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WHITEPAPER

How can you avoid the fallout from incompatibility between your API and its formulation?

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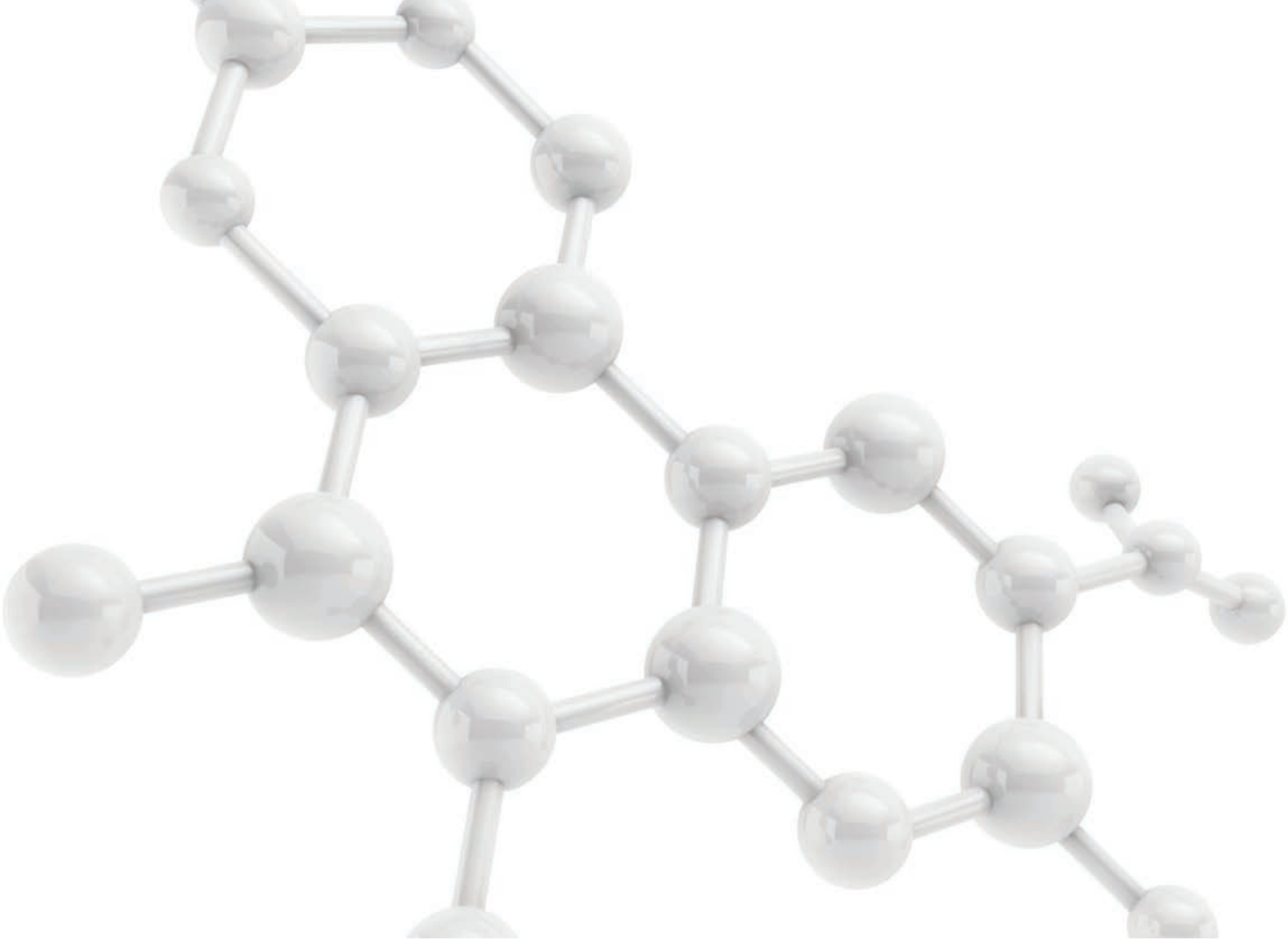

