Ardena Insight

Optimising Solubility: Selecting the Right Technology for Early Drug Development

The majority of drug candidates emerging from contemporary drug discovery pipelines exhibit too low aqueous solubility to allow for adequate absorption after oral intake. Formulators have a myriad of technologies at their disposal to enhance solubility or dissolution rate, but there is no such thing as a one-size-fits-all solution. Selection of a formulation approach must be done in light of the physicochemical profile of the drug candidate, its permeability and its dose. In the early stages of drug development, selection is biased towards technologies that enable high payloads, have low manufacturing complexity and high administration flexibility. This document provides guidance to support decision-making when designing oral formulations for poorly soluble drug candidates in early development.

Low water solubility of active pharmaceutical ingredients (APIs) presents varied and significant challenges throughout drug development. The greatest concern is generally the risk of low and variable absorption after oral administration. A wide variety of technologies exist to tackle poor solubility, and in general, these either reduce particle size (nanosuspensions), present the API in predissolved form to the gastrointestinal environment (lipid-based and related systems, cyclodextrin complexes) or utilise high-energy solid forms to generate supersaturation (amorphous solid dispersions).

Application of solubility-enhancing technologies in early drug development presents a number of specific challenges. In preclinical toxicity testing, systemic exposures at doses considerably in excess of the predicted clinical dose are required, which further enhances the need for solubility support. To achieve these high doses, administration via oral gavage is the most straightforward – and in the case of rodent studies often the only – option. In early-phase clinical studies, and especially in Phase 1 studies, clinicians have a strong preference for dosage forms that flexibly enable the administration of a wide dosing range. These considerations of dose and administration flexibility imply that solubility-enhancing formulations in early development are generally liquid. Solution or suspensions formulations indeed can easily be diluted to lower concentrations or be administered in variable volumes to achieve differences in dose.

Nearly all the most widely used solubility-enhancing technologies can readily be processed into a liquid formulation (nanosuspensions, lipid-based systems, cyclodextrin complexes). Amorphous solid dispersions are – as the name suggests – solid products, but can be formulated into a suspension by dispersing them in an aqueous or other vehicle shortly prior to administration (provided that controls are built in to verify that this dispersion procedure does not negatively impact the amorphous character of the formulation). In the table below, a number of criteria and technology attributes are summarised on the basis of which an appropriate technology may be selected.

TECHNOLOGY	PERFORMANCE DRIVEN BY	PAYLOAD	MANUFACTURING COMPLEXITY	TOLERABILITY	PHYSICAL STABILITY	CHEMICAL STABILITY
NANOSUSPENSIONS	Dissolution rate enhancement	High payloads (20–30%) achievable for physicochemically diverse APIs	Moderate	Well tolerated	Some development required to prevent particle growth during storage	Generally good as API is crystalline
LIPID-SURFACTANT-COSOLVENT BASED SYSTEMS	Avoidance of dissolution process. Enhanced solubility in gastrointestinal fluids	Depends highly on API solubility in excipients. May not be suitable for high-melting point APIs	Low	Some excipients may cause side effects at higher doses	No concerns as API is in solution	Worse relative to crystalline form as API is in solution. Multiple excipient-derived degradation pathways possible.
CYCLODEXTRIN COMPLEXES	Avoidance of dissolution processes. Enhanced solubility in gastrointestinal fluid	Depends highly on complexation efficiency, but is rarely in excess of 5%	Low	Well tolerated	No concerns as API is in solution	Worse relative to crystalline form as API is in solution
AMORPHOUS SOLID DISPERSIONS	Supersaturation	High payloads may be achievable in the substrate matrix (20–60%), but re-dissolution required when dosing as a suspension	High	Well tolerated	Generally a lot of development required to prevent crystallisation during storage	Worse relative to crystalline form as API is amorphous

Nanosuspensions are a very attractive option in early development, by virtue of their broad applicability, high payloads and low excipient concentrations. Some development is required to prevent particle size increase (crystal growth, agglomeration) during storage, but an excipient mix that prevents particle growth for the study duration can usually be identified quite rapidly. Despite the need for milling equipment, the production of nanosuspensions is relatively straightforward and readily scaled up. Their performance, however, stems from dissolution rate enhancement, which means that they may be inadequate to formulate the most problematic molecules.

Lipid-based and related formulations (lipid solutions, self-emulsifying systems, solutions in cosolvents and surfactants) circumvent potential problems of slow dissolution from the crystalline form by presenting the API to the gastrointestinal fluids in a predissolved state. The performance risk that needs to be assessed here is the susceptibility of the API to precipitate as a result of dilution (and in the case of lipid-containing formulations: digestion) in vivo. A downside to this formulation approach is that payloads achievable may be too low to be practically useful, especially for APIs with high melting point. In addition, many excipients used to make lipid formulations contain reactive molecules or impurities such as esters, formaldehyde, formic acid, acetic acid and peroxides, which may lead to unacceptable chemical degradation (oxidation, acylation and transacylation). Such problems can be bypassed by dissolving the API in the vehicle right before administration.

Cyclodextrins are sometimes used as solubilisers in early development as well, their main advantage being their higher resistance against dilution-induced precipitation compared to other solubilisation techniques such as the use of cosolvents, where dilution leads to exponential decreases in solubilisation capacity and significantly elevated risks of precipitation. Practical utility of cyclodextrins is largely driven by the binding efficiency of the API with the cyclodextrin, which is highly molecule-specific and rarely leads to formulations with payload in excess of 5%. This usually ecludes the use of cyclodextrin-based formulations in rodent toxicity studies.

Amorphous solid dispersions may be considered a last-resort option in cases where nanosuspensions do not provide satisfactory bioavailability and/or when payloads achievable in lipid-based and cyclodextrin formulations are too low. Many APIs can generally be formulated into an amorphous solid dispersion at payloads of 20% and higher. In terms of manufacturability, however, amorphous solid dispersions arguably involve a high level of complexity as their production requires the use of organic solvents (spray drying) or high temperatures (hot-melt extrusion). Beyond process-related technicalities, a key development challenge is also to prevent – and reliably detect – potential crystallisation that may occur during storage. Administration via gavage presents the additional difficulty that the amorphous solid dispersion should be resistant against crystallisation when dispersed in an administration vehicle.

The potential solubility benefit that each of these technologies may offer should be carefully balanced against the above-mentioned considerations of payload, manufacturability, ease of administration and stability. Further along in development (typically as of Phase 2), the use of liquid formulations is generally abandoned and formulation optimisation efforts are then directed toward processing the dose into one unit of a traditional dosage form like a tablet or a capsule.

At Ardena, we support drug developers in selecting and implementing solubility strategies that not only enable appropriate exposure in early studies, but also lay a solid foundation for downstream development activities.

info@ardena.com
www.ardena.com