Zwitterionic Liquid Design for Drug Dissolution and Anti-Precipitation

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In the early stages of drug discovery, the drug is often dissolved in dimethyl sulfoxide and subsequently diluted with the culture medium to evaluate the drug activity. However, the precipitation of poorly soluble drugs occurs when diluting.[1] Precipitation complicates the estimation of actual drug concentrations, thereby affecting the reliability of activity assessments. Approximately 70% of the developing drugs is poorly soluble. To suppress the precipitation, zwitterions can be good candidate due to their unique interactions with drug compounds and their low cytotoxicity.[2]

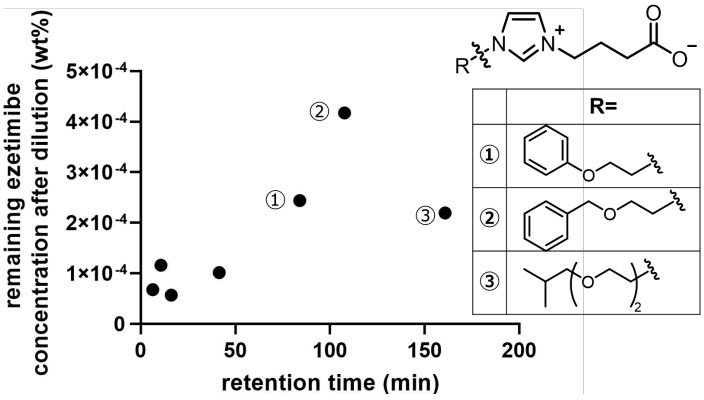

Fig. 1 Relation between retention time of zwitterions analyzed by reverse-phase chromatography (hydrophobicity) and remaining ezetimibe concentration after dilution from the zwitterion solutions

In this study, we utilized 12 types of zwitterions to evaluate the precipitation of a poorly soluble drug, ezetimibe. Three carboxylate-type zwitterions significantly suppressed the precipitation of ezetimibe. It indicates that the interaction between poorly soluble drugs and the zwitterions persisted even after dilution with water. To further investigate, the hydrophobicity of zwitterions was measured using reverse phase chromatography to check the correlation between the hydrophobicity of zwitterions and anti-precipitation effect (Fig. 1). As a result, zwitterions with higher hydrophobicity generally showed a stronger anti-precipitation effect. In addition, zwitterions containing a benzyl ring exhibited particularly strong suppression of ezetimibe precipitation, presumably due to π–π interactions.

References

1. Galvao, J.; Cordeiro, M. F.* *et al*. *FASEB J.* **2014**, *28* (3).
2. Kuroda, K.; Hirata, E.* *et al*. *Commun. Chem.* **2020,** 3(1).

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