drug hunter
discover together

4 min read

Published
Saturday
April 16, 2022
read online

Solid Form Strategies for Increasing Oral Bioavailability

written together with Nanoform

Small-molecule drug candidates are increasingly falling "**beyond the rule of 5**[1]," making oral administration more challenging. Optimizing a drug's solid form can improve its solubility and bioavailability when further molecular modifications are prohibitive. This minireview covers solid form strategies for increasing the solubility and oral bioavailability of small-molecule drugs including:

Cryo-milling | Salt formation | Spray drying | Co-crystallization | Hot-melt extrusion | Controlled Expansion of Supercritical Solutions (CESS®) technique (Nanoform)

This is a sponsored article written together with the Nanoform team.

Nanoform is a nanoparticle medicine enabling company that works with pharma and biotech partners globally to provide hope for patients. We are focused on reducing clinical attrition and on enhancing drug molecules' performance through our nanoforming technologies and formulation services. Our capabilities include GMP manufacturing, and our services span the small to large molecule development space with a focus on solving solubility and bioavailability challenges and on enabling novel drug delivery applications.

Solid Form Solutions: Strategies for Improving Bioavailability with Drug Solid Forms

Traditional medicinal chemistry strategies for improving drug bioavailability such as property-based optimization[2] sometimes hit a wall due to the complex nature of the lead or the intrinsic properties of the target pharmacophore. Chemical modification to a prodrug[3], complexation with cyclodextrins, lipid formulations, and other strategies[4] can be appropriate at times but have their own challenges. The solid form of a drug can often be leveraged to improve bioavailability, and is often preferred to designing a new compound entirely.

Solid forms may consist[5] of polymorphs, amorphous states, hydrates, solvates,

solid solutions, salts, cocrystals, hydrates, eutectics, and may vary by orders of magnitude in particle sizes. For poorly soluble drugs, the solid form can make a significant impact on both kinetic and thermodynamic solubility and hence overall oral bioavailability.

This begs the question, once a poorly soluble commercial drug has been committed to development, what are the solid form preparation options to improve its oral bioavailability? Some examples are shown in the table below.

Examples of Drug Solid Form Methods Employed in Drug Development

Examples of Solid Form Methods to Improve Drug Bioavailability

Method	Strengths	Limitations	Examples with Reported In Vivo Data	Example Reference
Cryo-milling	Applicable to drugs with a wide range of physicochemical features, including heat-sensitive and water-soluble drugs	Intrinsic tendency to form agglomerated masses can lead to stability issues	Ibuprofen, salbutamol sulfate	Niwa et al., Eur. J. Pharm. Sci. **2010**, 41, 78-85
Salt formation	Can greatly improve solubility and bioavailability in certain cases, and is widely used and understood	Only suitable for ionizable drugs.	Cilostazol, Ciprofloxacin hydrochloride hydrate	Seo et al., Drug Des. Devel. Ther., **2015**, 9, 3961-3968
Spray drying	Allows for control of particle properties, such as size and morphology	The polymer adds weight to the preformulated material that can make it challenging to form tablets or capsules. Organic solvents typically required, leading to potential safety/environmental concerns. Energy-intensive and relatively expensive process.	Artemisinin	Sollohub and Cal, J. Pharm. Sci., **2010**, 99, 587-597
Co-crystallization	Can be applied to non-ionizable drugs. Does not introduce the physicochemical stability issues of amorphous solid dispersions.	Higher mass of dosage form. Second ingredient to screen and optimize; often serendipitous.	Entresto™, Suglat®	Kavanagh et al., Drug Di-scov. Today, **2018**
Hot-melt extrusion (HME)	Good scalability, compatible with drugs insoluble in organic solvents. Green process; smaller footprint compared to e.g. spray drying;	Not suitable for thermally sensitive API molecules and some polymers. Can be challenging to achieve high drug loads. Choice of pharmaceutical grade polymers and surfactants that are suitable for HME is limited.	Nurofen, piperine	Ashour et al., J. Pharm. Phar-macol., **2016**, 68, 989-998
CESS®	Nanoparticles are tunable in size (as small as 10 nM), shape and polymorphic form. Process does not require excipients. Can potentially facilitate high drug loading. Green process, allows for scalable continuous manufacturing.	Non-ionogenic species, free bases, and acids as salts are typically not soluble in the $scCO_2$ used as a solvent in the CESS® process.	Piroxicam	NCT05104931 (Ph. I data summary)

