BIOVIA

3DEXPERIENCE®

ACCELERATE SOLVENT SELECTION IN PHARMACEUTICAL DEVELOPMENT

Solution Brief

Solvent selection is vital in pharmaceutical development, impacting safety, environmental concerns, and regulatory compliance. However, traditional experimental approaches are time-consuming and resource-intensive. Computational methods like **COSMO-RS** offer a valuable solution, accurately predicting solvent properties for various unit operations. By integrating molecular calculations with statistical thermodynamics, **COSMO-RS** provides a robust approach applicable to diverse compounds without re-parameterization. Its effectiveness in predicting properties such as solubility, partition coefficients, and phase equilibria makes it indispensable for process development in the chemical and pharmaceutical industries, facilitating efficient solvent selection.

DASSAULT SYSTEMES

In Pharmaceutical Development, researchers and engineers design and develop processes to manufacture an Active Pharmaceutical Ingredient (API) according to specifications and with its intended performance both in the product and in the patient. The unit operations forming the manufacturing process need to be optimized to perform on an industrial scale. Since nearly all processing steps, such as synthesis, separation, and cleaning operations, require pure or mixed solvents, determining the best performing solvent or solvent mixture for each step is an important task during early stage process development. Furthermore, if individual steps in the process use different solvents, it is reasonable to determine if and how the required solvent swap will be feasible with minimal loss of product. Aside from process related considerations, there are general concerns for solvent selection: impact on safety, health and environmental (SHE) as well as regulatory concerns.

Determining the best solvent or solvent mixture for different unit operations experimentally is a time-consuming and costly efforts. Additionally, the amount of API substance available may yet be insufficient to conduct extensive experiments. Thus, computational methods are valuable tools to guide experiments for the selection of adequate solvents or solvent mixtures. Among the methods available for property prediction the fluid phase thermodynamics theory **COSMO-RS** stands out due to its general applicability and universal predictivity. It combines molecular first-principle calculations with fast and accurate statistical thermodynamics in a unique and robust approach. All parameters in **COSMO-RS** are general or element specific, and thus there is no need for any re-parameterization if compounds are new, non-standard, or have unusual chemistry. Because of this, **COSMO-RS** has become an important toolkit for fluid phase property prediction in process development in the chemical and pharmaceutical industries.

COSMOtherm, BIOVIA's implementation of **COSMO-RS**, is applicable to a large range of structures without requiring additional data for parameter fitting. In order to predict properties of compounds, **COSMOtherm** relies on pre-calculated compound information from quantum chemical density functional theory (DFT). The required quantum chemical calculations are a one-time effort, and the resulting compound descriptor files can afterwards be re-used for any other property prediction. Thus, it is straightforward to set up a customized collection of compound descriptor files, including a typical in-house solvent database of a pharmaceutical company with several hundreds of solvents as well as the desired APIs and any other candidate compounds. The number of computationally demanding quantum chemical calculations can be reduced using a database of pre-computed compound descriptor files, **COSMObase**.

This solution brief subsumes some typical **COSMO-RS** applications in process development in the pharmaceutical industry.

Generally, all process steps from synthesis to final isolation in the desired form require suitable solvents, as well as the subsequent preparation of the equipment for re-use:

- **Reaction:**
  - Dissolve reagents
  - Reaction profile depends on solvent
- **Work-up and Isolation:**
  - Remove co-products and other impurities
  - Crystallize pure product
  - Control form and particle size for solid products/crystals

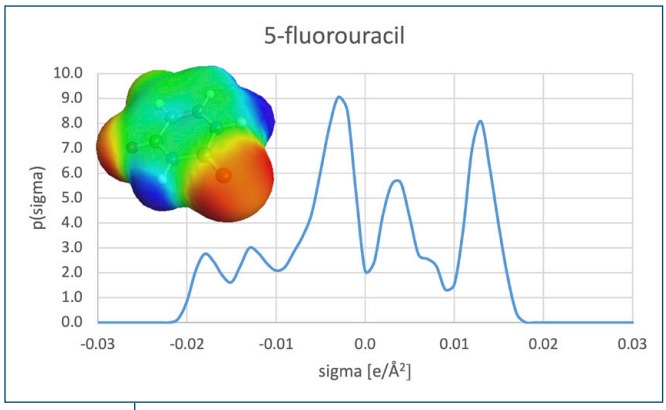

Figure 1: Sigma profile of 5-fluorouracil, used as descriptor for property prediction

