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# A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: Characterization, dissolution, *in vitro* digestion and incorporation into solid pellets

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## ABSTRACT

The aim of the current study was the development of a new pellet based self-emulsifying (SE) drug delivery system for the oral delivery of poorly soluble drugs. Furthermore, we wanted to investigate the influence of physiological dilution media and enzymatic digestion on the solubilization capacity of the formulation for the model drug Progesterone.

Lipid mixtures composed of Solutol® HS 15 and medium chain glycerides were optimized with respect to their self-emulsifying properties. The liquid SE lipid was mixed with microcrystalline cellulose and transformed into pellets by extrusion/spheronization. The pellets were characterized for size, shape, surface characteristics and friability. *In vitro* dissolution and digestion experiments were carried out using physiological dissolution media.

The droplet diameter of the dispersed SE mixtures was largely affected by changing the oil to Solutol® HS 15 ratio. Moreover, digestion of SE mixtures changed the solubilization capacity for Progesterone. Pellets with good properties (size, shape and friability) have been produced through the incorporation of a selected SE mixture into MCC.

In conclusion, extrusion/spheronization is a suitable process to produce solid self-emulsifying pellets with up to 40% load of a liquid SE mixture. Digestion induces a change in lipid composition which affects the solubilization capacity of the lipid phase.

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## 1. Introduction

The fact that a large majority of the newly discovered chemical entities and many existing drug molecules are poorly water soluble presents a serious challenge to the successful formulation and marketing of new drugs in the pharmaceutical industry (Lipinski et al., 2001). Since in many cases the dissolution step is the rate limiting step, formulation design can be a useful approach to improve the absorption and thus the oral bioavailability of such drug candidates (Pouton, 2006).

Many formulation approaches are presently employed to tackle the formulation challenges of poorly water-soluble

drugs, either by means of improving the dissolution rate or via presenting and maintaining the drug in solution throughout its period in the gastrointestinal tract.

Self-emulsifying drug delivery systems (SEDDS) are among the methods used to improve the oral bioavailability of poorly soluble drugs by presenting and maintaining the drug in a dissolved state, in small droplets of oil, all over its transit through the gastrointestinal tract (Pouton, 2000). SEDDS are composed of a mixture of oil and surfactant and they are capable of forming oil-in-water emulsions upon gentle agitation provided by the gastrointestinal motion. The SEDDS properties strongly depend on the selected lipids and emulsifiers and their mixing

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ratios. In addition, the characteristics and load of the incorporated drug are critical parameters. The use of lipid mixtures with different polarities and emulsifiers give the possibility to optimize the SEDDS for a particular drug.

The digestion of lipid-based formulations, in the presence of endogenous materials (bile salts, phospholipids and cholesterol), induces a change in lipid composition and result in the formation of different colloidal phases (micelles, vesicles, and liquid crystalline phases) in the intestinal lumen (Patton and Carey, 1979; Carey et al., 1983; Fatouros et al., 2007; Staggers et al., 1990). The change in lipid composition, induced by digestion, plays a major role in the solubilization capacity and consequently the absorption of co-administered drugs (Kossena et al., 2005; Porter et al., 2004, 2007).

The idea of combining the advantages of SEDDS with pellets through the inclusion of a self-emulsifying mixture into microcrystalline cellulose (MCC) and the production of pellets using extrusion/spheronization was introduced by Newton et al. (2001). Furthermore, it was found in a comparative bioavailability study made by Tuleu et al. (2004) that the bioavailability was equivalent when the drug was administered to dogs in a self-emulsifying system either in a liquid form or as a solid pellet dosage form.

In our previous work, the possibility of incorporating a semisolid self-emulsifying system into pellets and the production of pellets by means of extrusion/spheronization was shown (Abdalla and Mäder, 2007).

The aim of the current study was the development of a new pellet based self-emulsifying (SE) drug delivery system for the oral delivery of poorly soluble drugs. Furthermore, we wanted to investigate the influence of physiological dilution media and enzymatic digestion on the solubilization capacity of the formulation for the model drug Progesterone.

In the current study, the SE mixture that combines good self-emulsifying properties, acceptable solubilization of the model drug, and optimum surfactant concentration, was selected to be incorporated into pellets by means of extrusion/spheronization. Pellets were characterized for size, shape and friability. Environmental scanning electron microscopy (ESEM) was used to get a deeper understanding of the pellet structure. Furthermore, the release of Progesterone from the pellets into physiologically relevant media was measured to investigate whether or not MCC might interfere with the release properties of the lipid mixture.