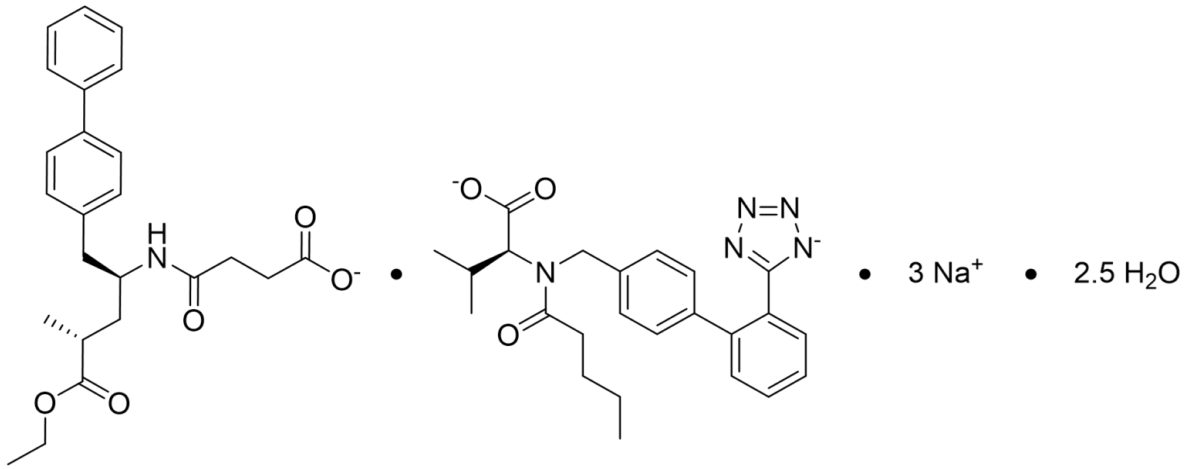
drug hunter

drughunter.com

Traditional techniques to generate a solid form with improved bioavailability include spray drying[6], milling[7], co-crystallization[8], hot melt extrusion[9] and salt formation. Some well-known examples of drugs that have employed these techniques include:

Ciprofloxacin hydrochloride hydrate, a salt form of the antibiotic ciprofloxacin which employed the salt formation technique[10] to improve the dissolution rate. Entresto® (sacubitril/valsartan), a drug used to treat heart failure which made use of the co-crystallization[11] approach.

Nurofen (ibuprofen), a common painkiller drug which made use of HME[12].



sacubitril and valsartan (EntrestoTM)

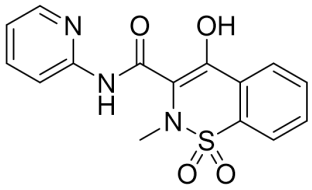
The list goes on, and each of these techniques have their own strengths and weaknesses. However, not all drugs can be used in each technique. For example, hot melt extrusion[13] is typically unsuitable for thermally sensitive API molecules, and salt formation[14] is only applicable for drugs with ionizable functional groups.

Recent Clinical Data with a Next-Generation Nanoparticle Engineering Approach

An emerging nanoparticle engineering approach that has demonstrated proof-of-concept[15] in a human Ph. I trial (NCT05104931)[16] is the Controlled Expansion of Supercritical Solutions (CESS®) technique (patented by Nanoform).

