The determination of the solubility enhancement from nanosizing using carrier particle mediated isolation and stabilisation of drug nanoparticles.

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Background: Nanosizing is used in the pharmaceutical industry to overcome solubility, dissolution rate and bioavailability issues for poorly water-soluble APIs. However, API nanoparticles usually need soluble stabilizers to help them maintain their small particle size and high surface areas, otherwise they will tend to agglomerate and undergo Ostwald ripening over time and during downstream processing. Even with these stabilisers, it can be difficult to prevent the nanoparticles from growing during their isolation to dryness, and their powder flow properties can be challenging to control also. Determining the actual enhancement in solubility accruing from nanosizing is not straightforward due to (i) the aforementioned instability of the nanoparticles, and (ii) the experimental challenge of quantifying the amount of drug dissolved in the dissolution media when using the commercially available filters (i.e., low micron-sized) to separate undissolved drug nanoparticles from the dissolution media. Previously, our group developed a one-step crystallisation approach that generates and promptly stabilises API nanoparticles by attaching them to a carrier particle's surface, forming a *nanocomposite* powder that is readily isolated by vacuum filtration. We found that the dissolution profiles of the APIs in our nanocomposites under sink conditions were similar to those of the corresponding stabilised API nanosuspensions. Our follow-on study of these carrier particles' surface properties found that carrier particles possessing hydrophobic and hydrophilic groups and a porous surface afford nanocomposite powders that display faster (i.e., nanosuspension-like) dissolution rates.

Methods: In this work, we studied the dissolution kinetics and API solubility enhancement under non-sink conditions in simulated gastric fluid for nanocomposite powders composed of API nanoparticles (valsartan, celecoxib or nilotinib) and carrier particles (montmorillonite (with/without surface modification) or mesoporous organosilanes).

Results: Two distinct types of behaviour were observed: (i) nanocomposite powders dissolved quickly and enhanced the solubility of the API, or (ii) a "spring" dissolution profile, where the nanocomposite powders generated a supersaturated solution that precipitated over time. On this, we identified precipitation inhibitors that maintained the supersaturation for up to one hour.

Conclusions: The increased solubilities and/or dissolution rates observed for nanocomposite powders produced by our method can potentially increase the bioavailability of a drug and therefore reduce the dose needed in the commercial formulations, thus mitigating some side effects produced by high doses (e.g., gastrointestinal irritation) and potentially improving patient adherence to their dosing regime.