Making Sense of Science

Chemical Development

Pharmaceutical Preformulation Services

At Ricerca Biosciences, we believe an adequate understanding of the properties of your drug substance will minimize problems in later stages of drug development, reduce drug development costs and decrease your product's time to market.

Preformulation is a branch of pharmaceutical sciences that utilizes biopharmaceutical principles in the determination of physicochemical properties of a drug substance. The goals of preformulation studies are to choose the correct form of your drug substance, evaluate its physical properties and generate a thorough understanding of the material's stability under various conditions, leading to the optimal drug delivery system.

Ricerca offers a wide range of analytical approaches to achieving these goals. These approaches are designed to help move your compound from drug candidate to marketable product.

Ricerca works closely with its clients in designing and conducting preformulation studies. Depending on the nature of your drug candidate, Ricerca can conduct special studies expanding the scope of information obtained on the drug molecule.

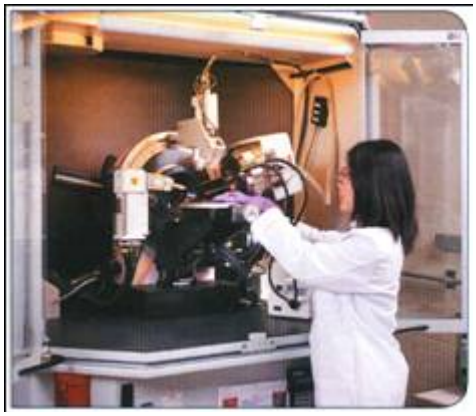
Preformulation Services

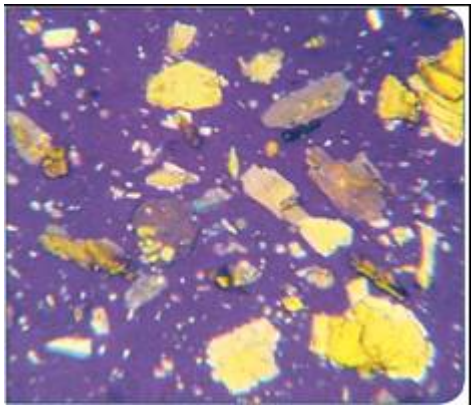
Product properties

- Polymorph screening (free base and salt forms)
- Solubility (aqueous/buffers/organic solvents)
- Dissociation constant (pKa)
- Partition coefficient (log p or log D)
- Salt screening (determination of preferred salt forms)

Stability evaluation

- Stability (heat/light/acid/base/oxidizer)
- Moisture isotherm (formation of hydrates/deliquescence)
- Excipient compatibility (depending on dosage route)





Core chemistry services

- Analytical chemistry
- Process chemistry
- Engineering & API manufacturing
- Radiochemistry

Solid-state characterization

- Powder properties (flow/compaction/density/ particle size/surface area)
- Kilo labs
- Thermal analysis (DSC, TGA)
- Molecular spectroscopy (FTIR, NMR, MS)
- X-ray diffraction

Ricerca Biosciences: Your research partner of choice

Ricerca Biosciences, a contract drug development organization, provides science-based services to the pharmaceutical, biotech, and specialty chemical industries for the development and commercialization of new innovative products. Ricerca's 260,000 ft^2 complex is located on a 43-acre site in Concord, Ohio. The facility is equipped with a full complement of well-maintained instrumentation and processing equipment operated in rigorous regulatory compliance to the highest quality standards.

Polymorph Screening to Support Pharmaceutical Development

Polymorphism

Many pharmaceutical compounds are polymorphic, i.e., they exhibit more than one crystalline form. Different polymorphs of an active pharmaceutical ingredient have different physical and chemical properties. These variations give rise to differences in solubility, stability and bioavailability that can impact the safety and efficacy of new therapeutic agents. It is therefore important to evaluate each drug candidate for polymorphism (polymorph screening). For drug systems exhibiting polymorphism, each form should be characterized in order to establish which is the most stable. After characterization of the polymorphic system, a robust production process must be developed to reliably produce the desired polymorph (polymorph process development).

Polymorph screening

Ricerca uses robotic equipment to perform solvent recrystallization for evaluating APIs for polymorphism. The recrystallized solids are analyzed by powder X-ray diffraction to determine if different crystalline forms exist. Any additional polymorphs can be characterized and produced in amounts sufficient for additional characterization studies.

Pseudopolymorphism (hydrates & solvates)

The chemical and physical properties of pharmaceutical solids also depend on moisture content. Many compounds undergo changes in hydration state with corresponding changes in ambient humidity. Because water vapor is present during virtually all facets of pharmaceutical development, a fundamental understanding of the relationship between water sorption and relative humidity is necessary. Water sorption isotherms are generated by monitoring water content as the relative humidity is manipulated. X-ray diffraction and thermal analysis are used to determine if different states of hydration exist. Compounds exhibiting multiple hydrated states are often referred to as pseudopolymorphs.

Polymorph process development

Ricerca has the process development and engineering capabilities to develop a robust process for the production of the desired form of a given drug.

Polymorph characterization

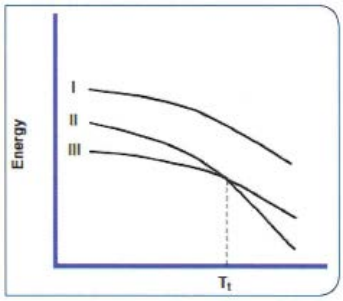
Ricerca characterizes polymorphic active ingredients by determining the chemical and physical properties of each form. The thermodynamic hierarchy of the polymorphs is evaluated to provide insight into the stability relationships among the different polymorphs. The spectral and powder characteristics of each form are also determined. Solubility, dissolution rate, bioavailability and pharmacokinetics of each polymorph can also be characterized.

An example of a stability hierarchy for a compound having three polymorphs is shown to the right. Under ambient conditions, generally only one polymorph is stable. All other solid state forms are metastable relative to the stable form. Characterization of polymorphs at Ricerca includes determining the energy (or stability) relationship among different polymorphs of a given active ingredient. The polymorph with the lowest energy at any temperature is the most stable form.

Analytical Techniques used in polymorph investigations

- X-ray diffraction analysis
- Thermal analysis
  - Differential Scanning Calorimetry (DCS)
  - Thermogravimetric Analysis (TGA
- Particle morphology characterization
  - Scanning Electron Microscopy (SEM)
  - Polarized light microscopy/ birefringence
  - Hot Stage Microscopy (HSM)
  - Particle size distribution
- Solid state FTIR spectroscopy
- Sorption isotherm analysis
- Karl Fischer (KF) analysis
- Vapor pressure analysis
- Heat capacity measurements
- Solubility relationships
- Dissolution rate studies
- Slurry conversion studies
- Bioavailability Pharmacokinetics

Stability hierarchy for a polymorphic system



An energy plot of an active pharmaceutical ingredient having three polymorphic forms. The form with the lowest energy is the most stable form. The plot shows Form III is the most stable form below the transition temperature (Tt) while Form II is the most stable form above Tt. Form I always has more energy than the other two forms.