## 2. Materials and methods

### 2.1. Materials

Avicel PH 101 (microcrystalline cellulose (MCC)) was purchased from FMC BioPolymer (PA, USA), and was used as a pellet forming material. Solutol® HS 15 (macrogol-15-hydroxystearate) was kindly provided by BASF AG (Ludwigshafen, Germany). Captex® 355 EP/NF (triglycerides of caprylic/capric acid) and Capmul® MCM (medium chain mono- and di-glycerides) were kindly provided by Abitec Corporation (Janesville, WI, USA). Progesterone was purchased from Sigma-Aldrich (Steinheim, Germany). Pancreatin (activity equal to 8× USP specification) and bile extract (used as

a heterogeneous source of bile salts) were obtained from Sigma (Steinheim, Germany). Acetonitrile and methanol were of HPLC gradient grade and were purchased from Mallinckrodt Baker (Deventer, Netherlands). All other materials were of analytical grade and were used as received.

### 2.2. Methods

#### 2.2.1. Preparation and assessment of self-emulsifying mixtures

2.2.1.1. Preparation of self-emulsifying mixtures. The compositions of the formulations are listed in Table 1. The preparation of the self-emulsifying (SE) mixtures involved the following steps:

- Mixing of Solutol® HS 15, Captex® and Capmul® at 50 °C.
- Dissolving Progesterone in the lipid mixture.
- Cooling to room temperature.
- Equilibrating the mixtures for 24 h, to examine for any signs of phase separation.

2.2.1.2. Assessment of self-emulsification. The USP 24 rotating paddle apparatus (Pharma Test PTW II, Hainburg, Germany) was used to evaluate the efficiency of self-emulsification of different mixtures. One gram of each mixture was added to 200 ml of distilled water with gentle agitation condition provided by a rotating paddle at 70 rpm and at a temperature of 37 °C. The process of self-emulsification was visually monitored for the rate of emulsification and for the appearance of the produced emulsions.

2.2.1.3. Droplet size determination. Photon correlation spectroscopy (PCS) was used for determination of droplet diameter of the formed emulsions. The measurements were performed by means of a Malvern HPPS system (Malvern Instruments Ltd., United Kingdom) utilizing a backscatter angle of 173°.

**Table 1 – Formulations composition of the different self-emulsifying mixtures produced.**

Formulation	Self-emulsifying mixture composition (% w/w)	
	Captex 355:Capmul MCM	Solutol HS15
<i>Formulation A with 1:1 Captex to Capmul ratio</i>		
A1	80	20
A2	75	25
A3	70	30
A4	65	35
A5	60	40
A6	55	45
A7	50	50
<i>Formulation B with 2:1 Captex to Capmul ratio</i>		
B1	80	20
B2	75	25
B3	70	30
B4	65	35
B5	60	40
B6	55	45
B7	50	50

Samples were taken from the previous experiment (Section 2.2.1.2) and were measured without dilution at 25 °C. Mean hydrodynamic droplet diameter, expressed as z-average, was recorded using the Malvern HPPS software. The F- and t-tests were used for statistical analysis of the data with a confidence level of 0.95 (also for the other experiments).

**2.2.1.4. Equilibrium solubility measurements.** Progesterone equilibrium solubility measurements were carried out in the following media: phosphate buffer pH 6.8, FaSSIF and FeSSIF (see Section 2.2.1.5 for detailed composition). Furthermore, blank SE mixtures were mixed with different dissolution media (1%, w/v) in order to evaluate the influence of the formulation on drug solubilization. For the assessment of the Progesterone equilibrium solubility in digested self-emulsifying systems under physiological conditions, blank aqueous digestion phases were obtained by carrying out the *in vitro* digestion experiment (Section 2.2.1.5) with drug free SE mixtures for 1 h, followed by ultracentrifugation (108,000 × g, 30 min, 37 °C, Avanti J-301 centrifuge, Beckman Coulter Inc., CA, USA) and separation of the aqueous phase from the pellet phase.

Progesterone was added in excess to 5 ml of the dissolution medium in sealed tubes. Samples were incubated in an end-over-end mixer at 37 °C for 24 h and then centrifuged for 10 min in an Eppendorf centrifuge (MiniSpin, Eppendorf AG, Hamburg, Germany) at 13,000 rpm. The supernatant was filtered through a 0.2 µm Millipore filters, diluted to a suitable concentration range and analyzed by HPLC for Progesterone concentration.

