White Paper

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STABILITY ISSUES RELATED TO SOFT GELATIN CAPSULE DEVELOPMENT

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Stability issues are a challenge and never ending concern for formulators. The reactivity of formulations depends on many factors but it is generally recognized that labile drugs in aqueous forms are sometimes the worst cases and in this regard, this should be a true statement for the development teams which work with SGC´s. Although product development has been described by many authors as a cycle, we would refer to it as a tower, where the main pillar is the preformulation phase. Most of the reference information about API´s and excipients is gathered at this stage in order to guide the next steps and to build the product file. What it was not said to the industry was that based on that definition, preformulation would be high consuming in time and in resources, in order to guarantee success at the final product. It was only said many years later when QbD concept was introduced!

It would help to illustrate the concept, thinking about the preformulation phase as the way to solve the incognita ABC through the equation: A+AC+B+BC=ABC, being A the fill formulation, C the stability conditions (temperature, humidity), B the gelatin formulation and ABC the softgel product. In the same way, since the gelatin softgel is a primary packing for the medicine, it would also help to apply the same reasoning of packing development to formulation development. In packing, some attributes such

as size (which sometimes is not considered relevant to formulation) could be associated to sealing problems. In this approach, the packing material (providing contention, protection and mechanical resistance, among others) is as important as or even more so than the product itself and must be adequate for both product and packing process. All of the details about packing materials such as properties, applications and limitations are the starting point for development. Why it is not the same criteria applied to gelatin formulations since it is the primary packing of the drug? Moreover, criteria to decide which packing material to use depends on product specifications (i.e. size, hardness, color, photosensitivity, flow, drug liability to temperature and humidity) and the same should be applied in regards to the fill formulation (i.e. pH, ionic force, flow properties, etc).

Formulation of pharmaceutical products has been considered a tailor-made approach for each product and based on it, defining a formulation guide is somewhat controversial. However, to stablish a guide with multiple considerations on formulation is a great help as the first step to discard predictable incompatibilities and to avoid the most common formulation non-compliances. On the other hand, some incompatibilities are difficult to detect at a lab scale. Usually, there is a constraint to obtain capsules at small scale, test the system as a whole and evaluate migration phenomena, one of the main causes of most of the defects presented in softgels (dissolution non-compliance, opacity, blooming, etc).The question in the air is What to do, then? What are the lab tests and the analytical tools that help to make it easier?. Shortcuts are highly desirable and we have driven some efforts to simplify preformulation studies as much as possible.

Based on our experience and depending on product complexity, preformulation phase accounts about 40-60% of the budget and the timeline of a Project. Moreover, a question would be: HOW MUCH time is foreseen to cover difficulties in preformulation? Here, using a weighted punctuation for the product complexity to estimate formulation times would be a recommended approach.
Another concern in the way to make preformulation as profitable as it could be, is to determine if lab tests correlate well with pilot scale (adding more work!!). Here, what we could say is that it could be reliable at least to test the excipients, when process parameters are kept as controlled as possible at lab scale.

WHO are the partners that help to build that knowledge? Invite your suppliers, analysis labs and costumers of contract manufacturing to participate since they have already faced similar or worst cases and therefore they could advise about critical points to consider on preformulation designs.

At Procaps, we started the QbD framework some years ago and what we learned about gelatin preformulation is the importance of consolidating the lessons, building the decision diagram and feeding the formulation bank including the criteria for the selection of a gelatin formula or another in a general basis as well as in some specific cases. QbD approach offers the exploration space to cover the most relevant aspects of development. However, in the future if you do have to review the process you will have the knowledge and know how to overcome the most probable causes of non-compliance. In brief, it is for sure a matter of time: the saved time from non-compliances and reformulation!

Finally, as the purpose of this space to share knowledge and experiences, we would like to hear from you about the questions planted above as well as your particular questions. To learn more insights on this matter join us in our upcoming webinar on Application of QbD principles in the development of the gelatin shell formulation of softgels.

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