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DEVELOPMENT AT OUR CORE

API in capsule vs. the Lost Art of Formulation Todd Daviau, Ph.D.

API in capsule vs. the Lost Art of Formulation

Very few businesses have as specialized a set of needs as those in the pharmaceutical sector. The combination of huge product development costs, large amounts of data and intense regulatory control makes it critical for companies to have needed information as soon as possible in order to meet a varied and closely monitored set of business processes.

Time is money – a fact well understood by those in the pharmaceutical industry, where developing a new product can take almost a decade and cost hundreds of millions of dollars. Avoidance of costly and time-consuming product development is, therefore, quite desirable for drug companies in the race to bring products to the marketplace before competition. API in capsule might then offer an appealing pathway alternative.

This route permits companies to obtain critical clinical trial data before the added expense of formulation development and in particular, excipient compatibility and process optimization experiments are performed.

Over the last few months we've had several new clients come to us to resurrect formulation development projects that had begun their life as API in bottle- or API in capsule- projects. This brought us to question: "Is API in capsule slaying the artists known as formulators"?

In a day and age where critical "go/no-go" and long-term development decisions are based on early success in order to receive follow-on tranches of venture capital financing, it should come as no surprise that limited financial resources are forcing pharmaceutical companies to do more with less. In other words, decisions regarding the fate of new chemical entities are more often than not, based on bottom lines.

We understand the dilemma - Not wanting to be the "decision bottleneck", pharmaceutical development teams have implemented API in capsule as an option for supplying drug product to meet aggressive Phase I clinical study start dates. Precision equipment that can accurately fill hard gelatin capsules or vials with neat drug substance, have become an often over-utilized approach to meet aggressive timelines and cost reduction pressures.



However, the old adage that “nothing in life is free” applies in utilizing such an approach. The short route of API in capsule, either manually or through the use of automated filling equipment for early clinical studies may defer, but it will not eliminate the need to conduct formulation development and process optimization. It is therefore critical to weigh carefully the impact on the overall development plan (as well as cost and time) of using neat drug substance filled capsules/vials vs. a formulated product in early studies:

- **Neat dosing of drug substance can result in greater total development costs.**

- Since the API in bottle/capsule approach only defers the downstream pharmaceutical development work needed to supply later phase clinical and commercial product, it is additive to the total development costs. The added costs are typically minor when taken in context of a typical development program, but should be recognized as not providing a formulation “free ride” through development.

- **Neat dosing of drug substance may result in greater total development time.**

- Because excipients and other downstream manufacturing processes may alter the drugs pharmacokinetics and oral bioavailability, formulation decisions based on neat API in capsule projects may cause decisions to be made that detrimentally affect downstream development. This may lead to added time and the need for additional excipient compatibility studies or additional bioavailability studies during critical downstream development.

- **Not all APIs are suitable candidates for neat dosing into capsules.**

- Because of the absence of a tamping mechanism on most API in capsule machines, the actual amount of powder that will fit in a capsule may be limited by the powder's physical characteristics. In some cases, neat drug substances may require preprocessing to increase density and enable high-dose API in capsule. High-dose capsule filling also poses challenges because of the inability to use material bulk density to accurately predict allowable capsule fill weights. The allowable fill weight in a particular capsule size depends on the materials physical characteristics which may be limited by the instruments filling mechanism.

Excipient compatibility studies should be done with capsule material anyway.

- Since excipient compatibility studies should be performed between the API and the capsule material, it only makes sense to begin excipient compatibility studies as early in the process as possible. A carefully designed excipient compatibility matrix should not take any more time on stability than that of API and capsule material(s). Added costs, of course, would be a result of the additional analytical time.

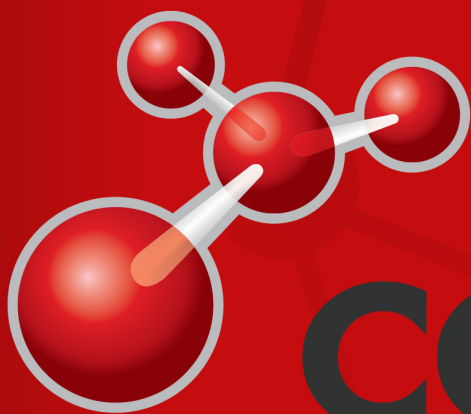


- **Not all drugs are suitable candidates for neat dosing of drug substance.**

- Before a client contemplates an API in bottle/capsule project, it is imperative that physicochemical properties of the drug substance be evaluated for suitability to the approach. Drugs with inadequate or limited bioavailability may require formulation intervention to achieve adequate bioavailability and/or improve adsorption kinetics. In addition, an increase in drug bioavailability due to formulation can significantly decrease the quantity of drug substance required to supply clinical studies. Since the supply of drug substance can often be rate-limiting in the initiation of early clinical studies, removing this drug substance bottleneck can actually decrease the time requirement to enter larger studies and significantly reduce program costs for drugs with complex and expensive manufacturing processes.

In the world of contract pharmaceutical research & development, success hinges on two things: the ability to produce quality drugs that meet all the necessary requirements and the ability to do so quickly. More often than not, the two are inextricably connected. However, in the final analysis, the strategic and tactical decisions for conducting a pharmaceutical development program become ever more complex as the business, regulatory, and scientific demands escalate. The manufacturing of early clinical supplies by automated dispensing of neat drug substance into capsules or vials may provide an attractive approach to shorten the lead time for acquiring essential clinical data. However, the downstream implications for later stage development must be carefully weighted in light of the total picture of corporate needs.





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