- **Cleaning:** Solvents for cleaning of reactor vessel/plant

Knowledge of thermodynamic properties is required to determine which candidate solvents are appropriate for the steps in the planned manufacturing process. Among other properties, **COSMOtherm** can predict:

- **Solubility**
  - for reaction (reagents and product)
  - isolation (main product and co-products or impurities)
  - cleaning
- **Water/organic and organic/organic partition coefficients**
  - for work-up via liquid-liquid extraction
- **Acid dissociation constants**
- **Liquid-Liquid Equilibria (LLE) and Vapor-Liquid Equilibria (VLE)**
  - Determine if solvent swap between steps is feasible for candidate solvents.

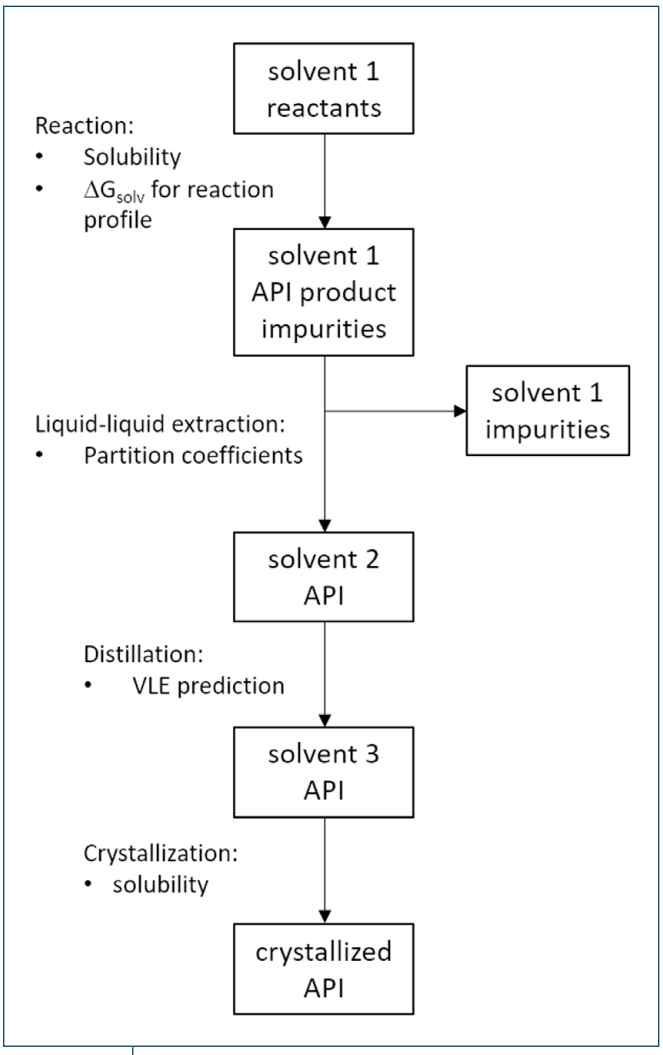

Figure 2: Solvent selection for reaction, work-up, and isolation

SOLVENT SELECTION FOR CHEMICAL REACTIONS

For the chemical reaction where the API is synthesized, researchers and engineers need to identify the preferred chemical route and establish ways of achieving that route on the industrial scale. Computational reaction modeling can help the understanding of the process and define ranges in which the process remains robust. The choice of the reaction solvent has significant effects on reaction kinetics and stereo-, regio-, and chemoselectivity patterns. Because of reaction side conditions and constraints, appropriate solvents usually have to be identified and selected from the in-house database prior to experiments. Prediction of the reaction energetics with different solvents has become an integral part of computational drug development and helps reduce the list of available solvents to a shortlist of solvents with the required properties.

The influence of different solvents can be described by **COSMO-RS** via the free energy differences of reactants, transition state and products: The equilibrium constant can be derived from the free energy of reaction $\Delta G_{reaction}$, while the kinetic constant can be derived from the energy barrier $\Delta G_{activation}$.

