Preparation and Characterisation of free flowing solid lipid based drug delivery systems using a twin screw extruder

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Introduction

Self emulsifying drug delivery systems (SEDDs) are lipid based formulations which spontaneously form stable emulsions under mild agitation in gastro intestinal (GI) fluids (Cerpnjak et al., 2013). Although liquid SEDDS and SMEDDS are beneficial to enhance drug bioavailability, low stability, leaching, 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 to 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 characterised.

Materials

SEDDS: Labrasil M1944CS, Labrasol and Capryol 90 were provided by Gattefosse (SAS, France).

Solid carriers: Syloid XDP3050 and Syloid XDP3150 were provided by Grace GmbH & Co.KG (Worms, Germany).

Buffers: All other chemicals were purchased from Sigma Aldrich and were of analytical grade.

Table 1: Syloid XDP specifications.

Trade name	Syloid® XDP 3050	Syloid® XDP 3150
Physical form	White powder	
Oil Absorbing Capacity (ml/100 g)	300 (Linseed oil)	
Mean particle size (µm)	48-66	120-170
Specific surface area (BET) (m^2/g)	320	
Tapped Bulk density (g/ml)	0.275	
pH (5%slurry)	4.0-8.0	

Methods

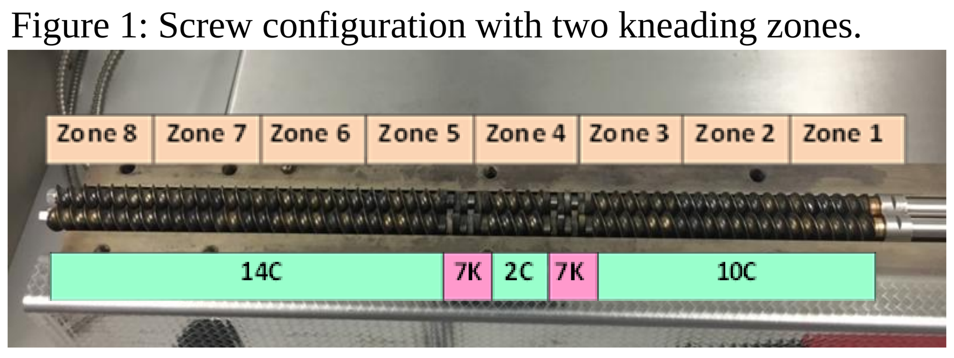
Preparation of liquid SEDDS

A stable SEDDS formulation was developed employing Labrafil M1944CS (5-35%), Labrasol (60-90%) and Capryol 90 (0-15%).

Manufacture of solid SEDDs

Solid carriers were fed into zone 3 of a Thermo Scientific® Process 11 twin screw extruder . Liquid SEDDS were added in zone 4. Lipid 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 60° (K)) (Figure 1).

Figure 1: Screw configuration with two kneading zones.



Lipid Loading - Loss on Ignition

Solid SEDDs were heated to 600ºC for 1 hour in a Nabertherm furnace and the loss in weight determined.

Droplet size analysis of liquid and solid self-emulsifying formulations was performed on samples obtained from a dissolution test (USP II, 60mins, 50rpm, 250mL water). After centrifugation, supernatants were analysed using a Zetasizer Nano ZS.

Powder flow characterization - Powder rheometry

The Dynamic test (stability and variable flow rate) was performed for the solid carriers and the lipid loaded carriers.

SEM

Samples were fixed on carbon tape and subject to analysis using a Keysight FE SEM.

Results and Discussion

SEDDS: The optimised formulation (F3) was composed of 15 % Labrafil M 1944 CS, 80 % Labrasol and 5 % Capryol 90 (%w/w). F3 spontaneously formed a homogenous 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 mixing 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.

Solid SEDDS manufacture – two kneading zones

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

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

Syloid XDP3050	Feeder speed	Screw speed (rpm)	Liquid rate (ml/min)	Ratio (Carrier: SEDDS)	Torque (%)
	29 conveying elements				
2a)	10	50	2.5	1 : 1	2
2b)	10	50	3.0	1 : 1.2	2

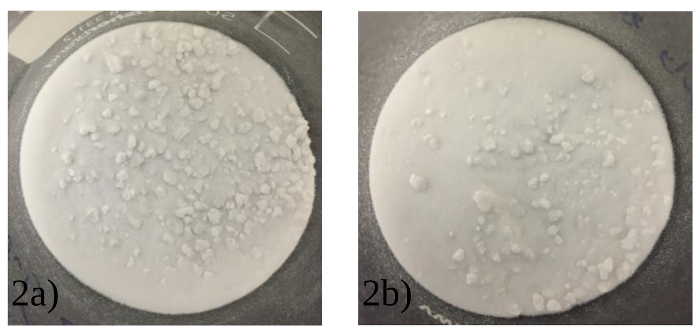
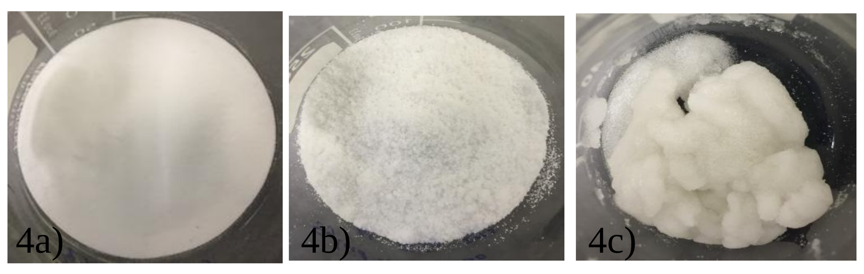


Figure 3: SEDDS loaded Syloid XDP 3050 manufactured with two kneading zones.