**2.2.1.5. *In vitro* digestion.** Digestion experiments were carried out by the dispersion of 1% (w/v) of the SE mixtures, containing the drug dissolved at around 70% of saturation solubility in the corresponding mixture, in 7.5 ml digestion buffer (53.4% KH<sub>2</sub>PO<sub>4</sub> 1/15 M and 46.6% Na<sub>2</sub>HPO<sub>4</sub>·2H<sub>2</sub>O 1/15 M, 150 mM NaCl, 5 mM CaCl<sub>2</sub>·2H<sub>2</sub>O, pH 6.8) containing either a low (5/1.25 mM bile salts/phospholipids) or a high (20/5 mM bile salts/phospholipids) concentration of bile salts and phospholipids to simulate the intestinal fluids in the fasting (FaSSIF) and the fed state (FeSSIF) respectively (Hernell et al., 1990; Ladas et al., 1984; Kaukonen et al., 2004). Experiments were carried out in an end-over-end apparatus rotating at a rate of 15 rpm and a temperature of 37 °C, and were started by the addition of 65.77 mg Pancreatin containing 450 U/ml of pancreatic lipase activity. 200 µl samples were taken at regular time intervals and centrifuged at 13,400 rpm for 4 min in an Eppendorf centrifuge (MiniSpin, Eppendorf AG, Hamburg, Germany) in order to separate the precipitate from the micellar phase. The supernatant was diluted with the mobile phase and analyzed for Progesterone by HPLC using a Merck Hitachi HPLC system consisting of a model AS 4000A auto-sampler, L 6200A programmable pump and a L 4250 UV-vis detector (Merck, Darmstadt, Germany) using a Hibar® RT 125-4 LiChrospher® 100 RP-18 (5 µm) column (Merck, Darmstadt, Germany). The mobile phase, composed of acetonitrile–water (70:30, v/v) adjusted to pH 3.5 with orthophosphoric acid, was pumped at a flow rate of 1 ml/min. 20 µl was injected and the column effluent was monitored at a wavelength of 240 nm. The retention time for Progesterone was found to be 2.9 min.

## 2.2.2. Formulation and characterization of pellets

**2.2.2.1. Formulation of pellets.** Self-emulsifying mixture B5 was selected for incorporation into pellets, in three different levels (10, 20, and 40%). The pellets were produced by the following extrusion/spheronization process: The self-emulsifying mixture is mixed with MCC in a kneader for 15 min. This was followed by addition of water until a mass suitable for extrusion is obtained. The wet mass produced was then extruded at 40 rpm in a radial screen twin-screw extruder (Fuji-Paudal, Japan) with a die of 1 mm diameter circular holes. The extrudate was spheronized for 3 min in a 250 mm radial plate spheronizer (Fuji-Paudal, Japan) using a cross-hatch frictional plate of 3 mm × 3 mm pitch and 1.2 mm depth. The produced pellets were then dried in a desiccator over silica gel at room temperature.

**2.2.2.2. Pellets size and shape analysis.** A set of  $\sqrt{2}$  progression standard sieves (Retsch, Hann, Germany) agitated for 20 min with a sieve shaker (Retsch, Hann, Germany) was used for performing the size analysis of 100 g of the produced pellets. The modal size fraction and the interquartile range (IQR) were determined from the cumulative percent undersize curve. The geometrical mean diameter ( $D_g$ ) and the geometrical standard deviation ( $\sigma_g$ ) were determined from the log-normal distribution curve (Martin, 1993).

Shape analysis was performed on 1000 pellets within the 1000–1400 µm fraction using a stereomicroscope (SZX9, Olympus, Germany), a digital camera (DIG 1300C, Micromotion, Germany) and an image analysis software, Image C (Imtronic, Germany). For each pellet, 36 Feret diameters were measured and used to calculate the mean Feret diameter. The maximum Feret diameter and Feret diameter perpendicular to it were obtained and used to calculate the aspect ratio.

**2.2.2.3. Electron microscopy.** Surface characteristics of pellets with 10, 20 and 40% content of SE mixture B5 were investigated by means of environmental scanning electron microscopy (ESEM, Philips XL 30 FEG, Philips electron optics). SEM micrographs were obtained by means of a special gas secondary electron (GSE) detector using the wet-mode method with a pressure of 1.3 mbar and acceleration voltage of 12 kV. Moreover, pure MCC pellets, prepared with the same method, were also investigated to serve as a control for comparison with the SE pellets.

**2.2.2.4. *In vitro* release.** *In vitro* release experiments were performed in an end over end apparatus rotating at a rate of 15 rpm and a temperature of 37 °C. Therefore samples of pellets corresponding to 1% (w/v) final SE mixture concentration in the release media were assayed. The composition of the investigated pellets is shown in Table 2.

Three different release media were chosen: phosphate buffer (pH 6.8) and *in vitro* digestion buffer with Pancreatin under either FaSSIF or FeSSIF conditions. Pancreatin powder containing 450 U/ml of pancreatic lipase activity was added at the beginning of the digestion experiment. 200 µl samples were taken at regular time intervals and centrifuged at 13,400 rpm for 4 min in order to separate a dispersed phase and a pellet phase. The supernatant was diluted with the mobile phase and analyzed for Progesterone by the previously

**Table 2 – Composition of the investigated pellets.**

Ingredients	Pellet composition (% w/w)
MCC PH 101	58.7
Solutol HS15	16
Captex 355	16
Capmul MCM	8
Progesterone	1.3

described HPLC method. All experiments were carried out in triplicate.

