Whitepaper: Nanoparticle engineering: revolutionising oral drug delivery

It is an established fact that the failure rate of drugs entering Phase I trials is over 90%.[1] This is a staggering figure, considering the huge expense and the many years of hard work across the drug discovery and development pipeline that lie behind every investigational drug. As healthcare systems around the world continue to be challenged to create more efficient and effective therapies, there is increasing interest in methods for improving this low success rate.

A significant obstacle to the release of new medicines is the increasing complexity of drug molecules, which contributes to increased hydrophobicity and poorer water solubility. This is clear from the contrast between the solubility of drugs within the development pipeline and those that reach the market: 70–90% of pipeline drugs fall into the low solubility categories of the Biopharmaceutical Classification System (BCS). Meanwhile, fewer than 40% of drugs on the market fall under the same classification.[2] With this in mind, it is apparent that technologies which can enhance drug solubility and bioavailability have great potential to improve efficiency within the drug development pipeline. Nanoparticle engineering – the process of shrinking down the size of drug particles – has emerged as a promising solution to this problem.

Enhancing solubility and bioavailability

Poor solubility and bioavailability are major causes of attrition in the drug development pipeline. Solubility, defined as the ability of a solute to dissolve in a solvent and give a homogenous system, is an important parameter for drug developers.[3] It is one of the factors influencing whether a drug can achieve the desired concentration in systemic circulation for optimal therapeutic effect. This characteristic is often linked to bioavailability, which refers to the extent and rate at which a drug enters systemic circulation in an unchanged form, thereby reaching its target area.[4]

A significant proportion of drugs delivered through the oral route are absorbed into the body through the gastrointestinal tract. Poor water solubility will result in decreased drug absorption through the intestinal wall, consequently reducing bioavailability. The trend for larger, more complex drug molecules that do not naturally fit Lipinski's 'Rule of Five' exacerbates this issue, as molecules of this nature often exhibit poor aqueous bioavailability. Consequently, with 70–90% of new chemical entities displaying poor solubility or permeability, the race is on to create technological innovations that can address the issue and create a pathway for novel treatments to reach patients.[2]

Nanoparticle engineering as a solution

Various nanoparticle engineering techniques have received attention for their ability to improve the solubility and bioavailability of drug compounds, thereby addressing a leading cause of drug development failure. Engineering APIs down to the nanoscale has a dramatic impact on specific surface area – a phenomenon directly correlated with dissolution behaviour. The relationship between surface area and solubility was developed from the Ostwald-Freundlich theoretical model, which is specific to nanoscale particles.[5]

$$\rho v \frac{RT}{M} ln \frac{S_r}{S_\infty} = \frac{2\lambda_{sl}}{r}$$

where ρ= density of the solid, v= number of moles of ions formed from one mole of electrolyte, R= gas constant, T= temperature, M= molar mass, S_r= the solubility of particles of radius r, S_∞= the solubility of the solid of a plane surface, λ_{sl}= interfacial tension.

Greater surface area enables more interaction between the solute and solvent, which leads to improved solubility. Indeed, reducing particle size below 100 nm increases surface area by 30- to 40-fold compared to a 10 µm particle. Extrapolating this further, a particle size reduction of around 50–100 nm can increase the surface area by up to 1000-fold.

Different nanoparticle engineering approaches that exploit this relationship can, in general terms, be split into 'top down' mechanical attrition-based approaches and 'bottom up' solution-to-particle formation processes. Nanomilling is a popular example of the former, and can successfully produce nanoparticles as small as 150 nm. By raising the surface free energy, however, nanomilling can introduce amorphous domains on crystalline particles, making it unsuitable for some sensitive APIs. Moreover, the need for surfactants to stabilise milled material in suspension can create challenges with respect to stability and shelf life down the line.

Spray-drying is an example of a bottom up, solution-to-particle process which has already been widely adopted within the pharmaceutical industry. This technique is particularly useful for creating API particles for respiratory delivery in the low micron range, and can be used to increase bioavailability by producing API particles in spray-dried amorphous solid dispersions. These dispersions are produced by spray drying the API with a polymer, which acts to stop the API particles from interacting. One disadvantage of this is that the polymer can add a lot of weight to the resultant preformulated material, which can make it impossible to create some formulations at the intended dose (i.e. drug load) and in the desired format. While these techniques have their merits, and are useful in certain situations, it is clear that there is a need for a technology that can reduce particle size to the low nanoscale range, in a controlled and uniform manner, without necessitating the use of surfactants or other excipients. Nanoform's propriety Controlled Expansion of Supercritical Solutions (CESS®) technology provides precisely this.

