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Characterizing drug substance properties early can optimize drug product formulation

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Abstract

Early on, the Drug Substance (DS) manufacturer will provide a wealth of preliminary characterization data. If the drug is active in early nonclinical and preclinical testing, a larger quantity of the DS will be prepared for more comprehensive animal safety and pharmacokinetics studies. These studies may require up to several hundreds of grams (sometimes a kilo) of purified DS with low levels of impurities and residual solvents that meet global regulatory standards.

Changes in the DS process as it scales up can affect the Drug Product (DP). As processes change, many properties of the DS can also change: its purity, potency, by-products, particle size distribution, morphology (crystal shape and structure), and rate and extent of dissolution.

Therefore, as DS manufacturers evaluate and optimize the synthetic route, process conditions, crystallization solvents, etc., they must understand and track these changes, and discuss them with DP formulators to anticipate challenges in formulation. DS characterization is critical to DP formulation but characterization and formulation are often not integrated during drug development. Needless difficulties can be avoided if DS chemists and DP formulators... clinical studies, saving time, money and avoiding rework.

Siloed development is neither efficient nor effective

Traditionally, DS and DP have related but distinct deliverables. The end-product for a DS development team is a pure chemical substance produced in five to 12 synthetic steps; the end-product for a DP development team is a patient-friendly drug. For DP formulators, the DS team's end-product is their starting point.

Typically, the industry has been conservative in characterizing the full properties of the starting material for the DS: a minimum number of tests are conducted to suit the requirement of the immediate next step, such as preclinical toxicity or animal exposure studies. This is unfortunate. As molecules become more difficult to formulate, this sequential, compartmentalized development model is no longer adequate.

DS and DP functions must collaborate on a sound formulation strategy

Early stage, pure DS is ideally suited for characterization tests which can catch problems early by identifying properties that could dictate future formulation choices.

Yet developers routinely assume the preclinical period is too soon to consider formulation, reasoning that "We are not formulating yet; we are just identifying challenges before we trip over them."

A systematic DS characterization should include a series of critical formulation-enabling tests, and establish a thorough understanding of a molecule's properties to flag issues that can be addressed early in the clinical stages.

A detailed DS profile can help DP formulators craft a strategy to make sure, for example, that the DS will not get degraded in the GI tract. A forced degradation study can ensure a molecule is protected via its formulation.

For example, recently a company produced a DP formulation in parallel with the human Phase I clinical study, based on a truncated DS characterization effort (shortened to reduce overall development time).

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The resulting formulation was a DS blend in a capsule, packed in blisters for stability. However, after one-month stability data showed that the DP had degraded, a thorough investigation and root cause analysis revealed that the DS was degrading due to alkaline conditions, and in response to exposure to a specific range of light.

Due to the rushed timeline and incomplete characterization effort, there were no baseline characterization data available that demonstrated the stability of the DS in different pH conditions, or in the presence of different intensities of light. This was an avoidable mistake that required reformulating the DP and slowed development. Systematic testing could have prevented it.

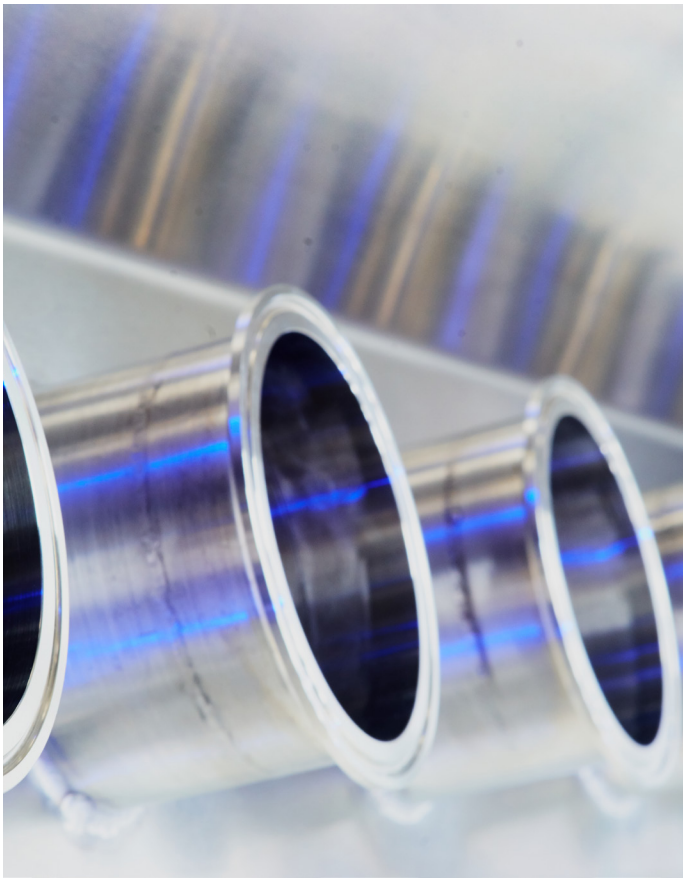
Data from forced degradation studies enable chemists and formulators to understand if a DS is stable under acidic or alkaline pH buffers, as well as in accelerated conditions of light, heat, humidity, and exposure to oxygen.