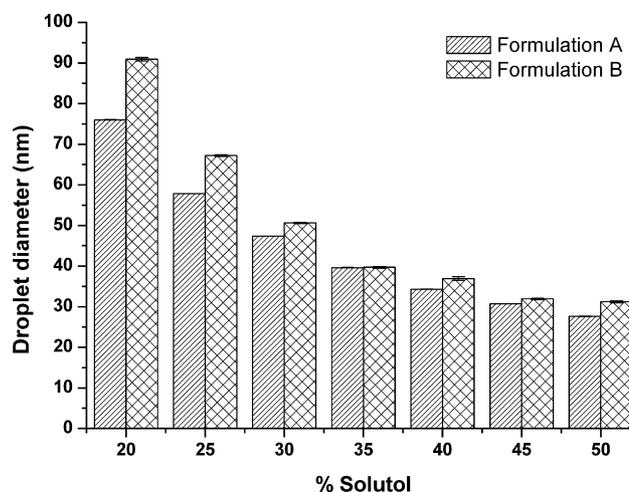
### 3. Results

#### 3.1. Preparation and *in vitro* assessment of the SE mixtures

Most of the SE mixtures produced belong to type IIIA in the lipid formulation classification system (LFCS) proposed by Pouton (2000, 2006) with an oil content between 40 and 80% (w/w), a water-soluble surfactant (HLB > 12) content of 20–40% and hydrophilic cosolvent content of 0–40%. In this study, Captex<sup>®</sup> 355 EP/NF (triglycerides of caprylic/capric (C<sub>8</sub>/C<sub>10</sub>) acid) was used as the oil, and the corresponding mono- and di-glycerides mixture (Capmul<sup>®</sup> MCM) was used to increase the solubilization and self-emulsification capacity. Solutol<sup>®</sup> HS 15 (main component: polyoxyethylene-660-12-hydroxystearate) was used as the water-soluble surfactant (HLB = 14–16).

All the formulated mixtures were efficiently emulsified within the first minute of contact with the dispersion medium and there was no evidence of phase separation or any instability problem for at least 24 h. The optical clarity of the produced SEDDS dispersions differed largely, from a bright white toward a clear or slightly bluish appearance, with increasing amounts of the surfactant proportion in the formulation, indicating that the surfactant plays a crucial role in determining the properties and functionality of the resulting dispersion.

The significance of emulsion droplet size in the *in vivo* performance of the formulation is not yet clear. Tarr and Yalkowsky (1989) have demonstrated enhancement of the rate of intestinal absorption of cyclosporine through the reduction of the emulsion droplet size. One possible explanation of the enhanced absorption observed with small particle size is the larger surface area available for partitioning of the drug and for lipase activity. However, we fully agree to a recent statement by Pouton, that the role of droplet size is less important than it was assumed by some authors due to the fact that digestion will take place directly after the lipid dispersion leaves the stomach and at this stage particle size will have no or little effect (Pouton, 2006). In our study, the droplet diameter of the dispersed SE mixtures was determined by means of PCS and expressed as the z-average. The results of droplet size determination experiment of the different formulation studied are shown in Fig. 1. The concentration of Solutol<sup>®</sup> HS 15 in the formulation affects the nature of emulsion formed. Increased Solutol<sup>®</sup> HS 15 concentrations lead to an obvious improvement in the optical clarity, which correlates well with the determined particle size of the corresponding dispersion. It was also noticeable that increasing the amount of Captex<sup>®</sup>,



**Fig. 1 – Effect of Solutol<sup>®</sup> HS 15 content on the droplet diameter (mean ± S.D., n = 3) of the emulsions produced by dispersing SE mixtures in water.**

the medium chain triglyceride oil, and decreasing the amount of Capmul<sup>®</sup>, in the formulation with a 2:1 (w/w) Captex<sup>®</sup> to Capmul<sup>®</sup> ratio, decreased the emulsification efficiency and caused higher particle sizes and lower optical clarity. This finding corresponds to the decreased polarity of the oily phase. At higher Solutol<sup>®</sup> HS 15 concentrations the decrease in the droplet diameter in relation to the Solutol<sup>®</sup> HS 15 concentration was very small for both Captex<sup>®</sup>/Capmul<sup>®</sup> ratios. This could be attributed to the fact that Solutol<sup>®</sup> HS 15 is a micelle forming agent.