Recent breakthroughs in nanoparticle engineering technology

Recent advances have led to the development of Nanoform's proprietary CESS® nanoforming™ technology, which reduces the size of API particles while maintaining tight control of system thermodynamics and, consequently, surface properties. The technique involves dissolving and extracting API particles from supercritical carbon dioxide ($scCO_2$). As the process does not require excipients, the need for extended compatibility studies is significantly reduced, accelerating the initiation of clinical trials. This patented technique is the only existing technology to successfully and uniformly reduce drug particle size down to 50 nm, and on occasion as small as 10 nm. This is a major breakthrough, as increasing surface area to this extent means that many novel drugs written off as unviable can be revisited. By significantly improving dissolution rates, intrinsic solubility, and bioavailability, Nanoform's technology has the potential to double the number of compounds reaching clinical trial.

Improving the bioavailability and solubility of drug compounds also confers another advantage: lowering the dose required for therapeutic effect. By reducing the quantity of API that needs to be administered, this feature helps to reduce manufacturing costs and limit waste, as well as reducing side-effects for patients in some cases. In addition, as the CESS® nanoforming™ process does not require the use of organic solvents and possesses a small manufacturing footprint, there is also a substantial environmental benefit associated with its use. As the industry works towards incorporating more sustainable practices, this feature is expected to become ever more important.

Nanoforming in action

The extraordinary capabilities of the CESS® nanoforming™ process were demonstrated in a study on piroxicam, a nonsteroidal anti-inflammatory drug. The difference in pharmacokinetic (PK) behaviour

in rats between d50: 230 nm piroxicam particles produced using Nanoform's CESS® technology and d50: ~2 µm piroxicam particles was assessed.

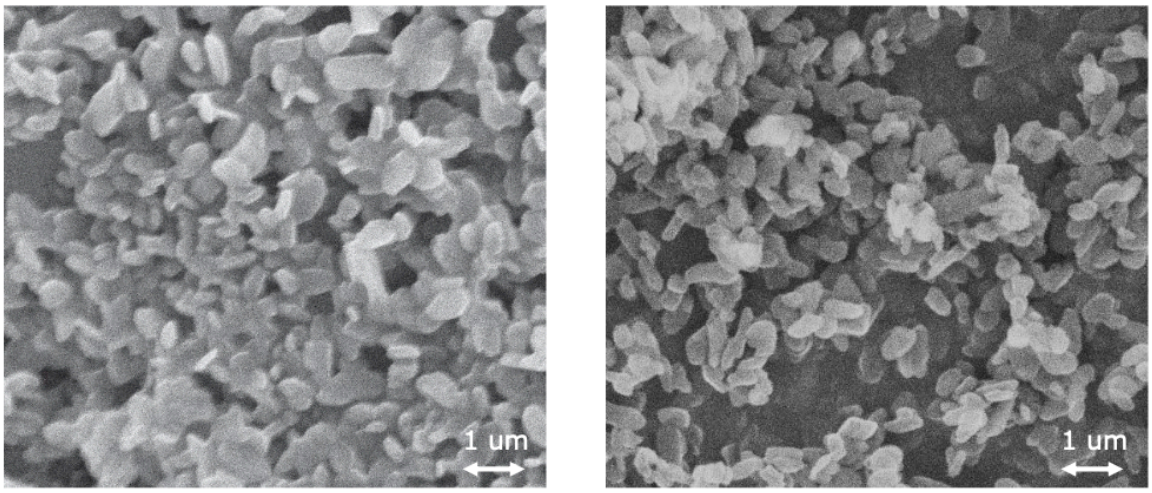

Figure 1: Scanning electron microscope (SEM) images show that nanoformed™ piroxicam remains as individual primary particles in suspension, and does not agglomerate.

A simple suspension formulation was developed to accommodate the PK study. Both the nanoformed™ d50: 230 nm piroxicam and d50: ~2 µm particles produced suspensions that were easily re-dispersible. Scanning electron microscope (SEM) images of the material showed that the piroxicam nanoparticles produced using Nanoform's CESS® nanoforming™ process remained as individual primary particles in suspension, and did not agglomerate (Figure 1). In addition, it was observed that the nanoformed™ piroxicam showed improved dissolution *in vitro* compared with the micron-sized particles (Figure 2).