Abstract

In drug development, designing a formulation for a drug product (a tablet, for example) calls for careful attention to both the physical and chemical properties of the active pharmaceutical ingredient (API or drug substance). It also requires awareness that certain physical attributes, such as particle size distribution of the drug substance, can change with processing conditions and changes in the synthesis route that is employed. The formulation, which includes all of the excipients used to make the tablet, ensures the active ingredient is released in such a way as to not only provide the best efficacy for the patient but also protect the drug substance. If the drug substance has unfavorable interactions with any of the excipients, it can have a negative effect on the shelf life and performance of the drug product and can potentially cause harm to the patient.

For these reasons, it is critical the experts creating the formulation are aware of any reactions that can occur between an API and a tablet's excipients. This enables the correct choice of excipients, avoids unpleasant surprises at a later stage and allows the focus to remain upon the manufacturing scale-up of both the drug substance and the formulated product. So what can a pharmaceutical company do to recognize both unfavorable drug substance properties and incompatibility between an API and its formulation? Finding the answer to this question early allows a drug manufacturer to avoid potential risks to the patient as well as costly interruptions during development.

The API characteristics your formulator can not ignore

One of the major difficulties in developing a new drug product is matching the timeline for a drug substance manufacturing development with a drug product formulation. In most cases, the chemists and engineers will have almost completed development of a drug substance manufacturing process when the formulators begin developing the final commercial formulation. More often than not, chemists and engineers finish development under the assumption that their role is complete—an efficient process to manufacture the drug substance to a purity specification has been developed—leaving the formulator to contend with a drug substance that is less than optimal for product development.

This separation, as well as the lack of overlap in processes, can lead to critical knowledge gaps between the chemists and formulators about powder properties. If these drug substance properties are characterized early, it helps to identify and flag any potential issues that may lead to problems in formulation development. This is because the physical and chemical properties of the drug substance have a direct impact upon the formulation requirements for the drug product. For example, solubility and particle size, both physical properties, control the dissolution rate and therefore the availability of the drug substance in the body. Chemical properties can lead to unwanted reactions with other components in the product, resulting in undesired impurities and loss in efficacy or even harmful side effects to the patient.

Without an open line of communication between each team, the development chemists are not fully aware of those factors that have an impact on formulation development; conversely, formulators may not fully appreciate the limits imposed by the manufacturing process on manipulating drug substance properties. In addition to a lack of communication, organizational barriers can also create challenges. Frequently, chemical development and pharmaceutical (product) development are separate organizational units, and good communication is required to minimize the impact of this mismatch in the development timelines.

The following list highlights the importance of a drug substance's physical and chemical characteristics:

- **Solubility**—The solubility of a drug substance in physiological fluids—gastric juice or intestinal fluids—is important as it represents the upper concentration limit for the drug in that environment.
- **Dissolution rate**—If the material does not dissolve fast enough in the body, it simply passes through with no therapeutic effect on the patient. On the other hand, if the material dissolves too quickly, it can become toxic, creating serious safety issues. Achieving optimal absorption of a drug is dependent on the particle properties combined with the formulation it is in.
- **Powder properties**—Mean particle size and size distribution are particularly important because they determine the dissolution rate, which, in combination with the substance's solubility, controls the drug's availability for uptake by the body. They also influence the flow properties of a powder.
- **Flow properties**—Whether a drug substance is free-flowing, like coarse table sugar, or has poor flow properties, like confectioner's sugar, it can have consequences on both the manufacturing process and the product. "Sticky" powders may result in reduced drug substance amounts in the product due to losses in the processing equipment. Poor flow properties of the drug substance-excipient mixtures might lead to segregation of the components and insufficient content uniformity in the individual dose.