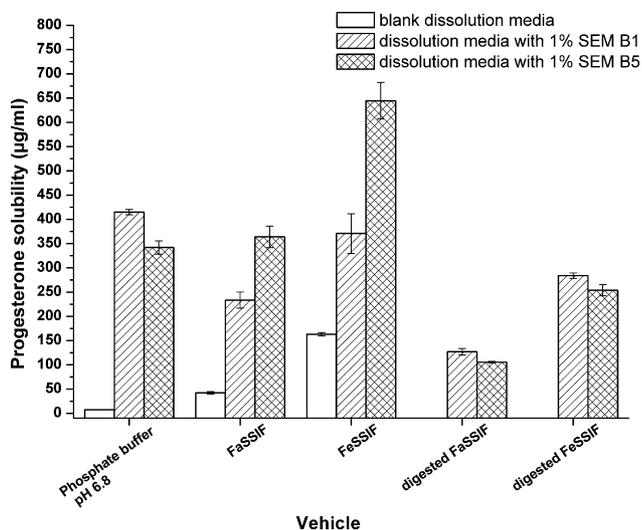
The preference between different Captex<sup>®</sup> to Capmul<sup>®</sup> ratios will depend on the solubilization characteristics of the drug. A higher proportion of triglyceride oil will be required for highly hydrophobic drugs but for less hydrophobic drugs an improvement of solvent capacity could be achieved through increasing the proportion of mixed mono- and di-glycerides. In general, a compromise between drug loading capacity and efficient emulsification has to be achieved.

#### 3.2. Equilibrium solubility

The equilibrium solubility of Progesterone in different vehicles is given in Fig. 2. The solubility increases from plain buffer solution to FaSSIF and FeSSIF media which corresponds to the higher concentration of lecithin and bile acids. A high solubility was achieved with 1% w/v of the self-emulsifying mixtures B1 and B5 in buffer.

Interestingly, the solubilization capacity was different when dispersions of SE mixtures in FaSSIF and FeSSIF were investigated. Depending on the formulation, the presence of mixed micelles and lecithin had either a positive or negative effect on the solubilization capacity. This finding could be attributed to interactions of formulation components with micelles or vesicular structures which lead to a change of polarity of the system.

The aqueous phases which were obtained after digestion of the diluted SE mixtures showed a significant lower solubilization capacity for Progesterone Again, the FaSSIF system



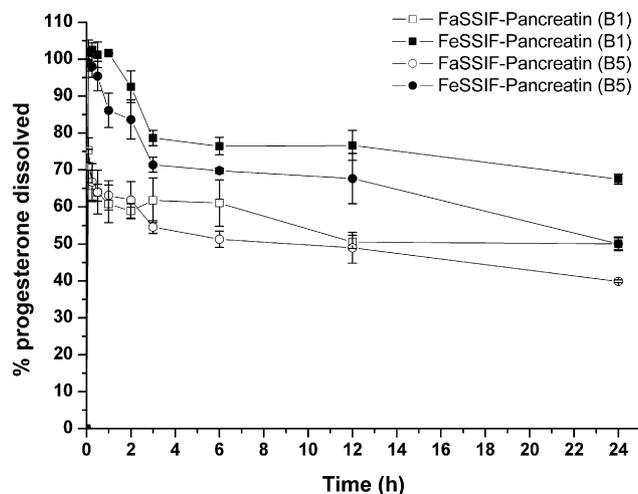
**Fig. 2 – Equilibrium solubility (mean  $\pm$  S.D.,  $n = 3$ ) of Progesterone in different media.**

solubilized less drug molecules compared to the FeSSIF system. The digestion of the lipid phase in the SE mixtures B1 and B5 loaded FeSSIF and FaSSIF systems leads to the formation of digestion products of the SE mixture (e.g. hydroxystearate, free PEG, middle chain fatty acids, monoglycerides), and digestion products of the mixed micellar phase (e.g. lysolecithin and long chain free fatty acids). As a result, the polarity of the lipids increases and the composition and structures of the lipid phase will change, which will affect the drug solubility.

Overall, the results of the solubility study show that (i) mixed micelles increase the solubility, (ii) diluted SE mixtures B1 and B5 (1% in phosphate buffer) have a high solubilization capacity, (iii) the presence of bile salts and phospholipids affects the solubilization capacity of diluted SE mixtures B1 and B5 and (iv) the solubilization capacity of enzymatic digests is lower compared to undigested SE mixtures.