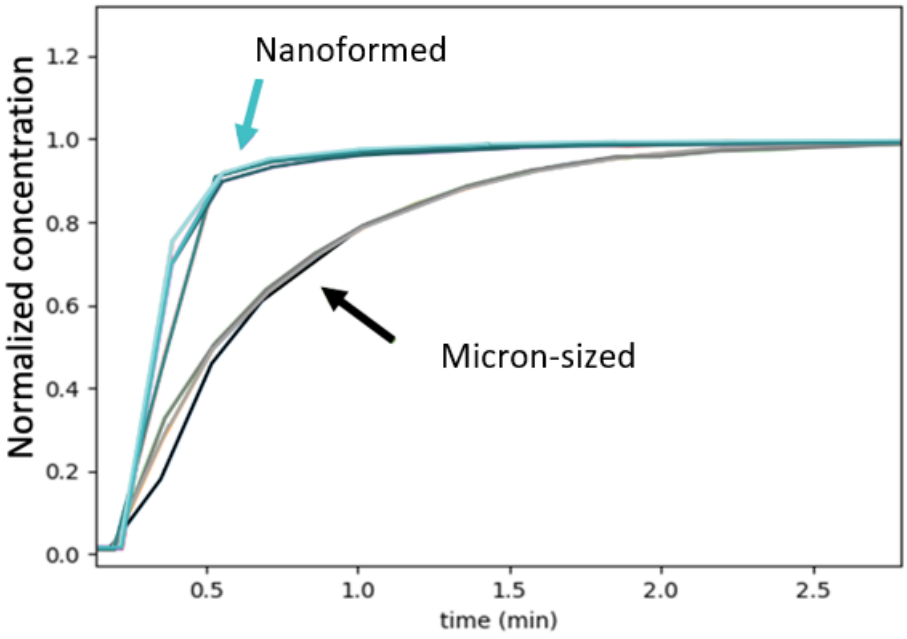

Figure 2: Nanoformed piroxicam shows improved *in vitro* dissolution compared with its micron-sized counterparts.

In the PK study, the nanoformed™ suspension had significantly increased piroxicam plasma concentrations over the micron-sized suspension form (Figure 3). The increase was most pronounced within the first 80 minutes, as the release of nanoformed™ material was faster. Up to 480 minutes, the Area Under the Curve (AUC) was 85–87% higher and T_{max} was reached two- to six-fold faster in the nanoformed™ suspension group compared with the micron-sized suspension reference group. In addition, the C_{max} was 55–89% higher in the nanoformed™ suspension group within the 480 minutes follow-up time. The results suggest that a reduction of more than 50% in the dose required for therapeutic effect is possible, which could be even more pronounced with a smaller particle size. This exciting dose reduction capability is highly relevant for BSC II and possibly BSC IV compounds – categories into which 70–90% of all drug development pipeline drugs fall.[2]

The results of the study also demonstrated that a 20 mg/kg oral dose of nanoformed™ piroxicam possessed superior pharmacokinetic properties compared with piroxicam microparticles, with a p-value of less than 0.01 at 80 minutes, faster T_{max}, higher C_{max} and larger AUC. In addition to suspensions, powder in capsule was also studied using a 5 mg/kg dose. When tested at 5 mg/kg, both the suspension and powder blend of nanoformed™ material in capsule performed similarly and to good effect (Figure 3). This provides strong evidence for the efficacy of both formulations, thus confidence can be drawn for moving forward with human trials. Altogether, the superior properties of nanoformed™ piroxicam formulations demonstrated in the study highlight the immense potential of the technology, and lay the groundwork for human trials.