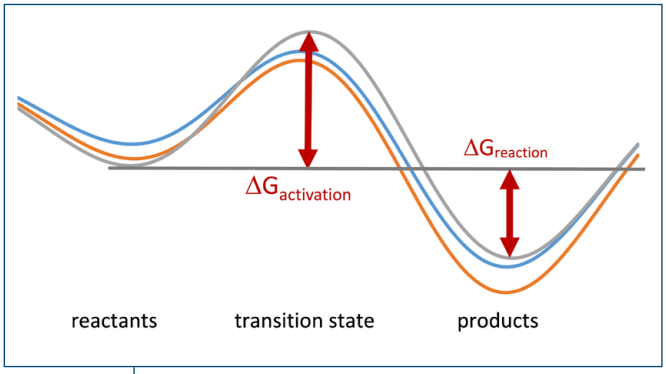

Figure 3: Schematic reaction profiles in different solvents

SOLVENT SELECTION FOR WORK-UP & ISOLATION

After synthesis, the reaction product is worked up to separate the API from remaining reactants, undesirable co-products, and other impurities. Since contamination of a manufactured drug poses a hazardous risk to patients, removing harmful impurities from the product is a vital step in the process.

Potential methods for extraction of the API from the reaction mixture are

- washing of impurities with water, if impurities are soluble in water (water/organic partition coefficient)
- organic liquid-liquid extraction (partition coefficients)
- induce precipitation and filter (solubility in solvent mixtures)
- removal of solvents by evaporation (VLE)
- distillation (VLE)

The efficiency of washing and extraction operations is described by the partition coefficient of compounds between two solvents or solvent mixtures. Predicting partition coefficients of organic compounds in any water/organic or organic/organic solvent system is a key functionality of **COSMOtherm**.

An example highlighting the importance of impurity control in the product is the contamination of valsartan and others sartans with potentially carcinogenic dialkyl N-nitrosamines. Downstream purge of N-nitrosamines via washing or extraction operations is a vital step to remove co-products which could make the product unfit for distribution. Finding a solvent with a high purge factor, which sufficiently removes impurities in a single step, leads to a higher yields and, consequently, better performance of the process.

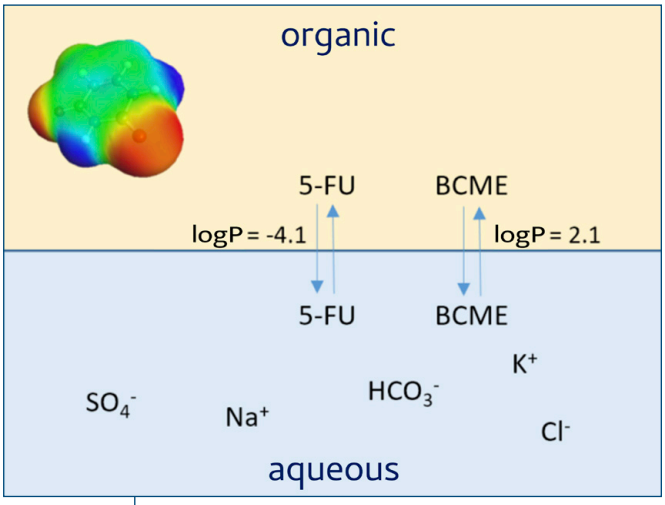

Figure 4: Predicting partition coefficients

Partition coefficients for nitrosamines in water/organic systems can easily be calculated and used to predict the fraction of a nitrosamine that will be removed in an aqueous wash. For lipophilic substances, water washes are often not effective to remove the impurity, and different separation strategies are required. If the reaction product can be extracted into the aqueous phase through ionization, an effective separation could be achieved as the non-ionizable nitrosamine would be left in the organic phase.

If impurities or reaction products possess acidic or basic groups, the pH of the aqueous phase in an extraction becomes a significant parameter in determining the effectiveness of the wash. Comparing the pH-dependent extraction curves for the reaction product and impurities can support the selection of extraction conditions where the optimum purge can be obtained in a pH-controlled extraction.

