Particle engineering with mesoporous silica: de-risking development of orally solid dosage forms via solid-state and particle homogenization

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Purpose

De-risking of polymorphism in drug development

Variation in crystal structure ("polymorphism") or variation in powder properties, are critical issues in pharmaceutical development1. The crystal structure of a drug is related to important properties including, but not limited to: biopharmaceutical performance, processability, galenical properties, safety, intellectual property, regulatory filings etc. Therefore, if polymorph variation is encountered during a development regime, the compound is at increased risk of attrition. In this study, we demonstrate how a porous silica carrier material can be used as a platform technology to homogenize solid state and particle properties for a range of chemically diverse compounds, thus reducing the aforementioned risks and potentially allowing the development of a template-based formulation process.

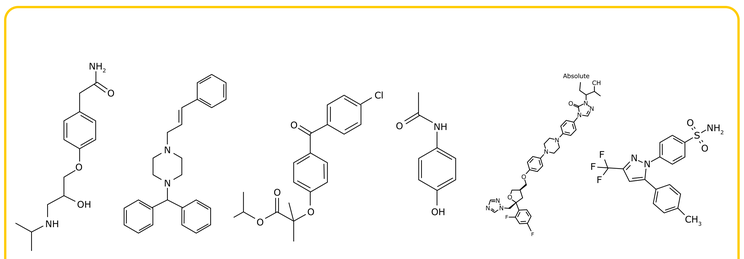
Objectives

A platform approach for solid-state and particle homogenization

Loading and stabilization of a diverse set of APIs onto mesoporous silica. Demonstration of particle homogenization via powder characterization methods. Development of templated formulation process for APIs with a wide variety of physicochemical properties.

Methods

Six chemically diverse compounds (celecoxib, atenolol, cinnarizine, fenofibrate, paracetamol and Posaconazole), across all BCS classes, were loaded onto mesoporous silica using the solvent impregnation method. The loaded powders were then assessed for a range of particle and galenical properties including solid state, morphology, surface area, density, particle size, flowability and triboelectricity. Secondly, each of the loaded silica formulations were processed into tablets, and various tablet properties were assessed. Finally, the powders were stored under the ICH Q1(A) accelerated stability conditions of 40°C and 70% relative humidity for three months, after which the powder analyses were repeated.



Solid-state remained consistent across all APIs investigated

Loading of a diverse set of APIs with different particle structures and polymorphs onto mesoporous silica yielded the amorphous form in all cases as measured by XRPD (Table 1). The amorphous form is stabilized *via* nanoconfinement in the *ca.* 6 nM pores of the silica.

	Solid State	Drug Load (%)	LogP	MWt	pKa	BCS Class
Atenolol	Amorphous	26	0.16	266	9.6 (basic)	III
Cinnarizine		27	5.77	378	7.4 (basic)	II
Fenofibrate		29	5.2	361	– (neutral)	II
Paracetamol		29	0.91	151	9.5 (acidic)	I
Posaconazole		28	5.5	701	3.7 (basic)	II
Celecoxib		35	3.99	381	11.1 (acidic)	II

Table 1.
A diverse set of APIs were loaded onto mesoporous silica.

Loading of all APIs onto mesoporous silica improved flowability

Flowability, as measured with the angle of repose and *ffc* was improved in all cases when APIs were loaded on to mesoporous silica. For each API-loaded silica, passable flowability was consistently obtained (Figure 1).

Powder properties are homogenized to common values across all APIs when loaded onto mesoporous silica

A range of powder properties were measured for all of the API loaded silica powders products. In spite of varying properties of the unloaded APIs, a homogenization was observed when loading onto mesoporous silica. For example, the particle size of the unloaded APIs ranged from 40–90 µm. However. After loading onto mesoporous silica, the particle size range for all of the loaded formulations was tightly controlled between 28–30 µm (Figure 2). Similar "homogenization" behaviour was observed for flowability, triboelectric charge, density, morphology, surfacer area and tabletting behaviour after loading onto mesoporous silica.

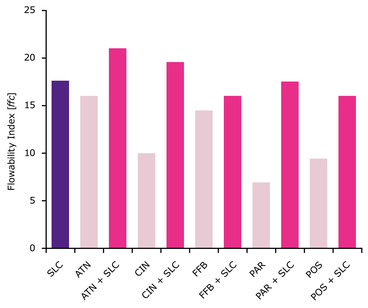


Figure 1.
A range of APIs were loaded onto Parteck® SLC, with an improved particle flowability in all cases as demonstrated by an increasing *ffc*.

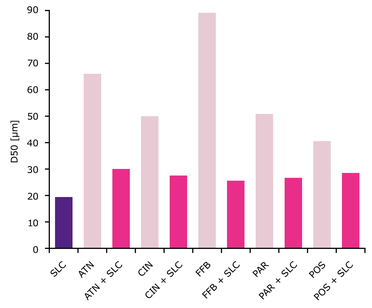


Figure 2.
Homogenization of particle size for a diverse set of APIs after loading onto Parteck® SLC.

All formulations remained stable for the duration of the three-month stability study

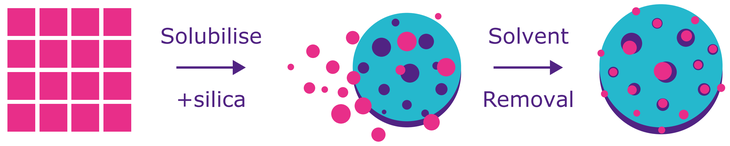
After storage under accelerated conditions, no changes were observed in the solid-state and powder behaviour of the loaded formulations.

Conclusions

Towards a templated formulation approach, compatible with a variety of manufacturing processes.

Herein we propose a novel approach to de-risk the development of oral solid dosage forms. By loading suitable APIs onto a mesoporous silica "platform" the risk of deviation in polymorphism and particle properties during the development process is minimized, as the same solid state will be stabilized every time. Furthermore, the novel observation that particle properties were homogenized, i.e. trended towards similar values, for all of the chemically diverse APIs studied, suggests that a "template" formulation development process could be employed. In such a system, the same formulation components and processing methods could be used for several APIs, thus reducing the overall development time and resource requirements. Such a templated process, based on a mesoporous silica platform, is especially attractive in the rapidly emerging field of continuous manufacturing, where early process development and optimization is essential.

Loading of APIs onto mesoporous silica is a quick and efficient process, compatible with basic lab equipment



References

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