Best Practices for Successful Softgel Development:

AVOIDING COMMON PITFALLS

INTRODUCTION

While soft capsules have seen nearly a century of industrial-scale production, they remain among the least comprehended dosage forms. Each soft capsule formulation represents unique challenges and requires a sound understanding of the excipient palette, process factors, analytical and regulatory aspects for successful development.

In this report, we have summarized our learnings from numerous soft capsule development projects.

PITFALL 1: NO SHELL FORMULATION SCREENING

Often customers are offered standard gelatin formulations based on the experience of the CDMO. In some formulations where only limited interaction between capsule shell and capsule fill can be expected, testing only few shell variants may be sufficient. However, for others this approach may cause substantial time losses due to the selection of inappropriate prototypes. Consequently, it is crucial to consider a broad variety of potentially suitable gelatin and plasticizer variants early in development.

PITALL 2: INSUFFICIENT CONSIDERATION OF COMPATIBILITY BETWEEN FILL AND SHELL

The interaction potential between capsule fill and shell is frequently underestimated. Especially in the case of drug substances with poor solubility and/or bioavailability challenges, the focus is often placed on the development of a suitable fill formulation without considering compatibility with the capsule shell. In case the capsule shell development is initiated only after pre-clinical or even clinical studies have been performed

on the fill mass, the task of finding a suitable shell may become challenging.

PITFALL 3: SELECTION OF CAPSULE FORMULATIONS BASED ON NON-REPRESENTATIVE TRIALS

Companies are sometimes tempted to omit a broad formulation screening programs on capsules and try to evaluate stability and compatibility based on mixtures of capsule fill and shell components. While this approach may give some indications of incompatibilities, it can never provide a complete view, thus wasting time and budget. Initiating a wide encapsulation screening program as soon as possible during development based on a preliminary risk assessment can therefore oftentimes be the more yielding approach.

PITFALL 4: SAVINGS ON STABILITY TESTING

One of the mistakes with the largest impact, cutting corners during stability testing often comes at a high cost. Skipping the analysis of some parameters entirely, especially some physical attributes, or discontinuing programs and removing prototypes from storage too early, may result in critical gaps in product understanding.
It is advisable to carefully select the parameters that may be impacted by storage conditions the most, and to store sufficient sample amount for a longer duration of the study.

PITFALL 5: OVERDISCRIMINATING OR INAPPROPRIATE DISSOLUTION METHODS

As USP apparatus 1 (basket) and 2 (paddle) are the most widely available and often used for

solid oral dosage forms (tablets), they are frequently selected for dissolution testing of soft capsules as well. However, as opposed to tablets, capsules must rupture first to release the fill. The capsule fill is furthermore often a lipophilic liquid that is not miscible with the dissolution medium. Thus, for many capsule products artifacts may be generated due to inappropriate hydrodynamics in basket or paddle apparatus or clogging of the basket mesh.
The three main product variables that impact the dissolution of capsules, i.e. rupture of the capsule shell, dispersion of the fill and solubility of the drug substance, have to be reflected adequately during method development.

USP Apparatus 3 (reciprocating cylinder) and 4 (flow-through cell) have been found superior to apparatus 1 and 2 in some cases, for example in capsules containing lipid solutions or suspensions.

It is therefore recommended to evaluate these less common apparatuses during method development to avoid analytical artifacts and overdiscriminating at a later stage.

PITFALL 6: INAPPROPRIATE PACKAGING

While oxygen exposure is typically not a critical issue, soft capsules are highly sensitive to moisture; their shell takes up or loses water until equilibrium with the ambient atmosphere is reached. In case of excessive water uptake, the shell may become too soft, and capsules may form agglomerates; changes in chemical parameters can also be observed. On the other hand, in case the shell loses water in a dry environment, the capsules may become brittle. It is therefore crucial to select appropriate packaging materials with sufficiently low water vapor permeability for the target climate zone. Caution is advised especially for packaging in materials with high WVTRs such as PE-bags or PVC-blisters.

PITFALL 7: NOT CONSIDERING THE EFFECT OF CAPSULE SIZE IN DOSE-PROPORTIONAL FORMULATIONS

When multiple dosage strengths are developed, the capsule fill is typically formulated in a dose-proportional way. However, true dose proportionality is not possible in the shell composition, as the ratio between fill and shell mass decreases with increasing capsule size. Consequently, the dosage strengths may behave differently in terms of physical properties and even dissolution. The development data generated on one (typically highest) lead strength is not always transferable to the others, an aspect that is often noticed in a late stage of the development.
Including all dosage strengths early in the development program is therefore recommended, especially in critical formulations.

PITFALL 8: UNDERESTIMATING IP ASPECTS

Engaging a CDMO for softgel development without securing complete IP rights often stems from a lack of clarity regarding the long-term implications. Without full ownership of the IP, customers may find themselves constrained in product modifications and supply chain security. For example, some softgel manufacturers use their own DMFs for the shell material, thus limiting the transparency of composition and process. The client's regulatory freedom to operate is therefore also limited. Companies should therefore request full transparency of the implications of the proposed IP rights distribution before subcontracting development services.

THIS IS HOW CAN WE SUPPORT YOUR SOFTGEL PROJECT:

- We prepare risk-based formulation development concepts in consideration of the entire capsule
- We utilize the appropriate shell excipient palette for the capsule fill right from the start of development
- In complex softgel development projects, we take lead formulation roles within the development team and manage CMO activities
- We bring specialized analytical expertise for characterization of common quality issues in soft capsules
- We help you bring the right partners for analytical, manufacturing and regulatory activities for a successful softgel development
- We help prepare the CMC sections of IND/NDA/MAA files for softgel products in CTD format
- We support troubleshooting activities

INTERESTED?

CONTACT US AT INFO@SOFTCAPS.SCIENCE AND TELL US ABOUT YOUR PROJECT.

AND DON´T FORGET TO VISIT OUR WEBSITE FOR MORE EXPERT RESOURCES ON SOFT CAPSULES.

THE AUTHOR

A pharmacist with 15 years of experience in the development of soft capsules, Yanitsa is expert in formulation and process development. She has managed a variety of R&D, transfer and troubleshooting projects. She has successfully supported numerous clients in solving complex challenges all around soft capsules.

Yanitsa is also a recognized speaker at technical conferences focusing on soft gelatin capsules.

We are independent experts in soft capsules.

Focusing on a systematic approach backed by decades of experience in the development and manufacture of soft capsules, we help companies understand the critical factors and develop robust softgel capsules.
Starting from the concept, we cover formulation, analysis, manufacture, biopharmaceutical and regulatory aspects until submission.