SOLVENT EXCHANGE

Solvent exchange is a common task in API manufacturing and important to optimize the overall process performance. Individual steps in the process may require different solvents for best results.

Using a VLE phase diagram prediction with **COSMOtherm**, it is possible to determine if a solvent swap by distillation is feasible. **COSMOtherm** allows for the calculation of phase diagrams for vapor-liquid equilibria (VLE) of binary, ternary and higher dimensional mixtures to predict

- the excess properties H^E and G^E,
- the chemical potentials $\mu_i + RT \ln(x_i)$
- the activity coefficient γi,
- the total vapor pressure of the system $p^{(tot)}$,
- and the concentrations of the compounds in the gas phase y_i

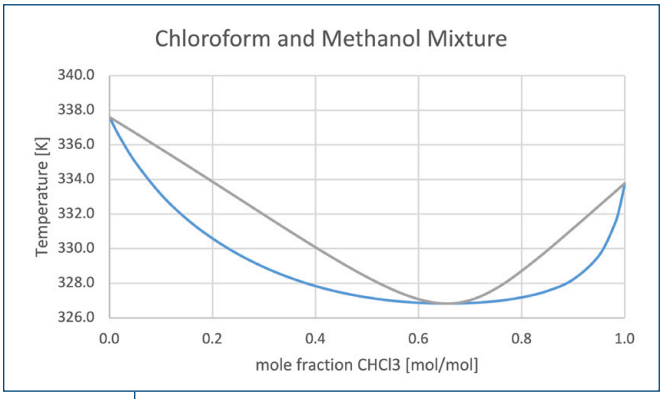

Figure 5: VLE phase diagram prediction

CRYSTALLIZATION

Once impurities are removed, the pure solid product needs to be isolated with form and particle control. Depending on the crystallization conditions, the product may form different polymorphs or particles may form agglomerates. The morphology of the crystal may affect physical properties that are relevant in the formulation stage of drug development. Filtration and dissolution rates, compressibility, and flow ability depend product particle form and size. If a drug product powder has optimal properties for downstream processing, steps like downstream milling can potentially be avoided and the overall manufacturing workflow will be much more time-efficient.

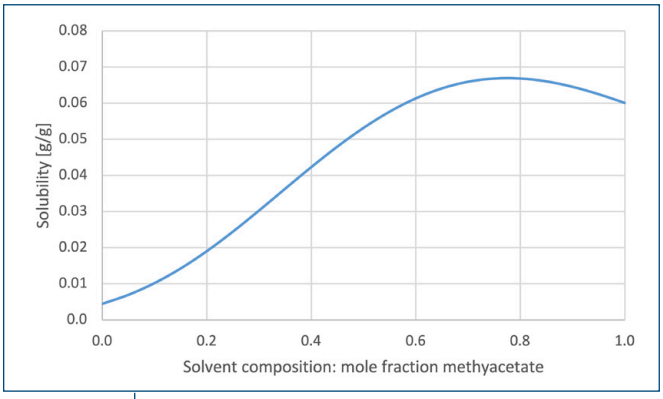

Figure 6: Solubility of Metroprolol in Cyclohexane / Methylacetate

COSMOtherm can support the development of workflows for crystallization of the drug product which reduce undesirable agglomeration of particles, and in combination with Materials Studio, has been used to optimize crystal morphology. Solvent Screening with **COSMOtherm** has been applied to find the optimal solvent for impurity purge through recrystallization.

The solvent selection for the crystallization step can benefit greatly from guidance provided by **COSMOtherm** solvent screening applications. Calculation of temperature-dependent solubilities can predict pure solvents or solvent mixtures delivering a maximum yield of crystalized products.

CONCLUSION

The utilization of computational methods such as **COSMO-RS**, particularly through tools like **COSMOtherm**, offers a strategic approach to solvent selection in pharmaceutical development.

By streamlining the process of identifying optimal solvents for various unit operations, from synthesis to final isolation, and facilitating solvent swaps with minimal product loss, this solution not only enhances efficiency but also addresses critical concerns regarding safety, health, environmental impact, and regulatory compliance. Embracing such computational approaches empowers researchers and engineers to navigate complex solvent-related challenges effectively, fostering innovation and sustainability within the pharmaceutical industry.