose

Salt formed by ionic interaction between active pharmaceutical ingredients (APIs) and counter-compounds are used in drug development as a means of improving drug solubility. In general, highly water-soluble substances such as metal salts and hydrochlorides are used as counter compounds to be paired with drugs, and crystals form between the drug and the counter compound. In recent years, there has been an increasing number of reports on amorphous complexes. Amorphous complexes are amorphous forms formed by molecular interaction between different compounds, and amorphization helps improve drug solubility. Whereas many of the reported studies show the results of experiments combining highly water-soluble compounds, such as amino acids and organic acids, with drugs, this study attempted to form an amorphous complex using ionic interaction between compounds with poor solubility. The effect of amorphous complex formation between poorly-soluble compounds on the solubility and membrane permeability of two drugs was evaluated using µFlux (Rainbow R6, AuPRO 7.0) from Pion Inc. (USA).

Experiment

Telmisartan (TLM) was used as an acidic drug, and amlodipine (AML) was used as a basic drug. An amorphous complex was prepared by mixing TLM and AML to produce a powder giving them a 1:1 molar ratio, and then dry-milling that powder in a vibrating ball mill. Hereafter, a sample prepared from a physical mixture will be referred to as PM (Physical mixture), and a sample prepared by dry grinding will be referred to as GM (Ground mixture). The µFlux experimental conditions consisted of adding a sample dispersed in Fasted state simulated intestinal fluid (FaSSIF) of pH 6.5 to the donor side and stirring the fluid at a rate of 200 rpm. Then, we measured the drug concentration on the donor side and the amount of drug that permeated into the acceptor sink buffer of pH 7.4. Figure 1 shows the detailed µFlux test conditions, including drug doses, etc.

Donor conditions
- Test liquid: FaSSIF (pH 6.5)
- Test liquid volume: 16 mL
- Drug dosage: 100 µg/mL as TLM
  80 µg/mL as AML



Acceptor conditions
- Test liquid: Acceptor sink buffer (pH 7.4)
- Test liquid volume: 16 mL

- Temperature: 37 ° C
- Stirring rate: 200 rpm
- Measurement interval: 10 sec.

Figure 1. µFlux test conditions

Nihon Validation Technologies Corporation

Contact MAIL : contact@validation.co.jp

Results

The sample prepared via dry-grinding exhibited an amorphous state in powder X-ray diffraction measurements. Measurement of the glass-transition temperature using differential scanning calorimetry showed the sample made from dry grinding to be 20° C higher than the glass transition point calculated from the Gordon-Taylor equation, suggesting the formation of an amorphous complex between TLM and AML through ionic interaction. Figure 2 shows the results of evaluation using μFlux of the solubility and membrane permeability of TLM and AML from the amorphous complex. Tables 1 and 2 show the results of TLM and AML membrane permeation rates (Flux (μg/min/cm ^{2})) calculated based on the results of Figure 2. In TLM, the formation of an amorphous complex significantly increased the solubility of TLM on the donor side and the amount of permeation to the acceptor side, with the membrane permeation rate being more than 50 times higher than that of the drug bulk powder. On the other hand, AML showed a slight decrease both in solubility and membrane permeation amount compared to AML bulk powder due to the formation of an amorphous complex. The results of dissolution behavior on the donor side indicate that the amorphous complex formed in the solid state also existed in the solution while maintaining ionic interaction. As a result, it was considered that the solubility of low-water soluble TLM could be improved by the formation of an amorphous complex with AML, but that dissociation from the amorphous complex was rate-limiting for the highly water soluble AML, causing decreased solubility of AML. On the other hand, it was confirmed that the membrane permeation of both drugs derived from the amorphous complex progressed rapidly, and that the free TLM and AML dissociated from the amorphous complex permeated the membrane.