Syloid XDP3050	Feeder speed	Screw speed (rpm)	Liquid rate (ml/min)	Ratio (Carrier: SEDDS)	Torque (%)
	2 mixing zones of each 7 kneading elements				
3a)	10	50	3.0	1 : 1.2	2
3b)	10	50	4.0	1 : 1.6	3
3c)	10	50	5.0	1 : 2	16
3d)	10	50	7.5	1 : 3	3

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

Syloid XDP3150	Feed rate	Screw speed (rpm)	Liquid rate (ml/min)	Ratio (Carrier: SEDDS)	Torque (%)
4a)	10	50	3	1: 1	2
4b)	10	50	5.9	1: 2	23-27
4c)	10	50	8.8	1: 3	2



Lipid loading - Loss on Ignition

Lipid loading values (1:1 up to 3:1) under different processing conditions were confirmed by the Loss on Ignition assay.

Solid SEDDS - Droplet size analysis

Syloid XDP 3150 at a 1:1 lipid loading showed similar unimodal droplet size distribution as liquid SEDDS F3 (200 nm). With increasing lipid loading, the droplet size of emulsified solid SEDDS increased and changed from a unimodal to a bimodal size distribution (Figure 5, 6). This effect was more pronounced for Syloid XDP3050, even at the low lipid loading of 1:1. This may be due to differences in excipient desorption from the silica particles Van Speybroeck et al., 2012). The desorption of excipients as a diffusion controlled process is also dependant on the particles pore channel length and volume, which in turn varies with particle size (Choudhary, 2014). The difference between Syloid XDP3050 and 3150 may be due to the difference in pore size.

Figure 5: Droplet size – solid SEDDS Syloid XDP 3150

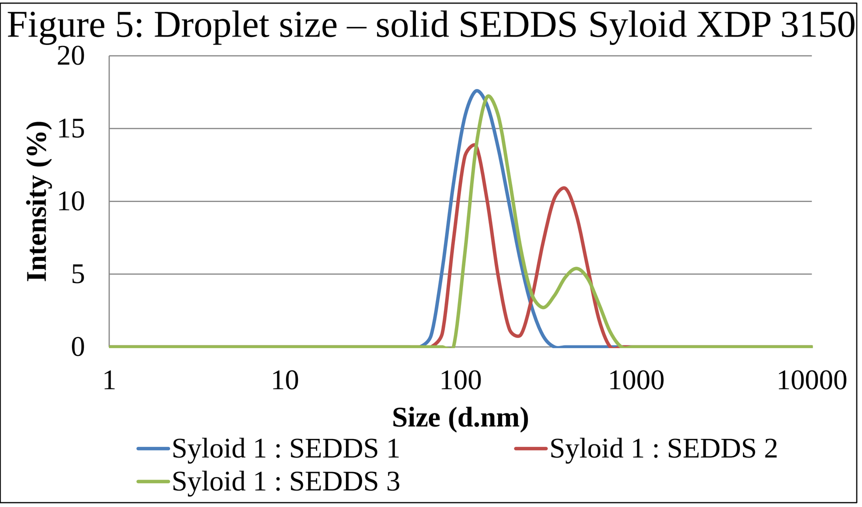
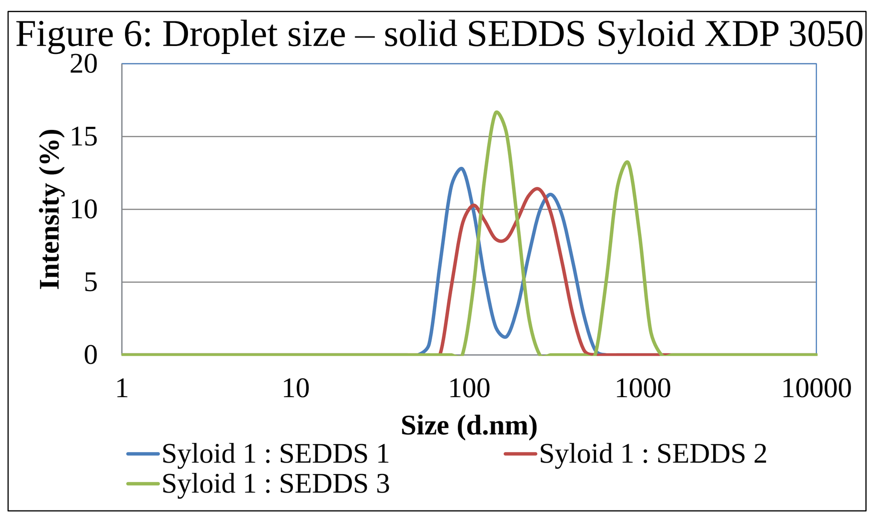


Figure 6: Droplet size – solid SEDDS Syloid XDP 3050



Powder rheometry

The Consolidated Bulk Density (CBD) and Basic Flowability Energy (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 FRI's inversely proportional to lipid 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.