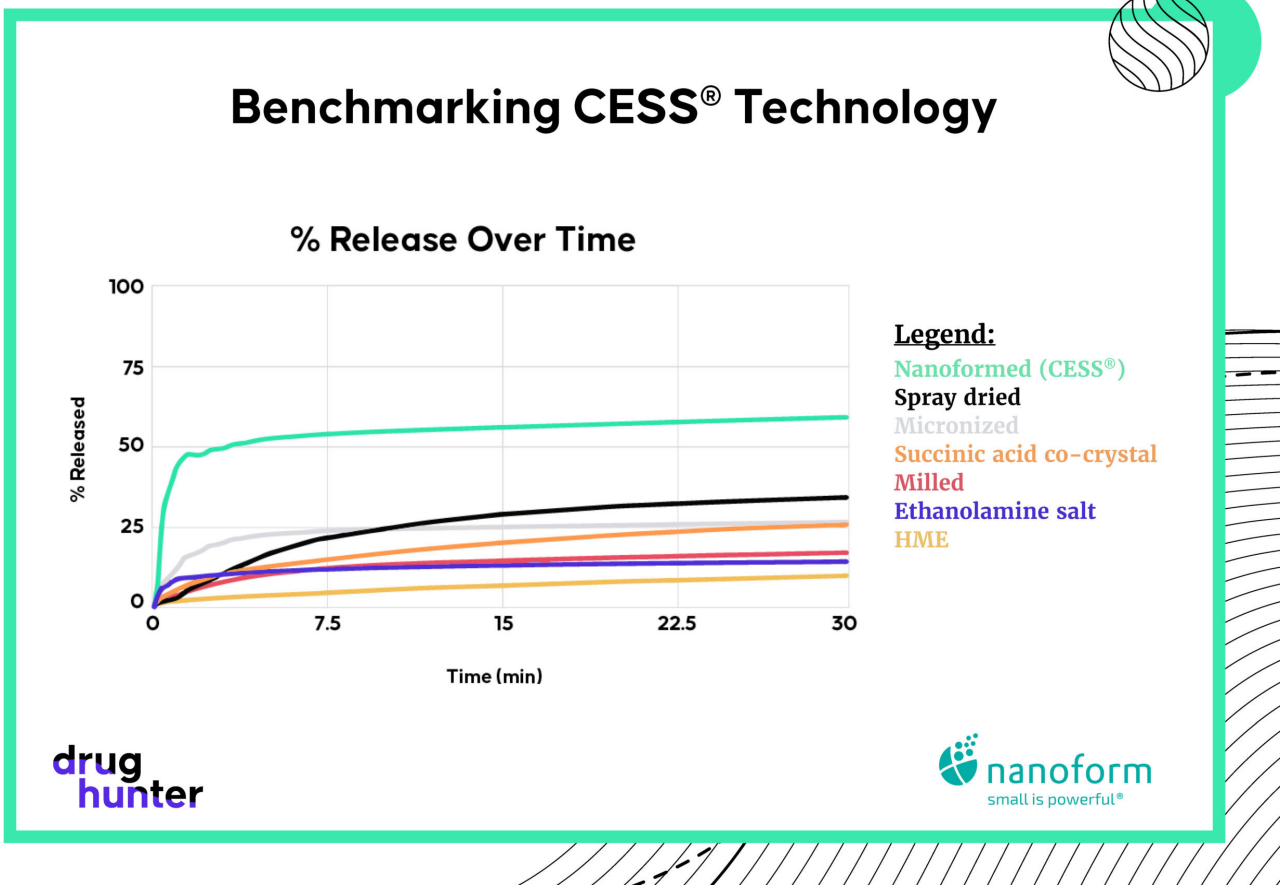
CESS® works by dissolving API particles in supercritical carbon dioxide and recrystallizing under controlled temperature and pressure. By doing so, control can be maintained over the particle shape, size and morphology, and particles as small as 10nm can be created.

In the human Ph. I trial, nanoformed piroxicam[17] showed an increase in plasma exposure[18] of 33% over a comparator tablet, comparable to that observed with cyclodextrin complexation (but without the extra excipient). The nanoformed piroxicam also showed a reduction in Tmax to 1.75 h from 2.25-2.75 h, demonstrating potential of the technology to preparing rapid onset, immediate-release (IR) drug products for indications like pain.



piroxicam

The dissolution rate of nanoformed piroxicam relative to material prepared by other common industry techniques corroborates the observed clinical PK improvement (see graph below).



