Excipient Selection in Topical Process Development

Conducting in-depth experimentation and assessment with a new product early on provides the formulator with the answers necessary to ensure the later scale-up to commericalisation runs smoothly and successfully

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Semi-solid drug product development presents complexities at every stage, which may hinder process development. These difficulties are compounded by the fact that topical and transdermal process development regularly involves factors that conflict with one another, particularly when changing scale or equipment.

These factors include, but are not limited to:

- Excipient grade and supply
- Temperature
- Type of mixing and mixing tool
- Stirring time
- Homogenisation.

Formulation Development

Once the active pharmaceutical ingredient(s) (API) has been selected and the developer has a target product profile in mind, one of the first steps of topical formulation development is selecting the excipients, and their levels, to be used in the formulation. Initial experimentation typically involves assessing the solubility and stability of the API in excipients, both individually and in combination. This experimentation is often performed in parallel with the assessment and development of a suitable analytical method.

Following API solubility and stability assessment, the formulation vehicle can be designed using those learnings. Based on the target patient population and disease, there may be restrictions on the excipients that can be included in the vehicle. Further limitations may arise depending on the chosen formulation type(s). For example, typically, creams require some amount of water. If the API is not soluble or stable in water, an alternative formulation type may be required to achieve the drug target concentration and still obtain the desired properties of a cream.

While the solubilising and stabilising properties of the excipients are critical, so are the aesthetics. The best-performing product will fall short if there is no patient compliance because the product looks, feels or smells unpleasant. Therefore, thorough vehicle

design takes into consideration the desired performance, target population and target therapeutic indication, all while creating a cosmetically elegant formulation. A range of prototype formulations can then be selected for stability testing and in vitro/in vivo performance testing.

Based on the stability and/or performance data generated, there may be additional formulation optimisation rounds involving alterations to excipient levels or perhaps including new excipients. For example, levels of penetration enhancer may be changed to improve performance, or an antioxidant could be included to help with API stability.

Excipient Considerations

While there may be multiple manufacturers/suppliers and distributors of an excipient, it is important to find the right one. Being the 'right' manufacturer is not limited to price. Consideration should also be given to excipient quality (eg, release specifications testing and a pharmacopeial standard), the supply chain and the relationship that will be developed with the manufacturer.

In an ideal development programme, the same excipient manufacturer would be used throughout all the stages. However, for a variety of reasons, this may not be possible, particularly at the start of development. For example, initial development may use excipient grades that would not be suitable for commercial products. Though this is not preferred, the risks of this approach would need to be assessed on a case-by-case basis.

Once the excipients in the formulation have been narrowed down, it is important to evaluate multiple manufacturers and excipient options. Time constraints and risk evaluation mean this is not always undertaken during the earlier stages of development. However, this assessment becomes increasingly critical the closer the product gets to commercialisation.

Certain excipients are more prone to variation, despite being tested to the same monograph, so it is advisable to obtain multiple batches of excipient (eg, at the high and low end of the product specifications) to determine what will work best when it comes to quality and scale-up. Working in this manner is a quality by design (QbD) approach. QbD aims to build quality into the product from the earliest stage possible to save time and resources in the long term. Being able to assess a range of excipients, such as different batches or from different manufacturers, builds up a design space of knowledge about what will work for the product and where the edge of failure lies.

This approach is increasingly difficult for topical and transdermal products because of the typically high number of excipients used and assessed throughout product development. Since it is difficult to predict every change that may be needed at the commercial scale, generating data about where the product may fail, and understanding the impact certain excipients and their critical material attributes (CMAs) may have on the drug product, makes it easier and cheaper to implement changes later.

Maintaining relationships with excipient manufacturers/suppliers can be crucial to enabling such experiments, as well as for innovation and improvement. Working cohesively with the manufacturer to provide feedback and suggest improvements to an excipient,

or gain further understanding about the excipient manufacturing/storage process, can help to create a more stable final product.

Process Development

The initial batch sizes during formulation development are usually comparatively small, at around 100g. In addition, these early tests may be conducted with excipients that are not the intended final grade, although this is not a recommended approach. On this scale, and with such excipients, difficulties with API solubility may not be apparent. However, at the scaling-up phase (process development), these issues may become more obvious. Therefore, it is critical to have thoroughly screened and understood the excipients and their interactions with the API.

This may be an appropriate stage to start building up knowledge on the batch-to-batch variation of excipients. The solubility of an active compound in an excipient or excipient blend is regularly affected by temperature. It may not be as straightforward as simply heating the excipients, as there may be stability issues to consider. Early stability screening can highlight any stabilisation techniques that may be required, such as an antioxidant or chelating agent. A potential problem with including such stabilisers is that they may inadvertently affect the amount of active compound loading in the formulation as the solubility competes with common solvents.

Stability screening of the initial formulations, combined with forced degradation studies on the drug products, provides valuable information on the types of conditions the API may need to avoid, such as exposure to heat. There are also several excipients that cannot be exposed to prolonged/extreme heat. Heat is a necessary part of the process for some formulation types, like creams and ointments, so the excipient choice is critical. It may be possible to switch excipients for those that can be cold-processed or manufactured to be more thermo-stable.

Design of Experiment

Design of experiment (DoE) can be an important tool to support QbD. Experiments can be designed to investigate some of the previously discussed excipient variations. Using DoE software can help add a statistical element to the experimentation and provide more confidence in the decisions made. The software enables the input of theoretical data, such as altered CMAs of an excipient, to see how that would affect the final product's critical quality attributes (CQAs). If the output is unacceptable, the edge of failure for the process has been found. This data can be used later in the product life cycle to de-risk the implementation of changes.

In addition to exploring excipient variations during DoE, manufacturing variations can also be investigated. As so many variables may necessitate numerous DoE runs, the earlier the work is completed in the development stage, the easier it will be to make later-stage changes. The manufacturing process should always be designed to be as efficient as possible. Some efficiencies can benefit the final product, too, such as using lower heating temperatures. During the manufacturing process, the tolerance of each excipient to shear, and other mechanical forces, must be considered. Identifying excipient CMAs early may shorten the investigation time.

Therefore, it is important to have a thorough understanding of the manufacturing process, how each piece of equipment interacts with the excipients and the impact that has on the final product CQAs. For instance, when homogenising (which is required during the manufacture of creams and some other formulation types) there are a multitude of workheads available, each of which has its own impact on product quality. Understanding how the product behaves with each workhead not only helps narrow down the right tools to use, but also helps to predict product performance with different equipment. This is particularly useful when the development laboratory and receiving sites do not have matching apparatus. Stirring and mixing may seem simple, but, for shear-sensitive excipients/products, factors like the way the construction of the mixing paddle introduces shear, and how this translates across a range of scales and equipment to enable commercial manufacture with minimal downtime, must be taken into account.

Ultimately, choosing which excipients to use and where to get them is not always straightforward. The experimentation outlined helps to finalise the excipient choices as early as possible during the development process. It also gives the formulator as much information as possible about the product so changes can be made without affecting the final product quality. The earlier that the critical processes and attributes are identified, the smoother the product development journey will be, and any changes required closer to commercialisation will be easier and cheaper.

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He joined the formulation development team in 2013. His expertise includes semi-solid product development, scale-up and tech transfer. He has supported the development of more than 50 semi-solid and liquid products over the past decade, with many moving forward to commercialisation.