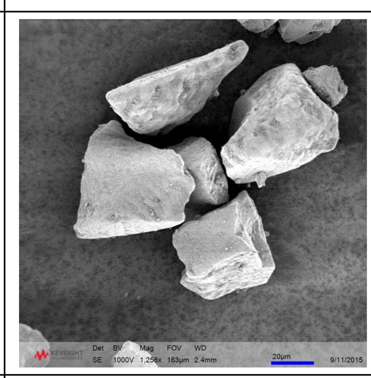
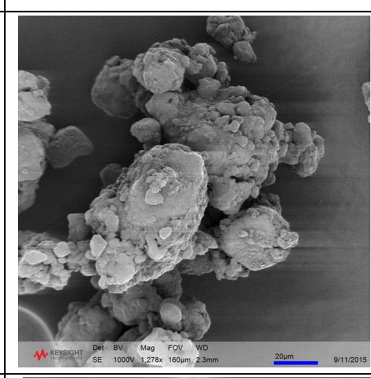
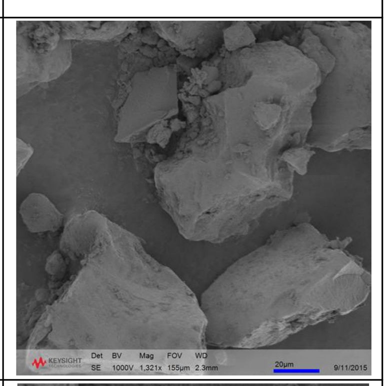
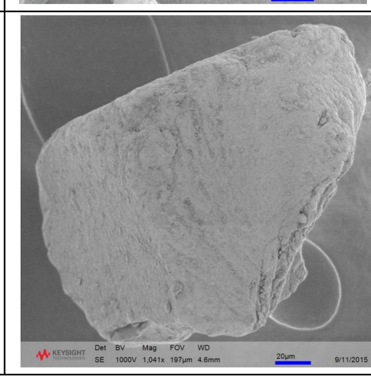
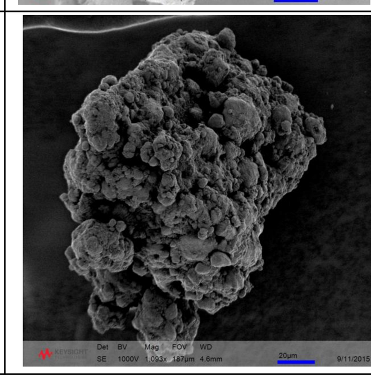
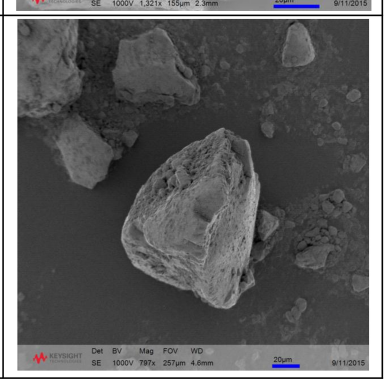
Table 2: Dynamic test results for Syloid XDP powders and solid SEDDS.

Ratio by weight of solid carrier to liquid SEDDS	BFE (mJ)	SI	FRI	SE (mJ/g)	CBD (g/ml)
Syloid XDP3050	42.32	0.89	1.54	4.12	0.2484
1:1	144.97	0.94	1.41	4.95	0.5417
1:2	89.25	1.28	1.18	7.56	0.3304
Syloid XDP3150	118.11	0.86	1.34	6.83	0.2556
1:1	185.63	0.96	1.32	5.29	0.5336
1:2	148.97	1.10	0.96	6.92	0.3976

SEM analysis of solid SEDDS

Both syloid grades showed similar changes when loaded with lipid formulation. At a lipid loading of 2:1 the surface changed from a smooth to a rough appearance. At a lipid loading of 3:1 the surface appeared smooth again. However, the appearance of smaller particles was noted for both Syloid XDP grades (Fig. 7).

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

Syloid XDP	Syloid XDP only	Lipid loading 2:1	Lipid loading 3:1
3050			
3150			

Conclusion

The investigated continuous process of adsorbing liquid SEDDs onto solid carriers produced solid SEDDS with good flow properties. Syloid XDP 3150 seemed more robust to the process than Syloid XDP 3050. Changes in droplet size distributions were observed after solidification of SEDDS.

Future Work

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

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