Predicting Solvent Exchange Recovery from Solvent Partition Coefficients

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Abstract

- Extract processing, such as solvent exchange (liquid-liquid extraction), is often a necessary step to render the extracts amenable to chemical analysis.
- Potential losses of extractables during extract processing can result in underestimation and/or underreporting of extractables, leading to incorrect conclusions in toxicological risk assessment.
- Currently, there is no clear framework for performance evaluation of extract processing for chemical characterization.
- By exploring the relevant physicochemical parameters, a general framework was created for the evaluation and reporting of extract processing including estimation of recovery through predictive models, selection of appropriate surrogate chemicals for evaluation, experimental verification of the recovery estimation, and reporting the information within the context of the applicable chemical space.
- For solvent exchange, recoveries were modeled and experimentally verified under different conditions.
- The models were applied to a universe of potential extractables to better understand the impact of extract preparation on an extractables profile.

Introduction

- Solvent exchange and evaporation are the two most common extract preparation techniques used in chemical characterization studies.
- For solvent exchange, the impact on analyte recovery is a well known, but is often only evaluated from the perspective of single chemical recoveries.
- While models can be developed to understand the behavior of these techniques, the models should also be applied to predict the applicable chemical space.[1] This can be done in a stepwise process:

  1. Define the chemical space and subspace
  2. Select an effective recovery model
  3. Select surrogate chemicals to bracket relevant physiochemical parameters
  4. Demonstrate predicted recoveries empirically

- For defining chemical space, a mock chemical universe was curated from multiple sources of relevant potential extractable. Over 125,000 chemical entries were evaluated.

Materials and Methods

- Direct injection gas chromatography – mass spectrometry (Agilent 6890B/5975B)
- Ultra-high performance liquid chromatography – triple quadrupole mass spectrometry (Agilent 1290/6495C)
- Samples spiked before solvent exchange or evaporation to determine recovery
- Distribution coefficients were calculated from Abraham Solubility Parameters and applied to predict recovery[2]

$$\text{Recovery} = 1 - \left[\frac{1}{1 + K_D \frac{V_o}{V_w}}\right]^n$$

K_D = Distribution Coefficient
V_o = Volume Organic Solvent
V_w = Volume Water
n = number of extractions

Table 1. Chemicals selected to bracket important ranges of chemical parameters.

	pKa ~4	pKa ~10	pKa > 14
logK_D < -1	Chloroacetic acid	1,3-Propanediol	Propionamide
logK_D ~ 0	Butyric acid	Hexamethylene-diamine	1,8-Octanediol
logK_D > 1	Hexanoic acid	Amylamine	Toluene

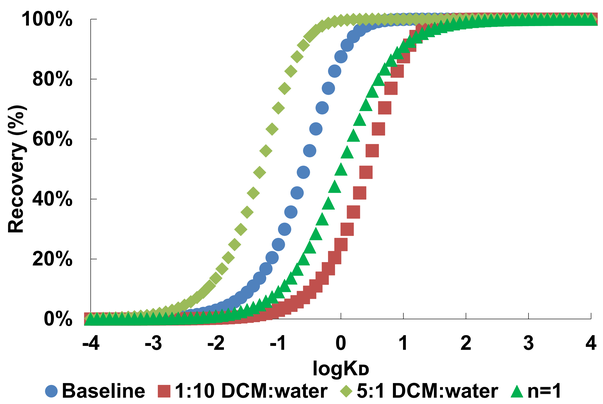

Figure 1. Representative Models for various solvent exchange methodologies

Results and Discussion

- Chemicals with a range of logK_D values demonstrate the change from 0 % to 100 % recovery.
- The recovery inflection point is most sensitive to logK_D and therefore tends to have the highest error.
- Alternative loss mechanisms can cause recoveries below the predictions of the models.

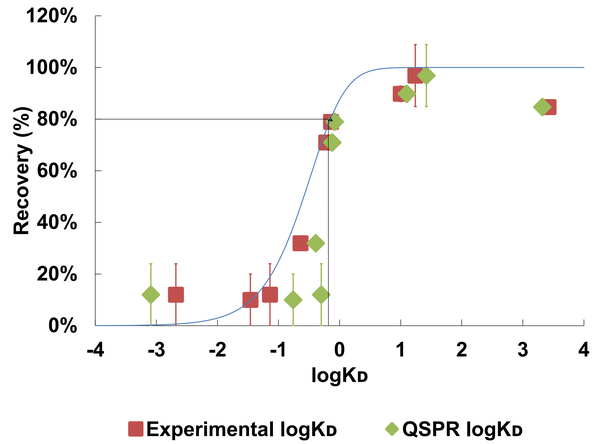

Figure 2. Representative Model (blue curve) and experimental fit using surrogate chemicals for solvent exchange into dichloromethane

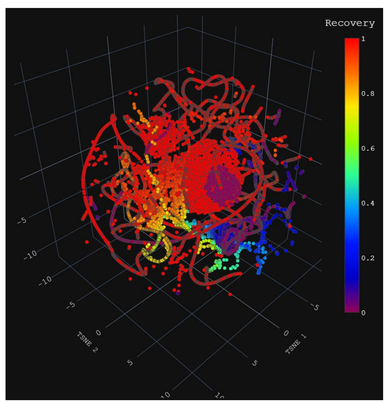

Figure 3. Mapping of the chemical universe considering expected recoveries for solvent exchange

Table 2. Recovery error for various sample preparation methods

Preparation Method	Critical Parameters	Individual Measurements	Root Mean Square Error
Solvent Exchange	**Solvent, Analyte pKa, Partition Coefficient, times extracted, solvent/water ratio, pH**	**198**	**18%**

Conclusion

- Recovery equation was experimentally found to accurately predict recovery (Root Mean Square Error <20%)
- The framework for application to the representative chemical space allows for easy comparison of methods to determine best practices for high recovery
- To apply the approach to alternative sample preparation techniques, it is necessary to have a model that includes all critical parameters
- Acceptance of a cutoff recovery at 80% was applied to determine effective coverage

Feedback

We appreciate feedback and the oopportunity to collaborate. Please forward inquiries to: joshua.young@fda.hhs.gov or kaleb.duelge@fda.hhs.gov

References

[1] *Black, G., et al. Anal. Bioanal. Chem. 2023; 415 (1): 35-44*
[2] *Brown, T.N. J Solution Chem. 2022; (51): 1101–1132.*

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