# 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.<br><br>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.<br><br>Does not introduce the physicochemical stability issues of amorphous solid dispersions. | Higher mass of dosage form.<br><br>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.<br><br>Green process; smaller footprint compared to e.g. spray drying; | Not suitable for thermally sensitive API molecules and some polymers.<br><br>Can be challenging to achieve high drug loads.<br><br>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.<br><br>Process does not require excipients.<br><br>Can potentially facilitate high drug loading.<br><br>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) |