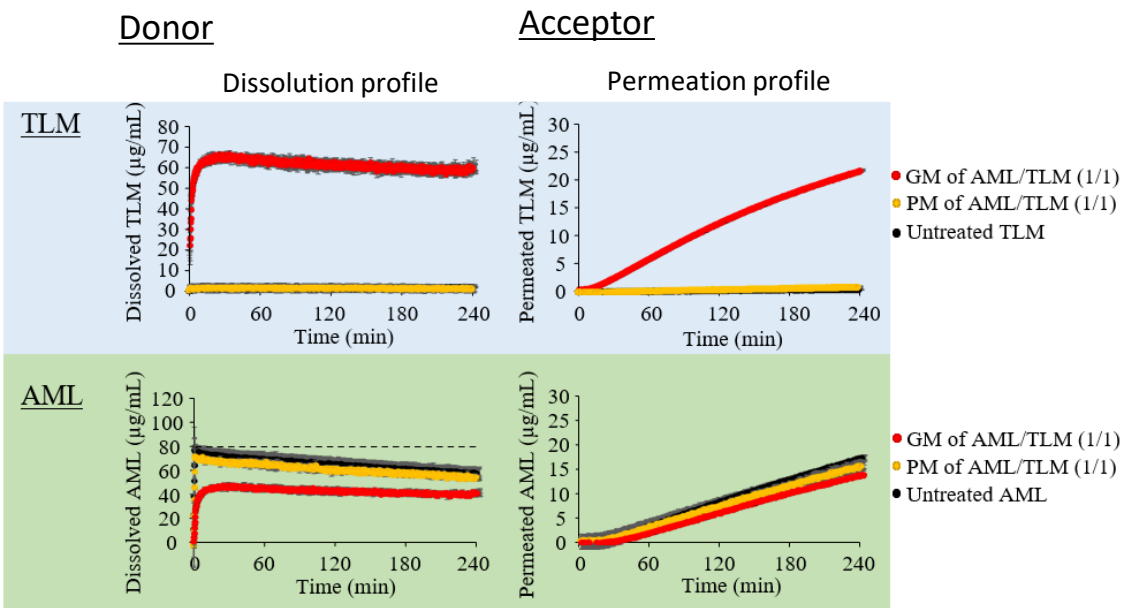


Figure 2. Evaluation of solubility and membrane permeability of TLM and AML from drug bulk powder, physical mixture (PM), and amorphous complex (GM)

Nihon Validation Technologies Corporation
Contact
MAIL : contact@validation.co.jp

Conclusion

Using µFlux, we were able to clarify the dissolution and membrane permeation behavior of the two drugs from an amorphous complex for which ionic interaction was maintained in the solution. As a counter compound for forming salts and co-crystals, compounds with higher hydrophobicity than metal salts are sometimes used. µFlux is considered to be an effective tool in clarifying the dissolution behavior of drugs from salts and co-crystals, as well as membrane permeation behavior after dissociation.

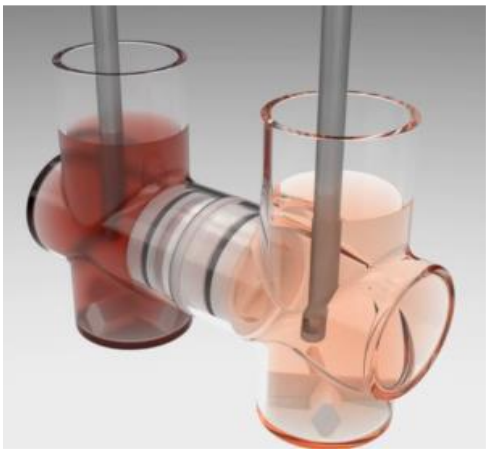
Table 1. Membrane permeation rate (Flux) of TLM from TLM bulk powder, physical mixture (PM), and amorphous complex (GM)

	Flux (µg/min/cm^2)
Untreated TLM	0.018 ± 0.002
PM of AML/TLM (1/1)	0.039 ± 0.018
GM of AML/TLM (1/1)	1.051 ± 0.010

Table 2. Membrane permeation rate (Flux) of AML from AML bulk powder, physical mixture (PM), and amorphous complex (GM)

	Flux (µg/min/cm^2)
Untreated AML	0.792 ± 0.085
PM of AML/TLM (1/1)	0.786 ± 0.053
GM of AML/TLM (1/1)	0.629 ± 0.048

The µFlux device for evaluating the scale of API absorbency



Nihon Validation Technologies Corporation
Contact MAIL : contact@validation.co.jp