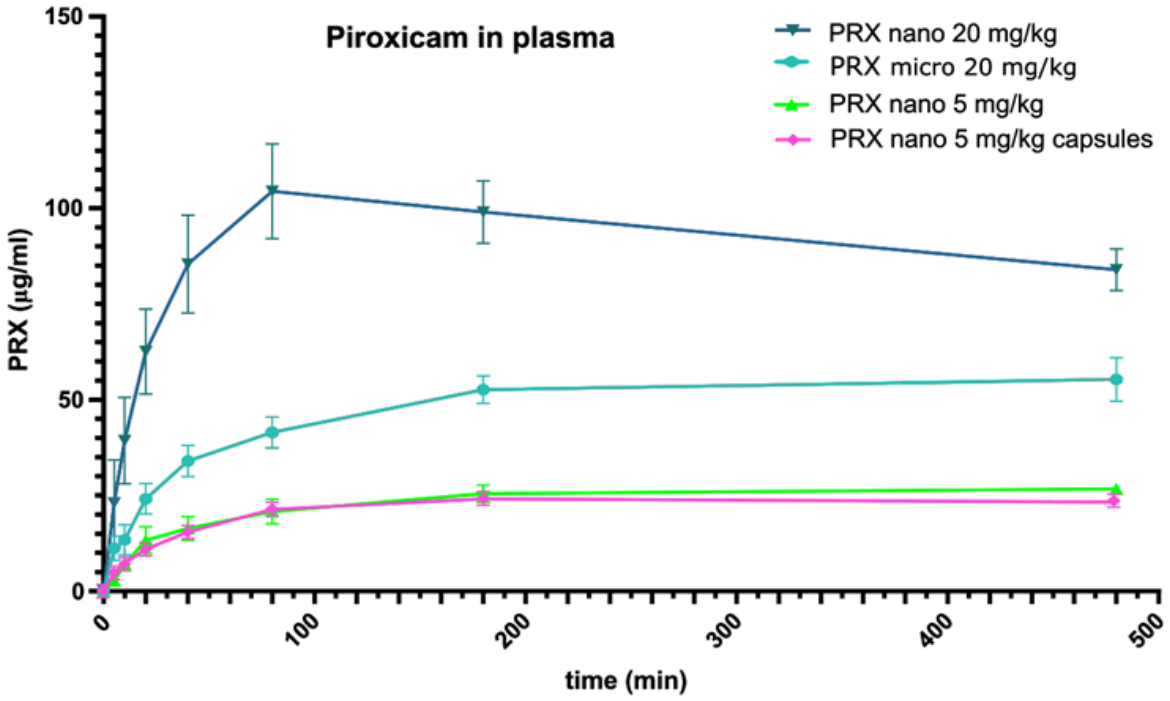

Figure 3: Piroxicam plasma levels in rats after 20 mg/kg and 5 mg/kg PRX administration. Nanoformed piroxicam shows improved concentration relative to other dosage forms. Suspension and powder in capsule show similar release profiles.

Building on the success of the initial studies on piroxicam, Nanoform has developed an immediate release tablet formulation in preparation for human clinical trials (Figure 4). The tablet is developed using typical pharmaceutical excipients and is manufactured using direct compression. To accommodate the 20 mg dose in the 500 mg tablet, the drug load was only 4%. Thus, as anticipated the compaction behaviour of the powder blends was very good. Typically, drug loads need to be higher than that so higher drug loads were also investigated to better understand the compaction

behaviour of nanoformed™ material. Tablets were compacted from powder blends. Namely: placebo, 25% (m/m) nanoformed™, 25% micron-sized, 50% nanoformed™ and 50% micron-sized. As can be seen from the Figure 5, the overall tablettability of nanoformed™ and micron-sized piroxicam was very similar. However, nanoformed™ material needed less compaction force to form adequate tablets that had tensile strength over 2 MPa which is considered to be the pharma industry standard for very good tensile strength. Results also show that high drug loads are possible when using nanoformed™ material, since the CESS® process does not require excipients. In this it differs from other techniques – for example, spray drying. In this study a 50% drug load is demonstrated but with some materials pure nanoformed™ material can also be compressed into tablets, even though unprocessed or micronized cannot form compacts. This indicated that the higher surface area of nanoformed™ material is beneficial for bond formation during compaction.

Figure 4: Nanoform is developing a tablet formulation in preparation for human trials.