If a systematic forced degradation study on the DS and DP had been carried out early on, the formulators could have designed the DP with excipients to stabilize the DS in an alkaline environment. And if a DS were sensitive to light, it could be formulated in a capsule with light protection, or in a tablet with an opaque coating.

It may need to be manufactured under specific lighting conditions. For example, a recent case study of a DS revealed that it was stable under red light but not yellow.

As a result, handling the DS in the lab, as well as during manufacturing, was only done under red light to maintain DS stability in the DP, and to avoid any degradation and the formation of photo-catalyzed impurities.

Here are some crucial DS properties that can inform and improve formulation strategies, but only if the testing is done in a timely fashion and results are communicated.



Properties critical to formulation that are not often available early (but should be)

- **Aqueous and pH solubility:** Solubility of the material in acidic, neutral, or alkaline pH buffers helps DP formulators know whether the molecule is stable at the pH ranges prevailing at its intended site of release, absorption, or permeation. A formulator can use this information to modify the pH of the microenvironment to improve solubility of the DS, or prevent precipitation in biological fluids of certain pH ranges.
- **pH stability:** The stability of a DS under various pH conditions is as important as its solubility. Formulators can add acidifiers or alkalizers to stabilize the DS in the relevant dosage form.

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- **Partition coefficient (log P, log D):** This tells the formulator if the molecule will dissolve better in a lipid or an emulsion. For poorly soluble lipophilic compounds, formulators can develop a lipid-based formulation, using surfactant, self- emulsifying systems, or other techniques. If a compound has better solubility in lipids than it does in aqueous buffered solutions, formulators can perform a systematic lipid vehicle screening test using phase diagrams to understand its solubility in mono, binary, or tertiary solvent mixtures, and then formulate a dosage form better suited to deliver the drug without precipitation. A systematic lipid digestion screen can ensure solubilization/emulsification of the drug in biological fluids on administration.
- **Ionization constant (pKa)**: The pKa of a drug influences many biopharmaceutical characteristics such as lipophilicity, solubility, protein binding, and permeability. These in turn directly affect pharmacokinetic characteristics such as absorption, distribution, metabolism, and excretion.

For instance, a molecule can be modified to link to a certain protein, such as complexation, or salts such as chloride or maleate. Knowing the pKa is important for salt screening, an early step in determining which candidate to advance (or terminate). It also helps formulators optimize drug delivery.

Different salts of a free base may have different solubilization, absorption, and stabilization properties. A systematic salt screening of a DS in early stage is key to identifying the right salt to use to take development to the next steps.

Other physico-chemical properties critical to formulation

- **Particle size and morphology:** The size and shape of particles determine their surface area and density, which in turns influence the flow of powders. While the shape of many crystalline substances changes due to the conditions of crystallization, crystal size is primarily a function of the rate of cooling. Limiting size to a narrow range can ensure uniform blending with excipients in the formulation. Particle size also affects solubility; micronization is a common first tool to apply to poorly-soluble substances. The dose of the drug and the drug loading both impact formulation. For example, a low-dose drug or a highly potent drug administered at a very low concentration are both examples of drug candidates at high risk for problems in blend uniformity, "content uniformity," and segregation/non-uniformity in the finished product. A high-dose formulation or a high loading dose formulation present fewer challenges in terms of blend uniformity, but increase the risks of product processing and compressibility problems. Particle size distribution becomes more important as the DS is formulated into the DP.

- **Stability under forced degradation:** The stability of the DS under accelerated conditions of acidity, alkalinity, light, humidity, and temperature is important to formulation of the dosage form. Knowing it helps the formulator select the right ingredients and excipients, as well as the process conditions that will ensure stability of the product during manufacture.