While it may seem like, in the case of incompatibility of physical attributes, the easiest solution is to redevelop the final isolation to fit the formulation, extensive changes to a process would likely require additional clinical studies to demonstrate equivalence of the product for approval. Even minor modifications are not feasible once the API manufacturing process has been locked and even registered with the regulatory authorities.

For a small company pursuing a new drug, there may not be funding for additional clinical trials. This could also cause considerable delays in the development timeline, which is something pharmaceutical companies often cannot afford.

With a typical time to market of 12 years, any delay reduces the already short time for recovery of investment once the product is commercialized. Decreasing development timelines by generating the right type of information early in the development process not only expedites a company's ROI, but also, and more importantly, gets the medicine to the patients faster.

One measure to prevent the fallout of incompatibility or unsuitable API properties, and thereby timeline delays, is to align the development of the synthesis and final isolation of the drug substance with the formulation development. Doing so can reduce the need for the two teams to go back and forth to optimize the drug substance properties and improve the formulation.

Yet, many companies struggle to make this transition due to organizational silos that have become common in the industry. Nonetheless, if a company can remove these perceived walls to communication, it can generate necessary collaboration between two groups whose roles are crucial to successful drug development.

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Communication and collaboration: A solution forward

While some may be reluctant to align the processes of API synthesis and formulation because of the perceived risks and costs associated with front-loading development work, it can be argued that the modest cost of gaining good insight into critical formulation-enabling knowledge early is worth the risk. This is especially true when considering that the vast majority of candidates typically fail to make it to market.

According to a recent BIO Industry Analysis study, "the overall likelihood of approval (LOA) from Phase I for all developmental candidates was 9.6 percent and 11.9% for all indications in oncology[1]."

Therefore, a company can potentially face added costs even if it does not create a more aligned approach to API synthesis and formulation, and the cost of a failed drug is sometimes too significant for some companies to overcome.

A simple way to approach this realignment is to create awareness and understanding as well as communication channels between organizational units. Once these channels are open, it is likely the benefits of a more aligned relationship will quickly become apparent. The formulator can now build a substantial base of knowledge from the development chemist or engineer during the design of the final isolation process for the drug substance.

The formulator will also become more aware of what factors have an impact on formulation development. At the same time, the development chemist will have a deeper understanding of the chemical properties of the API, which helps identify possible chemical interactions with the excipients the formulator intends to use.

The alignment ends up becoming a small step toward implementing procedures that can be critical to the overall process. As a result, this communication of information becomes a key to identifying potential issues and working together to resolve them.

Implementing significant changes such as these to a company's procedures can be difficult, and without the money and expertise, it can even be impossible. An alternative is to seek a CDMO partner that has already considered and addressed this issue.

Working with an experienced partner obviates the need for time-consuming and potentially disruptive organizational changes. It also allows rapid gain of understanding and time by making full use of your partner's knowledge and experience when defining the best strategy for a seamless development from drug substance to drug product.

References

1. Biotechnology Innovation Organization (BIO), Clinical Development Success Rates 2006-2015—https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf

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Matthew Jones joined the Thermo Fisher Scientific Linz site in 2016 and has over 25 years of experience in crystallization process development and solid state characterization. He has 12 years of pharmaceutical industry experience and has developed numerous crystallization processes for small molecule APIs for isolation, purification and particle engineering. Since joining Thermo Fisher, Matthew has established and manages a dedicated crystallization process development laboratory supporting chemical development and manufacturing across API manufacturing sites in Europe and the USA. He has also guided the modernization of and recruitment of experts for the solid state analytical laboratory in Florence, SC, establishing a state-of-the-art facility. Matthew has extensive experience in technical protein crystallization working as an assistant professor under Prof. Joachim Ulrich at the Martin-Luther-Universität in Halle, Germany. He is the author of over 50 publications, 2 patents, several book chapters as well as a book on industrial crystallization of proteins.

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