Small is powerful: Comparison of approaches to tackle poor solubility of drugs

Satu Lakio[1], Claire Wombwell[2], Martin Bates[2], Dyanne Cruickshank[2], Peter Haddow[2], Carrie Sheard[2], Risto Montonen[1], Edward Hæggström[1], Niklas Sandler[1]

[1]Nanoform Finland plc (Helsinki, Finland)

[2]Johnson Matthey, Pharmorphix® (Cambridge, UK)

PURPOSE

Poor bioavailability and low efficacy are common reasons for drug failure

To address this, particle engineering techniques have received attention for their ability to improve the solubility and bioavailability of active pharmaceutical ingredients (APIs). Controlled Expansion of Supercritical Solution (CESS®) technology is a particle production method that is based on supercritical carbon dioxide ($scCO_2$). The core of the technology is the precise control of the nucleation and crystal growth. The process produces pure drug nanocrystals so no excipients are required. The purpose of this study was to evaluate nanoforming with current methods used to tackle the poor solubility of APIs.

METHODS

Materials

Poorly soluble BCS class II drug piroxicam (PRX, Olon S.p.A., Italy) was used as model substance and CO_2 (AGA, Finland) as the solvent in particle production.

Methods

Nanoformed material was compared with material produced by JM using other approaches that are used to improve dissolution of poorly soluble APIs, including amorphous dispersions, salt, cocrystal, cryo-milled amorphous material and micron-sized API. Crystal and particle engineering employed methods from literature. Table 1 describes the method used in the study.

The dissolution performance of the produced materials were evaluated and compared. The dissolution method was developed so that the same mass of free form equivalents of PRX was analyzed for each material. The dissolution media contained 1% (w/v) Tween 80 and 1% (w/v) hydroxypropyl methyl cellulose in simulated gastric fluid (SGF).

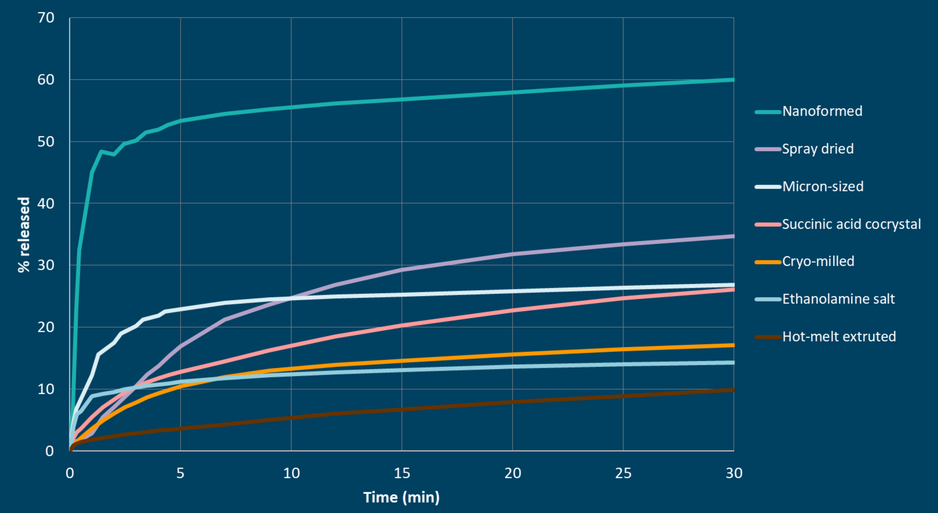

Figure 1. *Piroxicam release for different forms.*

Small is powerful

Table 1. Approaches used in the study

Method	Reasoning	Approach in this study
Nanonization	Small size leads to large specific surface area and thus faster dissolution.	Nanoforming by bottom-up CESS® method
Amorphous Solid Dispersion (ASD)	Well recognized method to stabilize the amorphous phase and enhance dissolution.	**Spray drying** and **hot melt extrusion** were used to form ASDs. Both were made using Plasdone S630 polymer (70% w/w polymer) [1].
Salt	Salt formation may increase the thermodynamic solubility by ionization and it is a routine approach to address poor aqueous solubility.	Ethanolamine salt of PRX was prepared using literature method [2].
Cocrystal	Cocrystal formation may be used to increase dissolution rate and thus improve bioavailability	Cocrystal of PRX and succinic acid prepared using literature method [3].
Amorphous material	Amorphous material has no long range order. It has higher Gibbs free energy than crystalline material and therefore has higher apparent solubility. Amorphous material tends to crystallize over time, so stability might be a challenge.	Cryo-milling was used to produce amorphous material.
Micronization	Micronization is industry standard to enhance dissolution behavior.	In this study, micron-sized PRX was analyzed as supplied.

RESULTS

Particles were successfully produced with all methods. Piroxicam has a low glass transition temperature (Tg, *ca.* 50 °C) thus amorphous piroxicam that was prepared using cryo-milling, was unstable and crystallized readily. Consequently, the performance of the phase pure amorphous material could not be evaluated. When designing the dissolution study the primary aim was to find one method that could assess the initial dissolution rate of all the different particle engineered samples. Comparison of the dissolution performance of different piroxicam forms is represented in Fig. 1. Nanoformed material showed the highest initial rate of dissolution with the potential to release 50% (1.6 mg/min) of the API within two minutes. After two minutes the dissolution rate plateaued with the %release increasing 10% in 30 min. The micron-sized samples also showed quite high initial dissolution rate (0.6 mg/min) within the first two minutes. The ethanolamine salt form, succinic acid cocrystal form the spray dried amorphous dispersion and cryo-milled samples showed comparable values of initial dissolution within two minutes (0.2 - 0.3 mg/min). The sample with the lowest dissolution rate over two minutes (0.07 mg/min) was the hot melt extruded sample, this also had the lowest %released over 30 min.

It is good to notice that nanoformed particles are excipient free so the subsequent drug load in the final dosage form, e.g. tablet, could be significantly higher than for example amorphous solid dispersion that can have 60% polymer load as this study and literature show.

CONCLUSIONS

Nanoformed nanoparticles have significantly improved dissolution performance compared to the other approaches tested. This can lead to faster absorption and onset of action *in vivo* [4,5].

References:

[1] Rahman et al, 2012. Comparison of amorphous dispersions of piroxicam in Plasdone S-630 copovidone prepared by spray drying and hot-melt extrusion. Pharm. Technol. Report (Ashland)

[2] Gwak et al, 2005. Enhanced bioavailability of piroxicam via salt formation with ethanolamines. Int. J. Pharm. 297(1–2), 156-161.

[3] Childs and Hardcastle, 2007. Cocrystals of piroxicam with carboxylic acids. Cryst. Growth Des. 7, 1291-1304.

[4] Savjani et al, 2012. Drug Solubility: Importance and Enhancement Techniques. ISRN Pharmaceutics, Article ID 195727, 1-10.

[5] Nanoform Finland plc data, www.nanoform.com

CONTACT INFORMATION: Dr. Satu Lakio, satu.lakio@nanoform.com