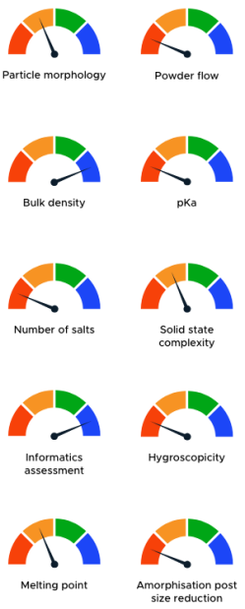
CatSci
EXCELLENCE IN MEDICINES DEVELOPMENT

Your free risk assessment

Your heat map



- Green: It is unlikely to entail excessive cost
- Orange: It is unlikely to increase cost and complexity of development
- Red: It is very likely to increase cost and complexity of development
- Blue: Knowledge gap

Please see our suggested mitigation strategies

Particle morphology

Particles will have poorer bulk physical properties if they have an extreme habit or the native particle is of small size. This may impact formulation performance and the isolation of the API.

Aspect ratio and particle size can both be manipulated by using seeding and better control of supersaturation during the crystallisation. Significant reduction in size can occur during agitated drying so limiting agitation on drying should be investigated.

If the problem challenges the ability to manufacture, then an alternate solid state form might be investigated.

Bulk density

Very low bulk density powders are likely to exhibit poor flow, be more difficult to formulate and present problems in transportation due to the larger number of containers required.

However, higher bulk density powders will exhibit good flow and can be packed and transported efficiently. Aspect ratio and particle size can both be manipulated by having better control, using various techniques that can be used to control the aspect ratio and particle size of powders, such as milling, grinding, and sieving.

By manipulating these factors, it is possible to improve the bulk density of powders and overcome some of the challenges associated with low bulk density powders.

Number of salts

Suggested mitigation depends on your appetite for risk.

If only a few salts have been identified, then the opportunity for a switch of salt form depending on the specific needs and requirements of the API and the manufacturing process.

The number of salts used can vary greatly from one product to another, and can have a significant impact on the performance, stability, and safety of the final product.

Informatics assessment

Informatics may confirm that the most stable form is being developed with limited ability to hydrate or form solvates.

Informatics may also confirm any unusual issues by predicting and confirming the most stable form of the API, and assess its potential to hydrate or form solvates.

Informatics can also provide valuable information on the thermodynamic stability of different crystal forms and the factors that impact their stability, such as temperature, humidity, and pH.

Melting point

Low melting point solids may undergo process induced melting during formulation. This may affect development time.

Melting point could be manipulated by adjusting the melting point of an API, it is possible to optimize its physical and chemical properties and ensure the quality, stability, and efficacy of the final drug product.

However, it is important to carefully evaluate the impact of any changes to the melting point on the overall properties of the API and the final drug product, and to ensure that the changes do not negatively impact the safety and efficacy of the drug.

Powder flow

Poor API flow may cause problems during formulation manufacture.

Aspect ratio and particle size can both be manipulated by avoiding inaccurate or incomplete data: If an API used in the pharmaceutical industry is providing incorrect or incomplete data, this could lead to incorrect drug dosing, adverse reactions, or other serious health issues.

By improving the flow of APIs, it is possible to reduce processing difficulties, improve the uniformity and quality of the final drug product, and increase efficiency and productivity in formulation manufacture.

pKa

APIs having basic sites with pKa of less than 5 are significantly more prone to dissociation

Dissociation risks may be addressed by using excipients in the formulation to control microenvironmental pH. Also, alternate solid state forms may be less prone to dissociation than others.

This dissociation can lead to changes in the physical and chemical properties of the API, as well as its solubility, stability, and efficacy.

Dissociation of basic APIs can result in the formation of cationic species, which can interact with anionic species (such as carboxylates or sulfates) in the environment, leading to the formation of salts. These salts can have different physical and chemical properties compared to the parent API, and can impact its stability, solubility, and efficacy.

Solid state complexity

If the API exhibits a complex solid state landscape then control of desired solid state form may be more difficult.

Development work may be required sooner to address the risk. Investigate if the desired polymorph can be altered to overcome these challenges, various techniques can be used to control the solid-state of APIs, including crystallisation, milling, and solid-state processing. By understanding and controlling the solid-state complexity of APIs, it is possible to improve the performance, stability, and efficacy of the final drug product.

Hygroscopicity

If the API picks up significant water, it may form hydrates.

This may impact biopharmaceutics, stability and manufacturability.

Selection of a desired polymorph can be obtained reproducibly even though the solid state landscape is complex. If control of solid state form is required (for example by following ICH Q6a decision tree) and this cannot be adequately controlled for the solid state form, then an alternate solid state form might be investigated. By managing the hygroscopic nature of APIs, it is possible to improve the stability, performance, and safety of the final drug product.

Amorphisation post size reduction

High level amorphous content can be linked to poorer chemical and physical stability.

Particle conditioning in solvent vapour or size reduction in wet media may be applied so long as filtration is not adversely impacted.

Particle conditioning in solvent vapour or water may be used to recrystallise amorphous content.

In extreme cases, an alternate solid state form may be investigated.