Future-proofing Drug Development with Nanoparticle Engineering

Nanoparticle formulations can help to address current and future drug development challenges, from poor bioavailability to the growing demand for patient-centricity, sustainability and scaled manufacturing

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Drug development is a complex and costly process, with challenges including poor bioavailability of active pharmaceutical ingredients (APIs), growing demand for more sustainable practices and patient-centric characteristics, as well as issues associated with scaling up manufacturing and securing supply chains.

Unforeseen hurdles can drastically increase the time and resources needed for a project, so it is vital to maximise efficiency. Working with a development partner can help here.

Alongside a future-focused mindset and a reliable partner, using the latest technologies, such as nanoparticle engineering, can help to address formulation and manufacturing challenges. This combination of innovative technologies and formulation expertise can streamline development and allow patients to receive life-changing medicines more quickly.

Enhancing Bioavailability in Drug Formulations

Many new chemical entities have complex molecular structures that exceed the 'Rule of Five' – a rule of thumb that predicts poor absorption of an oral drug.[1] As a result of the trend for increasingly complex, lipophilic new drug candidates, poor drug solubility is a major issue, affecting approximately 70% of new medicines.[2] Low solubility leads to low bioavailability (referring to the proportion of a drug that enters

circulation and so is able to have an active effect), which can hinder the therapeutic efficacy of a drug substance. This is a common cause of failure for drugs during their development, resulting in wasted time and resources.

By adopting game-changing technologies to address poor bioavailability, more therapeutics can be brought to market to improve patients' lives. This is especially important in light of the increased proportion of elderly patients with multi-morbidity.[3]

A wide array of technologies is available to address the need for increased bioavailability. Spray-drying of amorphous solid dispersions (ASDs) is one of the most common. This technique enhances solubility by disarranging the crystalline lattice to produce a higher energy state amorphous form of the API, stabilised by polymer material.[4] This makes it energetically more favourable for dissolution and therefore increases drug solubility. However, the polymer required adds weight to the preformulated material, which can make it difficult to form tablets or capsules.

Excipient-based approaches involve introducing an excipient compatible with the API to enhance the solubility of the drug product.[5] A common excipient in the pharma industry is hydroxypropyl methylcellulose (HPMC). Low-viscosity HPMC grades act as a surfactant, enhancing the wetting properties of the drug and thus improving solubility.

Particle size reduction, meanwhile, works by decreasing the size of API particles to increase their specific surface area. This expands contact with the solvent, leading to enhanced solubility. Nanomilling is a particle size reduction technique commonly used to achieve greater surface area by applying mechanical force to reduce particle size. However, an intrinsic tendency for milled particles to form aggregates can create stability issues.

In contrast, bottom-up particle size reduction approaches involve dissolving API bulk powder in a solvent and re-crystallising to form smaller, more soluble crystalline particles. This can yield nanoparticles that are more stable over time, with significantly increased surface area and solubility.

Improved Sustainability

Nanoparticle engineering offers a solution to the long-standing challenge of poor bioavailability, but it can also help with the drive towards greater sustainability. The pharma industry accounts for 4.4% of global emissions.[6] This makes it more emission-intensive than the automotive industry.[7]

However, according to a recent study by the University of Oxford, 85% of the 20 largest global pharma companies have taken action to reduce their internal manufacturing emissions, alongside setting targets for external supply chain emission reduction, recycling and renewable energy usage.[8,9]

Internal changes that can be adopted include transitioning away from common solubility-enhancement techniques that rely on environmentally unfriendly organic solvents and polymers, such as spray-drying of ASDs. With organic solvents making up 60% of mass consumption in the pharma industry and polymer loadings reaching as high as 70% for some ASDs, pharma companies may wish to consider alternative methods to increase bioavailability.[10]

A viable, greener alternative to spray-drying of ASDs is the use of nanoparticle engineering. Nanoparticle engineering methods that work with green solvents, such as supercritical CO_2, and have less of a reliance on polymers for stabilisation, can both streamline formulation and reduce environmental impact.

In addition, the increased bioavailability that advanced nanoparticle engineering technologies can achieve may also mean smaller dosages of API are required for the desired therapeutic effect. This can facilitate smaller pill sizes, potentially reducing the overall packaging and manufacturing footprint per unit and lessening the waste generated from the product.

Formulating for Improved Patient-centricity

Patient-centricity in drug development is gaining momentum and promises to become increasingly important in future. Formulating for an improved patient experience is an important way of differentiating drug products, in addition to improving patients' quality of life. By considering the patient's needs during the drug discovery and development process, products can be tailored for ease-of-use and achieve a greater impact downstream.

Nano-sizing can be applied to APIs to open new, more patient-centric drug delivery routes. This works by forming particles small enough to cross biological barriers typical of local drug delivery routes, such as topical, ophthalmic or even across the blood-brain barrier. This makes it possible to avoid adverse side effects from systemic circulation.

Increased drug loading from reduced particle size can also facilitate patient-centric formulations – both for small molecules and biologics. For example, a biologic traditionally administered intravenously could be reformulated for a longer treatment interval, reducing time spent in hospital and thus improving patient compliance.

Forward-thinking for Scaled-up Manufacturing

Forward planning can also aid the transition to GMP manufacture

and ensure that medicines can be produced on a sufficient scale to meet demand.

Investing in resources and facilities in line with growing demand is key. For example, high potency APIs (HPAPIs) are becoming increasingly popular in drug development due to their high specificity, especially in the oncology space. These can be further enhanced by nanoparticle engineering to improve bioavailability and drug development success rates. However, HPAPIs necessitate specialised containment facilities and there is a shortage of pharma companies able to handle them safely.

Additionally, by considering the scale requirements at the preclinical stage, the overall scale-up process for clinical manufacturing can be streamlined. In preclinical development, drug formulations are produced in small quantities prior to being adapted for the eventual scale of clinical and commercial operations. Nanoparticle engineering can produce API nanoparticles without using complex excipients, leading to simpler formulations and streamlined pharmaceutical development.

An experienced drug development partner with suitable facilities can help ensure that supply keeps up with demand.

Leveraging the Power of AI

AI promises to play a major role in streamlining drug discovery, development and manufacturing.[11] De novo drug design, drug screening and digital twins are examples of how AI can be used in drug development to optimise efficiency and improve outcomes. For instance, digital twinning can be used to predict which drug candidates are most amenable to a given technology, such as nanoparticle engineering, allowing time and resources to be invested in the candidates most likely to succeed.

In this way, AI can help to improve decision-making and de-risk the use of innovative new approaches. AI tools can also streamline and optimise formulation development, plus quickly identify optimal processing parameters and scale-up manufacturing processes. The result is reduced development time and resource waste. In addition, AI can ensure product quality throughout the manufacturing process, with quality control and maintenance, reducing downtime as a result of potential contamination or faults.

Bringing It All Together

Through effective planning and use of innovative nanoparticle engineering technology, challenges such as poor solubility, the need for greener, scalable processes and poor patient compliance can be overcome, streamlining a drug's journey to market.

By facilitating smoother development, drug substance and drug product manufacturing processes and being reactive to trends in the industry and patient populations, the impact of life-changing medicines can be maximised.

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