### 3.3. *In vitro* digestion

The solubilization of Progesterone during the *in vitro* digestion of SE mixtures B1 and B5 was monitored in both FaSSIF and FeSSIF conditions. Digests were centrifuged and were consequently separated into a dispersed phase and a pellet phase with no evident oil phase which complies with data presented in different studies (Kaukonen et al., 2004; Sek et al., 2002). For formulation B1, in FeSSIF, Progesterone concentration was reaching and maintaining the saturated solubility for at least 1 h. Thereafter, a drop of the solubilization capacity was noticed (Fig. 3). Precipitation of Progesterone in FeSSIF occurs more rapidly for formulation B5, which could be attributed to the lower oil content in the formulation leading to the liberation of a lower amount of monoglycerides and fatty acids as digestion proceeds (Kaukonen et al., 2004). In FaSSIF digestion experiments, precipitation starts at earlier stage for both formulations which is attributable to the lower concentration of bile salts and phospholipids in the digestion media. Furthermore, these data are in agreement with the results obtained from equilibrium solubility study of Progesterone. The results



**Fig. 3 – Mean ( $\pm$ S.D.,  $n = 3$ ) percentage of Progesterone dissolved as a function of time (h), after the digestion of 1% (w/v) of the SE mixtures B1 in the digestion buffer in FaSSIF ( $\square$ ) and in FeSSIF ( $\blacksquare$ ), and SE mixture B5 in FaSSIF ( $\circ$ ) and FeSSIF ( $\bullet$ ). Experiments were initiated by the addition of Pancreatin enzyme (450 U/ml of pancreatic lipase activity).**

clearly indicate that (i) enzymatic digestion decreases the solubilization capacity for Progesterone, (ii) the solubility is enhanced under FeSSIF conditions, (iii) the digested formulation B1 solubilize slightly more drug compared to the digested B5 SE mixture.

### 3.4. Formulation and assessments of SE pellets

#### 3.4.1. Pellets size and shape analysis

Due to its superior emulsification properties, formulation B5 was selected for incorporation into MCC in different ratios to assess the possibility of pellets production. Pellets were produced by extrusion/spheronization. Assessment of the quality of the produced pellets was made by evaluating their size and shape. Details of the results of size and shape analysis are shown in Table 3 which includes the values of the geometrical mean diameter ( $D_g$ ) and the geometrical standard deviation, the interquartile range (IQR, expected to include about 50% of the data), the mean Feret diameter ( $D_{feret}$ ) and the aspect ratio. The results show that it was possible to produce pellets with all MCC-lipid ratios used up to a lipid load of 40%. Statistical analysis proved that increased lipid loads cause a small to moderate, but significant increase of the Feret diameter and the aspect ratio. Attempts to produce pellets with equal parts of the components (SEDDES:MCC = 50:50) failed. The extrudate stuck together and formed a big clump rather than pellets.

#### 3.4.2. ESEM investigations

ESEM investigations show that pellets with different incorporation level of SE mixture B5 exhibit different surface structures. Micrographs with the lowest magnification shows that all produced pellets were spherical in shape, which confirms with the aspect ratio measurements (Fig. 4). More details about the surface characteristics of pellets were obtained with

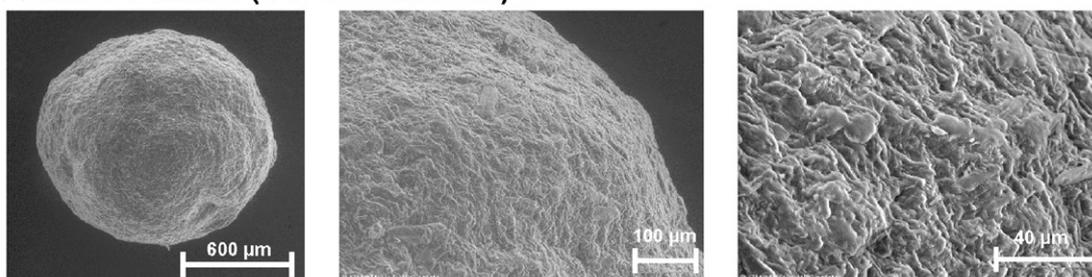
**Table 3 – Results of the size and shape analysis of the pellets.**

Pellets composition (% w/w)		Sieve analysis (100 g)			Image analysis	
SE mixture (B5)	MCC	$D_g$ ( $\mu\text{m}$ )	$\sigma_g$	IQR ( $\mu\text{m}$ )	$D_{\text{feret}}$ ( $\mu\text{m}$ )	Aspect ratio
10	90	1103.3	1.16	243	$1100.45 \pm 145.7$	$1.054 \pm 0.051$
20	80	1274.6	1.38	267	$1240.32 \pm 143.2$	$1.065 \pm 0.045$
40	60	1353.2	1.59	320	$1412.68 \pm 194.6$	$1.087 \pm 0.092$