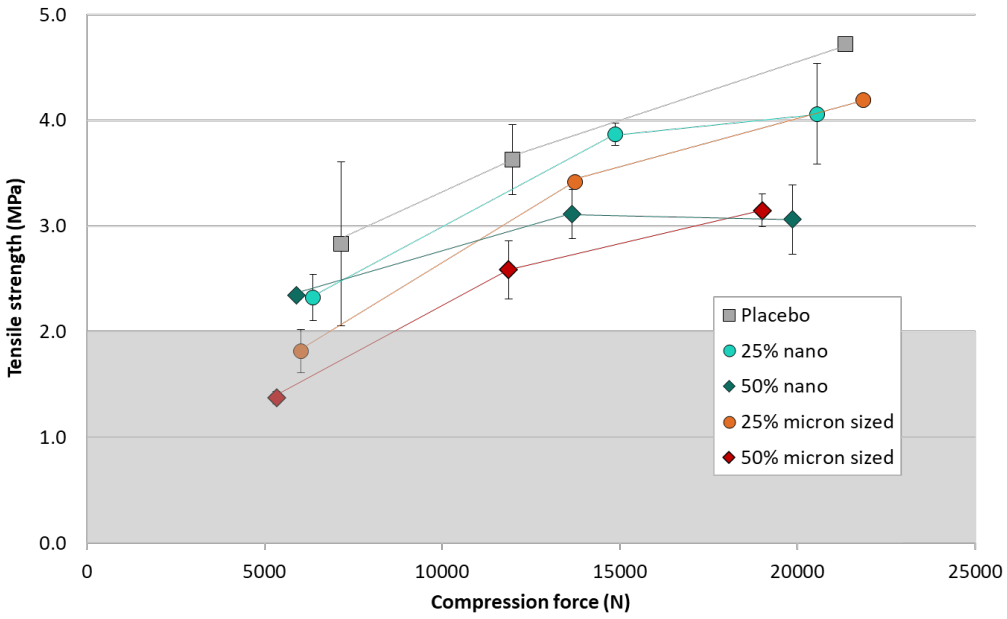

Figure 5: Tablettability of nanoformed™ piroxicam compared to micron-sized and placebo powder blends.

Future outlook

With 85% of the most sold drugs in the US and Europe being orally administered, this drug delivery route remains one of the most common in the world.[3] Armed with recent advances, Nanoform is now well positioned to access this route and begin dosing nanoformed™ piroxicam in humans in 2021.

It is clear that as a solution to the recurring problem of poor bioavailability and solubility of novel drugs in the discovery and development pipeline, the power of nanoparticle engineering technology promises to pave the way forward. By reducing the size of drug particles to increase their surface area in a controlled manner, and without the use of excipients, the latest CESS® technology in particular has shown its enormous potential for improving efficiency within the pharmaceutical industry. This exciting development has implications not only for new drug candidates, but also for previously developed therapies that were discarded due to problems with solubility and bioavailability.

REFERENCES:

1. https://blogs.sciencemag.org/pipeline/archives/2019/05/09/the-latest-on-drug-failure-and-approval-rates
2. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B. 2015 Sep;5(5):442-53. doi: 10.1016/j.apsb.2015.07.003. Epub 2015 Aug 24. PMID: 26579474; PMCID: PMC4629443.
3. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012;2012:195727. doi: 10.5402/2012/195727. Epub 2012 Jul 5. PMID: 22830056; PMCID: PMC3399483.
4. Editor(s): Richard A. Polin, Steven H. Abman, David H. Rowitch, William E. Benitz, William W. Fox, Fetal and Neonatal Physiology (Fifth Edition), Elsevier, 2017, Page xxx, ISBN 9780323352147, https://doi.org/10.1016/B978-0-323-35214-7.00180-3. (http://www.sciencedirect.com/science/article/pii/B9780323352147001803)
5. Sun J, Wang F, Sui Y, She Z, Zhai W, Wang C, Deng Y. Effect of particle size on solubility, dissolution rate, and oral bioavailability: evaluation using coenzyme Q_{10} as naked nanocrystals. Int J Nanomedicine. 2012;7:5733-44. doi: 10.2147/IJN.S34365. Epub 2012 Nov 12. PMID: 23166438; PMCID: PMC3500035.

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ABOUT THE COMPANY

Nanoform Finland Plc is an innovative nanoparticle medicine enabling company. Nanoform works together with pharma and biotech partners globally to reduce attrition in clinical trials and enhance their molecules' formulation performance through its nanoforming services. The Company's patented and scalable Controlled Expansion of Supercritical Solutions (CESS®) technology produces nanoformed API particles as small as 10nm. This enables poorly soluble molecules in the pharmaceutical pipeline to progress into clinical development by increasing their rate of dissolution and by improving their bioavailability. Nanoform's unique technology provides novel opportunities in many value-enhancing drug delivery applications**.**