Parteck® SLC Mesoporous Silica:

Three steps for successful Stabilization of Amorphous API for Bioavailability Enhancement

Solvent Test:
Optimization and selection of loading solvent

Loading:
Incipient wetness for pore impregnation and API adsorption

Analytics:
Residual Solvent, solid state and dissolution

The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.

SAFC®
Pharma & Biopharma Raw Material Solutions

1. Solvent test

It is essential to test the solubility of the API in order to identify the optimal loading solvent. Furthermore, the organic solvent used should have an appropriate boiling point, so that the solvent can be easily removed from Parteck® SLC after loading. Suitable solvents include: acetone (56.0 °C), methanol (64.7 °C), dichloromethane (39.6 °C), and ethanol (78.4 °C).

To determine solubility, an excess amount of API is suspended in the solvent and agitated for 18 – 24 hours. The mixture is then centrifuged, and the supernatant is analyzed via HPLC to determine the concentration of API in solution.

Typically, highly concentrated loading solutions (50 – 60 mg/mL) are preferred. However, concentrations as low as 10 mg/mL have been successfully loaded onto Parteck® SLC. Higher process times are required for loadings with lower concentrations as larger volumes of solvent are required.

2. Loading

2.1 Equipment

This simplified loading technique has been developed to utilize common laboratory equipment, thus eliminating the need for specialized equipment and avoiding extra capital expenditure. For loadings performed at the feasibility scale, the following equipment is necessary (*Fig. 1*):

- **Glass beaker:**
  - 5 mL (1 g loading)
  - 150 mL (10 g loading)
  - 400 mL (25 g loading)
  - 2000 mL (200 g loading)
- Ring stand and clamps
- Syringe pump, syringe and cannula (e.g. PEEK HPLC tubing)
- Overhead stirrer
- Stirring blade (PTFE), cut to the inner dimensions of the beaker
- Glass capillary (optional)
- Adjustable height platform, hot plate, water/oil bath
- Nitrogen connection and tubing
- Vacuum connection and tubing

Fig 1. Loading Equipment

Fig 2. Concentrated API solution is added dropwise to a stirred and heated beaker containing Parteck SLC

2.2 Loading Preparation

Parteck® SLC

1. First, determine the water content of the Parteck® SLC. The LOD should be < 5%.
2. Next, weigh the required amount of Parteck® SLC into the beaker and secure with a clamp to the ring stand.
3. Move the clamp/beaker up the ring stand until the PTFE stirrer is touching the bottom of the beaker.
4. Start the stirrer at 15 rpm and ensure that the Parteck® SLC is being adequately stirred.

API solution

1. A maximum concentration of 10% lower than the solubility is preferred. Measure the API into a beaker and add the required amount of solvent. Stir the solution on a stir plate until the API is dissolved.
2. Once the API has been dissolved, draw the solution into the syringe and place the syringe in the syringe pump.
3. Attach the PEEK HPLC tubing to the syringe using a Luer Lock (*Fig. 2*).
4. Position the opposite end of the PEEK HPLC tubing (where the glass capillary is located, if used) above the surface of the stirred Parteck® SLC.
5. At this time, lab sealing film can be placed over the top of the beaker. Nitrogen and vacuum lines can be inserted through the lab sealing film.

2.3 Loading Process

1. The loading process should take place under well-ventilated conditions. Therefore, nitrogen and a gas removal with vacuum is applied.
2. The nitrogen should be turned on at an approximate flow of 0.2 – 0.6 mL/min.
3. Next, the vacuum can be turned on. The purpose of the vacuum is to decrease the chance of solvent condensate forming on the lab sealing film by constant vapor removal. The loading process itself is not performed under vacuum.
4. Now, set the water bath to above the boiling temperature of the solvent. The height of the water bath should be adjusted so that the water level is slightly above the Parteck® SLC, this can be achieved using the adjustable height platform.
5. Input the volume of solvent into syringe pump and set the delivery rate to 0.1 mL/min (≤ 1 g) or 0.75 mL/min (> 1 g) and turn on the pump. It is important to ensure the API solution is dropping directly onto the Parteck® SLC and not onto the surface of the beaker, to avoid re-crystallization.
6. As the API solution begins to drop onto the Parteck® SLC surface, the liquid will be pulled into the pore structure due to the strong capillary forces created by the mesopores. Although the loading is performed at the boiling point of the solvent, a steady state process may not be achieved, and it is possible the Parteck® SLC will become oversaturated with solvent, increasing the risk of re-crystallization. If this occurs, agglomerates will begin to form.
7. If agglomerates are observed, the syringe pump should be stopped, and the Parteck® SLC should be allowed to mix at 30 rpm until the powder has dried and agglomerates are no longer visible (normally 5 – 15 minutes).
8. During this drying step, the capillary should be flushed with solvent to prevent any clogging due to API recrystallization. The flush should be received in the beaker that was used to make the API solution, not the loading beaker.
9. After the drying step, the loading can be re-initialized. The loading/drying should be repeated until the API solution has been completely added.
10. At the end of the loading, any excess API solution removed from the syringe (i.e. during the drying steps) should be rinsed with additional solvent and added to the Parteck® SLC. This is to ensure that all of the API weighed has been added to the Parteck® SLC.
11. To dry the loaded Parteck® SLC, spread the powder in a thin layer in an open vessel (e.g. ceramic evaporation dish) and cover with filter paper.
12. The product should then be placed in a vacuum drying oven and dried for 16 – 18 hours (overnight) at the boiling point of the solvent and at a reduced pressure of about 100 mbar.

3. Analytics

The samples can now be tested for residual solvents with NMR or headspace GC; amorphous character with DSC or PXRD; API content with HPLC or NMR and, finally, dissolution.

4. Formulation Scale-up

We have developed robust and effective processes for scale-up of Parteck® SLC loading from small-scale (< 500 g) to production scale (> 100 kg). For more information, please contact your local formulation specialist.

5. Abbreviations

API	Active Pharmaceutical Ingredient
DSC	Differential Scanning Calorimetry
GC	Gas Chromatography
HPLC	High Performance Liquid Chromatography
LOD	Loss On Drying
NMR	Nuclear Magnetic Resonance
PEEK	Polyether Ether Ketone
PTFE	Polytetrafluoroethylene
PXRD	Powder X-Ray Diffraction

6. Further Reading

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The typical technical data above serve to generally characterize the excipient. These values are not meant as specifications and they do not have binding character. The product specification is available separately at **SigmaAldrich.com**.

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