

Preformulation

**The Institute of Pharmaceutical Innovation offers
contract research services and consultancy
expertise in
Preformulation**

**For more information on availability and cost
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Preformulation Package

- Preformulation is an exploratory activity that usually begins early in late discovery/early pharmaceutical development
- Data obtained from these studies provide the necessary groundwork to begin formulation development
- Successful formulations take into account a drug's interactions with the physicochemical properties of other ingredients (and their interactions with each other) to produce a safe, stable, beneficial, and marketable product

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According to the Product Quality Research Division of the US Food and Drug Administration (FDA), the goal of preformulation is to

“investigate critical physicochemical factors which assure identity, purity of drug substances, formulatability, product performance and quality.”

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The IPI preformulation package includes study of:

- Solubility
 - Aqueous – intrinsic solubility, pH dependence, bio-relevant fluid solubility
 - solubility in solvents and pharmaceutical vehicles
- pK_a – solubility control, salt formation
- Partition coefficient (lipophilicity) – LogP, LogD

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- Crystal properties (crystal form, morphology, size, surface characteristics)
- Salt selection – To control dissolution, hygroscopicity, stability, handling properties
- Complete physical and chemical characterisation
- Assay development
- Small scale drug stability evaluation

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Solubility:

- To develop a pharmaceutically acceptable drug, solubility in aqueous fluids greatly influences the rate and extent to which drug is absorbed from a number of routes of administration. The solubility of a compound in pharmaceutical vehicles also dictates the ease to which a formulation can be developed.

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pK_a :

- pK_a determination is essential during solubility profiling as it allows the informed use of pH to maintain solubility and choose salts if required to achieve 'good bioavailability' from the solid state and improve stability and powder properties.

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Partition Coefficient:

- The partition coefficient ($\log P$) or distribution coefficient ($\log D$) is a measure of partition between two immiscible solvents.
- The solvents are usually water and octanol.
- Hence, both the partition and distribution coefficients measure how hydrophilic ("water loving") or hydrophobic ("water hating") a chemical substance is. This can provide information to help in predicting membrane permeability, tissue distribution and affinity for pharmacological targets.

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Crystal properties:

- Many pharmaceutical solids can exist in different physical forms i.e., polymorps and pseudopolymorphs
- Polymorphism is often characterised as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice
- These different forms, while similar in chemical structure, possess different physical and chemical properties that may affect solubility, stability, processability and bioavailability

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Crystal properties:

- Additionally, water or residual solvent may become incorporated into the crystal lattice of these materials resulting in pseudopolymorphic forms, referred to as hydrates (water) or solvates (solvent), which may both possess different physical and chemical properties than the non-solvated compound
- Crystal form is important in pharmaceutical drug development, as the crystal form can dictate the processibility, stability and bioavailability of a drug product

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Crystal properties:

- A number of methods are employed at the IPI for the characterisation of crystal forms, including x-ray diffraction, microscopy, thermal analysis methodology, solid state NMR and Raman spectroscopy.

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Crystal properties – salt selection:

- A major improvement in dissolution rate, bioavailability and physical and chemical stability can be achieved by selection of a salt
- Salt formation is another mode of modifying the physical and chemical properties of active pharmaceutical ingredient
- By testing a mixture of counterions, solvents and crystallisation conditions, we are able to find stable crystalline salt forms, which will differ in their physicochemical properties and suitability for development

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The IPI considers different criteria when selecting an acid or base for salt formation. The type of salt to be prepared is dependent on the chemical properties (pK_a) of the drug and the counter ion, the mode of preparation, the safety of the counter ion, and the route of administration. The yield, rate, and quality of crystallization, as well as cost and availability of conjugate acid/base are some of the things considered during the salt screening process.

Assay development

- The majority of preformulation method development is chromatographic with differing detection mechanisms:
 - HPLC with UV, DAD, ELS and MS detection
 - GC with FID, TCD and ECD
- Specialised method development can also be performed using Capillary Electrophoresis and Supercritical Fluid Chromatography
- The analytical programme consists of
 - Method development
 - Forced Degradation studies
 - Validation

Drug stability

- To determine the stability of a drug substance in preformulation studies, it is usual to expose it to high stress conditions to enhance its deterioration and therefore reduce the time required for testing (high temperature, humidity, light, oxidation etc). This enables an understanding of the relative stability of different molecules but also gives information on potential degradation pathways
- Small scale stressed accelerated drug stability can be conducted at the IPI

Conclusion

- Preformulation studies have a significant part to play in anticipating formulation problems and identifying logical paths in both liquid and solid dosage form development.
- The IPI offers a complete preformulation package that is tailored to the requirements of the client.
- At the IPI not only do we offer preformulation studies, we can also provide a full consultancy service with complete project management for every stage of your pharmaceutical development process

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