Procedure for Applying Framework

Tool Reference

RST Reference Number: RST24MC06.01

Date of Publication: 09/18/2025

Recommended Citation: U.S. Food and Drug Administration. (2025). *Extract Preparation in Chemical Characterization Studies – Evaporation* (RST24MC06.01). https://cdrh-rst.fda.gov/extract-preparation-chemical-characterization-studies-evaporation

For more information

Catalog of Regulatory Science Tools to Help Assess New Medical Devices

Disclaimer

About the Catalog of Regulatory Science Tools

The enclosed tool is part of the Catalog of Regulatory Science Tools, which provides a peer-reviewed resource for stakeholders to use where standards and qualified Medical Device Development Tools (MDDTs) do not yet exist. These tools do not replace FDA-recognized standards or MDDTs. This catalog collates a variety of regulatory science tools that the FDA's Center for Devices and Radiological Health's (CDRH) Office of Science and Engineering Labs (OSEL) developed. These tools use the most innovative science to support medical device development and patient access to safe and effective medical devices. If you are considering using a tool from this catalog in your marketing submissions, note that these tools have not been qualified as Medical Device Development Tools and the FDA has not evaluated the suitability of these tools within any specific context of use. You may request feedback or meetings for medical device submissions as part of the Q-Submission Program.

For more information about the Catalog of Regulatory Science Tools,
email RST_CDRH@fda.hhs.gov.

Procedure for Applying Framework

The instructions below describe the models used for estimating evaporation recovery. The instruction also includes a procedure for how to apply the models to establish the impact of evaporation method parameters on recovery of extractables in a chemical characterization study.

1. Define the Chemical Space and Chemical Subspace

The **chemical space** refers to a comprehensive list of all possible extractables which can be found in the chemical characterization study. The **chemical subspace** refers to a subset of the chemical space applicable to the specific analysis within the chemical characterization study. For example, for evaporation conducted prior to semi-volatiles or non-volatiles analysis, a chemical subspace may pertain to only chemicals within the chemical space with a boiling point of >50°C. Volatile organic compounds would therefore be excluded from this subspace as they are typically evaluated separately using headspace gas chromatographic methods.

The user must determine their own appliable chemical space and chemical subspace based on the intent of the analysis. In establishing the chemical space and chemical subspace, consideration must be made to ensure a comprehensive coverage of chemicals which are applicable to needs of the specific chemical characterization study. The chemical subspace described in the supporting publication is a general chemical subspace applicable to evaporation when used for direct injection gas chromatographic and liquid chromatographic analyses of medical device extractables which can be initially considered.

2. Select an effective recovery model

For each chemical within the chemical subspace, recovery following evaporation should be determined using the following equation:

$$Recovery\ (\%) = 1 - \left[1 + K\left(\frac{V_{L,f}}{V_G}\right)\right]^{-1} \text{x } 100$$

Where:

K = the gas/liquid partition coefficient of a given solute

$V_{L,f}$ = The post-evaporation final volume of the solvent

V_G = The gaseous volume of the evaporated solvent

The gaseous volume of the evaporated solvent can be determined from the change in liquid volume due to evaporation, the molecular volume of the liquid solvent ($M_{Vol,L}$), and the molecular volume of the gaseous solvent ($M_{Vol,G}$):

$$V_G = \Delta V_L / (M_{Vol,L} / M_{Vol,G})$$

The molecular volumes in each state are trivially determined, where $M_{Vol,L}$ is the ratio of molecular weight (MW) to density (ρ) and $M_{Vol,G}$ which can be derived from an equation of state, such as the ideal gas law:

$$M_{Vol,L} = MW/\rho$$

$$M_{Vol,G} = RT/P$$

Where:

$R = 0.0821\ L \cdot atm \cdot K^{-1} \cdot mol^{-1}$

T = The evaporation temperature (K)

P = The vapor pressure of the solvent at temperature (T)

The values of $V_{L,f}$, ΔV_L, MW, ρ, T, and P are determined from the experimental conditions selected for performing the evaporation and based on the specific solvent used.

Determination of K can be experimentally determined or predicted using quantitative structure-propery relationship models. As described in the publication, validated prediction models have been previously established for estimation of these parameters and which are available in the public domain.

3. **Select surrogate chemicals to bracket relevant physiochemical parameters**

From the chemical subspace, determine the recoveries of each solute using the recovery model established in step 2 based on the experimental conditions being used. Choose at least three surrogate compounds per condition which is expected to show a recovery of <10%, between 40-60%, and >90%, respectively. A minimum of three surrogates should be used per condition. Changing the solvent, evaporation method, evaporation temperature, and extent of evaporation should be verified by measurement of recovery.

4. **Demonstrate predicted recoveries empirically**

Perform evaporation on the surrogate compounds selected in step 3 using the predetermined experimental parameters. Verify the recoveries obtained for low (<10%) and high (>90%) recovery are within 20% of the expected values based on the model. The middle recovery (40-60%) should align with the inflection of the recovery curve, as shown in Fig. 1.

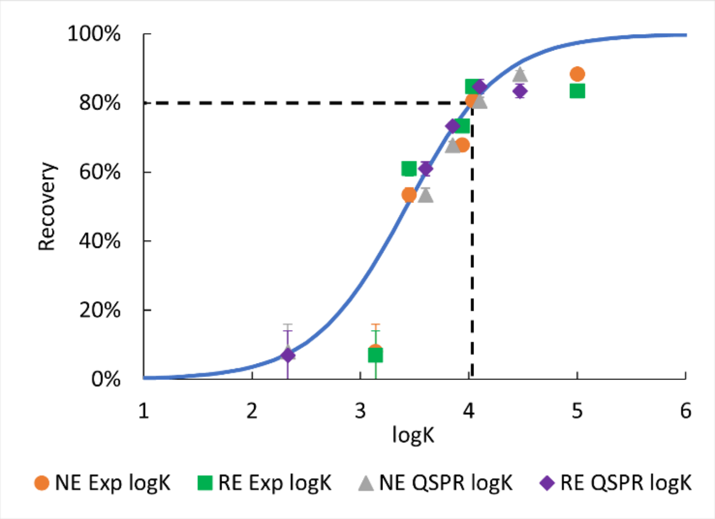

Fig. 1 Recovery plot for the baseline evaporation method for hexanes at 35°C. The orange circles and green squares are experimentally determined logK values using NE and RE, respectively. The gray triangles and purple diamonds arecalculated logK values using NE and RE, respectively. The black dashed line is the recovery cutoff (less than 80% recovery is considered unrecovered). The error bars are the standard error of the measurements.

If the recoveries obtained are within the expected range, then the evaporation method and model utilized is functioning as expected. The recoveries calculated for the chemical subspace in step 3 can be used to estimate the impact of the method on recovery of the intended chemical space. Establish an 80% acceptable recovery limit (as shown in Fig.1) and determine the number of chemicals within the chemical subspace achieve this minimum value. Adjust the experimental parameters as necessary to maximize coverage of the chemical space. If the experimental parameters are adjusted to values outside of what was evaluated in step 4, step 4 should be repeated to demonstrate method performance using the new values.

If recoveries obtained are not within the expected range, the impact of the chosen evaporation parameters cannot be estimated. Attempts should be made to refine the model to align with laboratory results or refine laboratory techniques to align with the selected model. If either is chosen, the adjustments must be verified by repeating steps 3 and 4.