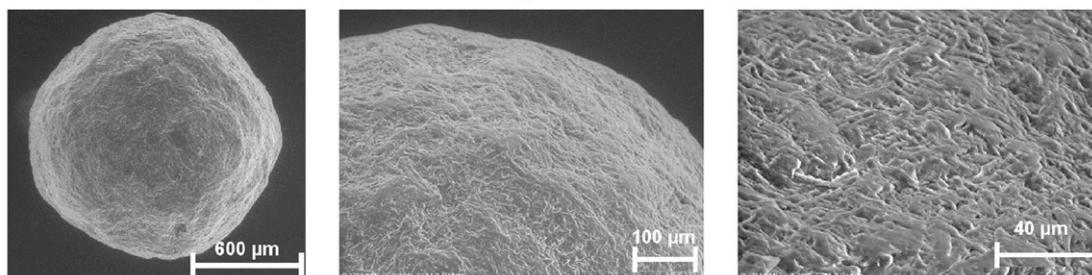
increasing the magnification. Fig. 4a shows typical features of the surface of MCC pellets with a highly rough and porous surface with apparent cellulose fibers network. For the pellets with 10% SE mixture, the surface become smoother, less porous but the cellulose fibers network were still observed in

the surface (Fig. 4b). As the SE mixture load increases to 20 and 40%, the pellets surface becomes smoother. There is obviously an incorporation of the SE mixture within the cellulose fibers network which causes a decrease of the pellet porosity (Fig. 4c and d).

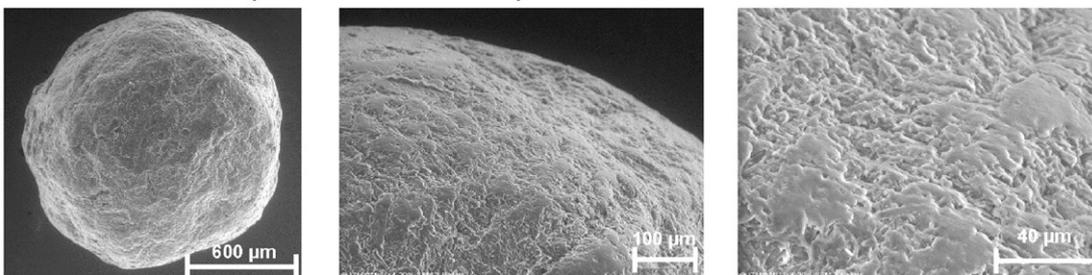
**(a) MCC Pellets (0% SE mixture)**



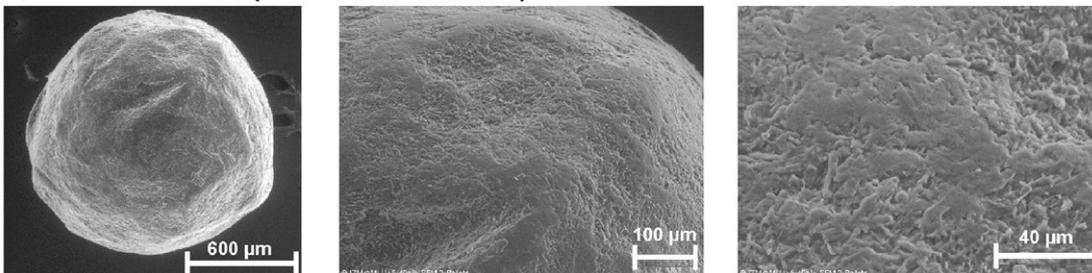
**(b) MCC Pellets (10% SE mixture)**



**(c) MCC Pellets (20% SE mixture)**



**(d) MCC Pellets (40% SE mixture)**



**Fig. 4 – ESEM pictures of self-emulsifying pellets with different load of the liquid self-emulsifying lipid mixture. (a) MCC pellets (0% SE mixture). (b) MCC pellets (10% SE mixture). (c) MCC pellets (20% SE mixture). (d) MCC pellets (40% SE mixture).**