The CESS®-nanoformed material demonstrated improved dissolution performance compared to all other techniques tested for piroxicam. Altogether, the data support further exploration of the clinical utility of CESS® in modulating the PK of poorly soluble drugs. Further research to investigate the application of CESS® to a range of drug development projects is being conducted in collaboration with partners including Boehringer Ingelheim, TargTex, and Celanese.

We hope you found this solid form minireview and primer on the emerging nanoparticle technology, CESS, useful. You can learn more about Nanoform's

CESS® technology here, or meet the Nanoform team at the Drug Discovery Chemistry conference in San Diego from Apr. 18–21, 2022 at booth 310.

(1) Oral Druggable Space beyond the Rule of 5: Insights from Drugs and Clinical Candidates https://www.sciencedirect.com/science/article/pii/S1074552114002890?via%3Dihub (accessed 2022–05–15).

(2) Property-Based Design: Optimization of Drug Absorption and Pharmacokinetics https://doi.org/10.1021/jm000407e (accessed 2022–04–15).

(3) Property-Based Design: Optimization of Drug Absorption and Pharmacokinetics https://doi.org/10.1021/jm000407e (accessed 2022–04–15).

(4) Overview of milling techniques for improving the solubility of poorly water-soluble drugs https://www.sciencedirect.com/science/article/pii/S1818087615000100?via%3Dihub (accessed 2022–04–15).

(5) Solid form changes during drug development: good, bad, and ugly case studies http://aapsopen.springeropen.com/articles/10.1186/s41120-016-0003-4 (accessed 2022–04–15).

(6) Spray Drying Technique: II. Current Applications in Pharmaceutical Technology https://jpharmsci.org/article/S0022-3549(16)30412-9/fulltext (accessed 2022–04–15).

(7) Overview of milling techniques for improving the solubility of poorly water-soluble drugs https://www.sciencedirect.com/science/article/pii/S1818087615000100?via%3Dihub (accessed 2022–04–15).

(8) Cocrystals to facilitate delivery of poorly soluble compounds beyond-rule-of-5 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4910885/ (accessed 2022–04–15).

(9) Hot melt extrusion as an approach to improve solubility, permeability and oral absorption of a psychoactive natural product, piperine https://academic.oup.com/jpp/article/68/8/989/6128321 (accessed 2022–04–15).

(10) Pharmaceutical salts of ciprofloxacin with dicarboxylic acids https://www.sciencedirect.com/science/article/abs/pii/S0928098715002997?via%3Dihub (accessed 2022–04–15).

(11) (12) Continuous manufacturing of co-crystals: challenges and prospects https://link.springer.com/article/10.1007/s13346-018-0479-7 (accessed 2022–04–15).

(13) Recent advances in improving oral drug bioavailability by cocrystals https://bi.tbzmed.ac.ir/Article/bi-17553 (accessed 2022–04–15).

(14) Improved oral absorption of cilostazol via sulfonate salt formation with mesylate and besylate https://www.dovepress.com/improved-oral-absorption-of-cilostazol-via-sulfonate-salt-formation-wi-peer-reviewed-fulltext-article-DDDT3 (accessed 2022–04–15).

(15) Overcoming Drug Development Challenges with Nanotechnology: Positive data from a first- in-human trial with a nanoformed drug https://nanoform.com/en/wp-content/uploads/sites/2/2021/05/positive-results-from-first-in-human-trial-of-nanoformed-piroxicam.pdf (accessed 2022–04–15).

(16) PK Evaluation of a Nanoformed Oral IR Piroxicam Tablet in Healthy Subjects https://clinicaltrials.gov/ct2/show/NCT05104931(accessed 2022–04–15).

(17) Piroxicam https://en.wikipedia.org/wiki/Piroxicam (accessed 2022–04–15).

(18) Overcoming Drug Development Challenges with Nanotechnology: Positive data from a first- in-human trial with a nanoformed drug https://nanoform.com/en/wp-content/uploads/sites/2/2021/05/positive-results-from-first-in-human-trial-of-nanoformed-piroxicam.pdf (accessed 2022–04–15).