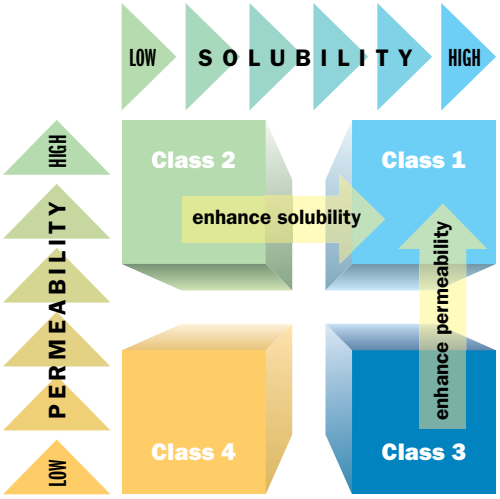
Formulation development for small molecules — liquid or lyophilized products

The formulation development process characterizes the physiochemical characteristics which are unique to each molecule, such as solubility, stability, and permeability. Formulation development will inform those characteristics as well as mode of administration, market demands, manufacturing process, and product costs. Following the development of a suitable analytical method, formulation research and development can be executed and includes the following tasks:

- Intrinsic solubility
- Solubility and stability in key physiologic fluids
- Solubility and stability with respect to pH (for molecules with ionizable groups)
- Effect of buffer species, ionic strength
- Hygroscopicity
- pKa, partition coefficient
- Thermal properties via differential scanning calorimetry (DSC)
- Moisture content by Karl Fischer (KF), loss on drying
- API stability studies and forced degradation studies
- Excipient selection and screening via compatibility studies
- Dissolution optimization
- Compound stabilization
- Design of various dosage form prototypes
- Short-term accelerated stability studies on prototypes
- Determination if lyophilized drug product is required
- Sterilization studies
- Container-closure compatibility studies
- Characterization of clinical dosing: dilution studies or dose recovery
- Optimization studies to justify formulation composition and process
- Real-time and accelerated stability studies of drug product and placebo

A molecule's solubility and permeability are two parameters that characterize the molecule with respect to the FDA's Bio-pharmaceutics Classification System; i.e. the BCS Class of the molecule. The following figure represents the BCS system and how formulation may generate Class 1-like properties.



Knowledge about the molecule's BCS category will inform formulation development efforts and correlate *in vivo* performance. Furthermore, formulation development can enhance the molecule's bioavailability by improving solubility (for Class 2 molecules) or permeability (for Class 3 molecules). Low solubility, low permeability, low dissolution rate, and susceptibility to first-pass metabolism in the liver comprise the primary set of reasons drugs fail on the path from discovery to market.

To enhance solubility, strategies may include selection of a (different) salt form, reduce particle size, or include surfactants or encapsulating agents in the formulation. To enhance permeability, strategies may include the use of cosolvents or other absorption enhancing excipients in formulations, liposomal formulations, or semi-solid (hydrophobic) capsules.

SP Formulations (SPF) carefully reviews the generated data with clients to identify pathways forward to a formulated drug product. If data does not reveal adequate stability in solution, a lyophilized product can be developed. The development of a lyophilized drug product, including cycle development, takes into consideration the unique thermodynamic properties of the API to deliver a successful formulation. This includes a robust and scalable fill solution, an efficient cycle that reliably provides the lyophilized product vials, a readily transferable process, as well as optimized product stability and reconstitution characteristics.

The goal of formulation development is to obtain a rational formulation strategy — both the product and the process — that meets client needs in regulatory planning, market strategy, and commercialized product costs. Weekly reports support documentation needs prior to the compilation of the final project report. Portions of reports are frequently incorporated directly into filing documents. When clients contract the SPF team, they obtain access to decades of experience in formulation development across all stages of drug development, including discovery, preclinical and clinical phases. The SPF team also has extensive experience in IND, IMPD, and NDA filings.

www.spformulations.com
SP Formulations, LLC
790 Main Street
Wareham, MA 02571-1037
Phone: +1·508·273·2236
Fax: +1·508·273·0452
Email: info@spformulations.com

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SP Formulations