- **Long-term stability:** The stability of the DS under ICH conditions over a longer period also helps formulators select excipients and process conditions that maintain the stability of the product during manufacture, and in subsequent storage.

- **Hygroscopicity and water sorption:** If the drug substance absorbs moisture under ambient and plant conditions, it will need to be protected from normal humidity. It is also important to know the degree of moisture pick-up, and if it is prone to convert to hydrates, solvates, or to other polymorphs. Different solvates, hydrates, or polymorphs of the same parent drug can have different solubility, rate of absorption, or stability profile characteristics. A Dynamic Vapor Sorption (DVS) study can help understand the molecule's sorption and desorption properties under various humidity levels.

- **Flow properties:** Bulk and tapped density are important for formulators because they indicate the flow of powder into the dies of a high-speed tablets press, the potential of the blend to segregate, and its potential to have compressibility challenges. When a DS exhibits poor flow characteristics, formulators can select excipients that improve flowability—e.g. Fast Flo lactose/MCC)—or reduce the inter-particulate forces with colloidal silica, among other substances. They can select process steps that adjust the particle size of the blend, such as wet or dry granulation. Flow properties become more important as you scale up manufacturing.

- **Compressibility:** It is useful to understand the behavior of the DS under compression. For example, do the particles fracture? Do they deform? Is the material ductile, fragile, and does the blend have sufficient elastic or plastic properties? Based on the answers to these questions, a formulator can add suitable excipients such as cellulose derivatives, dicalcium phosphate, and/or various grades of lactose or mannitol to optimize the compressible behavior of the finished blend for a tablet formulation.

Properties that DS chemists routinely provide (and that are not likely to change)

- **Melting point:** A low melting point substance may need to be handled differently by the formulators during dosage form development.
- **Organic solvent solubility:** Important to understand for specific cases such as if the compound must be spray dried by dissolving it in an organic solvent, or if a solvent-based drug layering or polymer coating is to be applied.

DS chemists and DP formulators must communicate early & often

To succeed in an increasingly complex environment, companies need a more holistic approach to crafting their formulation development strategy.

Ideally, DS chemists investigate properties in parallel with DP formulators, and characterize things that will not change—e.g., log P, log D, solubility, MP, pKa, etc.).

Meanwhile, DP formulators determine the best solution for formulation, and tell the DS chemists what properties they are looking for, such as direct compression, limits on particle size distribution, and polymorphs.

As development proceeds, strong lines of clear and frequent communication can screen out risks because DS chemists can inform DP formulators if something critical has changed. The two disciplines also can collaborate by agreeing on high-risk areas, committing to a sound set of characterization tests, and bracketing the DP characteristics needed or preferred.

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Molecules continue to get more challenging from the perspective of solubility, bioavailability, and exposure. Advances in formulation technologies continue to provide more solutions. Necessity is the mother of invention, but recent inventions have drawn companies into developing more difficult molecules.

It's time to establish effective communications between DS chemists and DP formulators if we are to manage the risks and maximize the rewards of transforming less soluble and less bioavailable molecules into effective new drugs.

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Dr. Kane has more than 25 years of experience in the science and business of taking molecules through the entire drug development process. His extensive knowledge spans early stage development to scale-up and commercial manufacturing, and includes technical transfers between global sites and drug life cycle management. Dr. Kane received his Bachelors, Masters and Ph.D. degrees from the Bombay College of Pharmacy, University of Bombay, India, and served as a post-doctoral fellow at the School of Pharmacy, University of Cincinnati, Ohio. He has also earned an executive MBA from Richard Ivey School of Business, University of Western Ontario, Canada. Dr. Kane is a member of various international pharmaceutical professional organizations, and is often asked to speak about scientific topics on formulation, technology other technical aspects, QbD, etc at major industry events. He has also published many articles in International journals and delivered many talks at meetings and conferences cross the globe.

In his current role, Dr. Kane leads a team of "Subject Matter Experts" to support our clients in developing sound formulation and process development strategies and closely works with the scientific teams at Thermo Fisher Scientific's global sites for execution, provides leadership in the complete development of novel lead compounds and line extensions. He is also responsible for evaluating drug delivery technologies to support the business. Dr. Kane has been an invited speaker at many global conferences, workshops, seminars and training programs and has published several articles, interviews and white papers across the world including North American, European, Japanese and Korean publications.

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