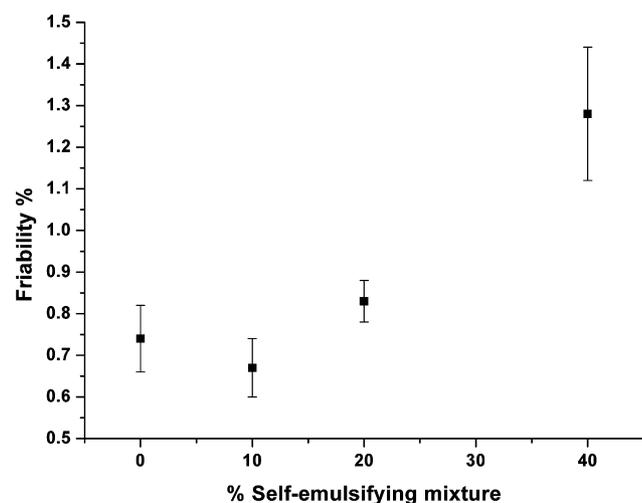
### 3.4.3. Assessment of friability

The results of the friability test show that the friability was low (less than 1%) even for lipid loads up to 20% and acceptable (less than 1.5%) for the high lipid load of 40% (Fig. 5). There was no significant difference between 0% and 10% lipid load. However, it was found that the friability of the pellets with 20% and 40% lipid load were significant higher compared to the lipid load of 10% (t-test, confidence 0.95). Most likely, a low percentage of liquid lipid is strongly bound by MCC. Increasing amounts (>10%) will most likely be less strongly adsorbed and therefore weaken the interactions within the pellets and increase friability. Nevertheless, the low friability values are very encouraging.

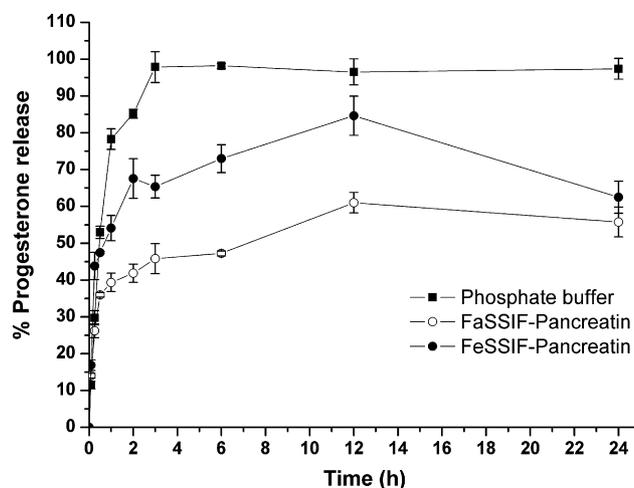
### 3.4.4. In vitro release testing

In vitro release experiments were conducted to evaluate the effect of different media on the release of Progesterone from the pellets. The results are shown in Fig. 6. In phosphate buffer, Progesterone was completely released within the first 2 h of the study and no precipitation was noticed until the end of the experiment. On the other hand, release of Progesterone in the digestion media under both FaSSIF and FeSSIF conditions was incomplete and precipitation of Progesterone was observed in the first few minutes of the experiment. Therefore, the presence of mixed micelles interferes with the performance of the SE lipid system under digestion conditions and leads to a decreased solubilization of the drug. Enhanced Progesterone precipitation in the FeSSIF and FaSSIF digestion media compared to the mixed micelle free medium could be attributable to several reasons including:

- Decreased digestion rate in the buffer medium due to insufficient solubilization of the digestion products.
- The presence of mixed micelles changes the composition of the lipid phase in the SE mixtures (e.g. translocation of SE components in the mixed micelles and of bile acids/lecithin into the SE droplets) which results finally in a decreased solubilization capacity compared to the parent SE system.



**Fig. 5 – Friability % (mean ± S.D., n = 3) of MCC pellets prepared with different % of self-emulsifying mixture incorporation.**



**Fig. 6 – Mean (± S.D., n = 3) percentage of Progesterone released as a function of time (h) from Progesterone loaded SE pellets in 7.5 ml phosphate buffer, pH 6.8 (■), and in digestion buffer in both FaSSIF (○) and FeSSIF (●) conditions. Sample of pellets corresponding to 1% (w/v) final SE mixture concentration in the release media was assayed.**

It is also likely that both reasons contribute to the Progesterone precipitation in the FeSSIF and FaSSIF media.

## 4. Conclusion

Stable isotropic SE mixtures have been formulated using a mixture of medium chain mono- and di-glycerides, medium chain triglycerides, and Solutol® HS 15 as a surfactant. The droplet sizes after dilution decreased with (i) increasing Solutol® HS 15 contents and (ii) for more polar lipid mixtures (e.g. increased ratio of partial glycerides compared to triglycerides). SE mixtures are able to solubilize Progesterone in buffer. Digestion of the lipid phase decreases the solubilization capacity. Therefore, applying in vitro digestion experiments for lipid formulations is important to enable prediction of the possible fate of the co-administered drug. It was also shown that the solubilization capacity strongly depends on the concentration of endogenously secreted materials such as bile salts and phospholipids.

The liquid lipid SE mixture was successfully transformed into solid pellets by means of extrusion/spheronization with a maximum load of 40%. The pellets had a uniform size, a spherical shape and low friability. ESEM pictures show the adsorption of the liquid oil between the MCC fibers. Moreover, the self-emulsifying properties are still preserved in the pellets. Therefore, extrusion/spheronization of SEDDS systems is an alternative to encapsulation in gelatine capsules.

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