
This version is available at https://strathprints.strath.ac.uk/61422/

Strathprints is designed to allow users to access the research output of the University of Strathclyde. Unless otherwise explicitly stated on the manuscript, Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Please check the manuscript for details of any other licences that may have been applied. You may not engage in further distribution of the material for any profitmaking activities or any commercial gain. You may freely distribute both the url (https://strathprints.strath.ac.uk/) and the content of this paper for research or private study, educational, or not-for-profit purposes without prior permission or charge.

Any correspondence concerning this service should be sent to the Strathprints administrator: strathprints@strath.ac.uk
Introduction
Self-emulsifying drug delivery systems (SEDDs) are lipid-based formulations which spontaneously form stable emulsions under mild agitation in gastrointestinal (GI) fluids (Czepajlo et al., 2013). Although liquid SEDDS and SMEDDS are beneficial to enhance drug bioavailability, low stability, leakage, drug precipitation, shell-leakage and incompatibility with capsule shells as well as potential GI irritation have led to the development of solidification techniques, which transform liquid SEDDS into solid SEDDS (Kallakunta et al., 2012).

Batch manufacture is often associated with difficulties of scale-up, high cost, high resource needs and difficulties in consistent production. In contrast, a continuous process can increase yields, reduce development times, production times, failures of scale-up, resource uses and costs (Lee et al., 2015).

Here, a continuous manufacturing process (twin screw extruder) was developed for adsorbing liquid SEDDS onto mesoporous silica carriers in order to produce solid free flowing SEDDS powders. Key process parameters were identified and produced solid SEDDS characterisation.

Materials
SEDDS: Labrasil M1944CS, Labrasol and Capryol 90 were provided by Gattefosse (SAS, France). Solid carriers: Syloid XDP3050 and Syloid XDP1510 were provided by Grace GmbH & Co.KG (Worms, Germany).

Methods
Preparation of liquid SEDDS
A stable SEDDS formulation was developed employing Labrafir M1944CS (5-15%), Labrasol (60-90%) and Capryol 90 (0-15%). Manufacture of solid SEDDS
Solid carriers were fed into zone 3 of a ThermoScientific® Process 11 twin screw extruder. Liquid SEDDS were added in zone 4 of solid loading of 1:1, 2:1 and 3:1 (lipid/carrier) was targeted. Two screw configurations were tested a 29 conveying elements (C) only and b) two kneading zones (each with 7 mixing elements assembled at a 45° (K1). (Figure 1).

Table 1: SEDDS specifications.

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Syloid® XDP 3050</th>
<th>Syloid® XDP 3150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical form</td>
<td>White powder</td>
<td>White powder</td>
</tr>
<tr>
<td>Oil Absorbing Capacity (mL/100g)</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Mean particle size (µm)</td>
<td>48-66</td>
<td>120-170</td>
</tr>
<tr>
<td>Specific surface area (BET) (m²/g)</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>Tapped Bulk density (g/mL)</td>
<td>0.275</td>
<td></td>
</tr>
<tr>
<td>pH (5% slurry)</td>
<td>4.0-8.0</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Screw configuration with two kneading zones.

Figure 2: SEDDS loaded Syloid XDP 3050 manufactured with conveying elements only.

Figure 3: SEDDS loaded Syloid XDP 3050 manufactured with two kneading zones.

Table 2: Dynamic test results for Syloid XDP powders and solid SEDDS.

<table>
<thead>
<tr>
<th>Ratio by weight of solid carrier to liquid SEDDS</th>
<th>BFE (µm)</th>
<th>SI</th>
<th>FRI</th>
<th>SE (µm/g)</th>
<th>CBD (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syloid XDP3050</td>
<td>42.32</td>
<td>0.89</td>
<td>1.54</td>
<td>4.12</td>
<td>0.2484</td>
</tr>
<tr>
<td>Syloid XDP1510</td>
<td>118.11</td>
<td>0.86</td>
<td>1.34</td>
<td>6.83</td>
<td>0.2556</td>
</tr>
<tr>
<td>Syloid XDP3150</td>
<td>185.63</td>
<td>0.96</td>
<td>1.32</td>
<td>8.29</td>
<td>0.5336</td>
</tr>
<tr>
<td>Syloid XDP500</td>
<td>148.97</td>
<td>1.10</td>
<td>0.96</td>
<td>9.62</td>
<td>0.3976</td>
</tr>
</tbody>
</table>

Figure 4: SEDDS loaded Syloid XDP 3150 manufactured with two kneading zones.

Figure 5: Droplet size - solid SEDDS Syloid XDP3150.

Figure 6: Droplet size - solid SEDDS Syloid XDP3150.

Figure 7: SEM images of Syloid XDP powders and solid SEDDS.

SEDDS manufacture — two kneading zones
Good mixing efficiency, seen as a homogeneous particle size distribution was observed for both Syloid Grades. Increasing the lipid loading to 3:1, rendered the structure to a gel-like structure (Figure 3 and 4). At a screw speed of 100rpm and a 2:1 to lipid loading, a maximum throughput of 750-850 g/h was achieved for Syloid 3050 and 1000 g/h for Syloid XDP 3150.

Lipid loading — Loss on Ignition
Solid SEDDS were heated to 600°C for 1 hour in a Nabertherm furnace and the loss in weight determined.

Lipid size analysis of liquid and solid-self-emulsifying formulations was performed on samples obtained from a dissolution test (USP II, 60min, 100rpm, 235°C water). After centrifugation, supernatants were filtered using a Zetasizer Nano-ZS.

Powder flow characterization - Powder rheometry
The Consolidated Bulk Density (CBD) and Basic Flowability Index (BFE) increased after lipid loading of silica particles. Lipid loading of 2:1 showed lower values than 1:1 (Table 2). The stability index (SI) was directly proportional to the extent of lipid loading. All Flow Rate Indexes (FRI) showed non-cohesive behaviour (<3) with FRIs inversely proportional to liquid loading of particles. The Specific Energy (SE) of Syloid XDP 3150 was higher than 3050. Lipid loading affects SE of Syloids differently: SE increases for 3050 at 2:1 and 3:1; at 2:1 SE decreases for 3150, but SE is highest at 3:1.

Results and Discussion
SEDDS: The optimised formulation (F3) was composed of 15 % Labrafir M1944CS, 60% Labrasol and 5 % Capryol 90 (%w/w). F3 spontaneously formed a homogeneous emulsion with a droplet size of less than 200 nm (in water) and possessed pH robustness at pH 1.2 and pH 6.8.

Solid SEDDS manufacture — conveying elements only
Poor process efficiency, resulting in inhomogeneous distribution of liquid SEDDS on Syloid XDP 3050 (small and large particles) was observed (Figure 2a-b). Due to poor mixing, Syloid XDP 3150 was not tested.

Future Work
Further studies will look at excipient description studies, as well as silica particle size distribution and pore structure characterisation.

Acknowledgements
The authors would like to thank Fraser Mahbott for the help with SEM images.