**Tablets and minitablets prepared from spray-dried SMEDDS containing
naproxen**

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Abstract

The purpose of this study was to compare different solidification techniques (i.e. adsorption technique, spray-drying process, high-shear granulation, fluid-bed granulation) for preparing solid SMEDDS powders by using solid carriers identified as appropriate and to produce a single (tablets) or multiunit (minitablets) solid dosage form based on prepared solid SMEDDS loaded with naproxen in a dissolved (6% w/w) or supersaturated (18% w/w) state. Among the solidification techniques and carriers tested, the powders produced using the spray-drying process and maltodextrin (MD) as a carrier exhibited the best self-microemulsifying properties, comparable with liquid SMEDDS. Furthermore, DoE (Design of Experiments) showed that pressure at the nozzle and pump speed (regulating feed flow rate) applied during spray drying had a major and significant influence on self-microemulsifying properties (mean droplet size and PDI) of the solid SMEDDS prepared. Furthermore, it was shown that compression of solid SMEDDS into (mini)tablets influences its self-microemulsifying properties in a negative direction. This resulted in lowering the dissolution profile of naproxen from tablets and minitablets in comparison with liquid and solid SMEDDS. However, all compressed SMEDDS formulations still had considerable influence on the dissolution profile and solubility enhancement of naproxen.

Keywords: solidification, self-(micro)emulsifying properties, DoE, DSC, SEM, dissolution profile improvement

1 Introduction

2 Conventional Self-Microemulsifying Drug Delivery Systems (SMEDDS) are mostly
3 prepared in a liquid form and filled into gelatin capsules. This can produce some disadvantages of
4 the product, such as complex manufacturing methods and low stability due to interactions of
5 excipients with the capsule shell or precipitation of drug and/or excipients at storage temperature.
6 However, SMEDDS formulations are gaining increasing attention due to their ability to improve
7 drug solubilization and enhance drug release. In addition, drug absorption may be increased as a
8 result of the dissolved form of the drug and self-microemulsifying ability of the formulation
9 providing a small droplet size with a large interfacial surface area (Chang et. al., 1998; Porter et.
10 al., 2007; Pouton, 2000).

11 Therefore it is advisable to transform liquid SMEDDS into a solid dosage form with the
12 aim of combining the aforementioned advantages of SMEDDS with those of solid dosage forms
13 (e.g., low production costs, convenience of process control, high stability and reproducibility, and
14 improved patient compliance) (Jannin et. al., 2007; Sudheer et. al., 2012; Tang et. al., 2008).
15 Approaches for transforming conventional liquid SMEDDS into solid ones have been extensively
16 explored in recent years (Kallakunta et. al., 2012; Jannin et. al., 2007; Oh et. al., 2011).
17 Following various solidification techniques, various solid dosage forms with expressed self-
18 (micro)emulsifying properties can be prepared; namely, tablets, pellets, capsules, microcapsules,
19 solidified (micro)emulsions, solid dispersions, suppositories, implants, and so on (Jannin et. al.,
20 2007; Sudheer et. al., 2012; Tang et. al., 2008; Tan et. al., 2013).

21 The aim of this study was to comparatively evaluate several transformation techniques for
22 solid SMEDDS preparation; namely adsorption on porous carriers, spray drying, high-shear
23 granulation, and fluid bed granulation. First, method-specific solid carriers were selected in order
24 to identify the optimal transformation method in terms of self-microemulsifying and flow

properties. The method selection studies were performed on previously developed liquid SMEDDS consisting of Miglyol[®] 812, Peceol[™], Gelucire[®] 44/14, and Solutol[®] HS15 (Čerpnjak et. al., 2014).Based on the preliminary resultsobtained, DoE (Design of Experiments) was implemented as a key strategy in order to study the influence of process parameters on self-microemulsifying properties of prepared SMEDDS powders.Tablets and minitables were then prepared through direct compression of SMEDDS powders prepared throughspray-drying liquid SMEDDS containing dissolved (6% w/w) and partially suspended (18% w/w) naproxen as a model drug. Tablets and minitables were characterized with respect to their technological and self-microemulsifying properties and dissolution behavior in comparison with liquid and solid SMEDDS, physical mixture, and pure drug.

2. Experimental

2.1. Materials

Naproxen (NPX), maltodextrin (MD; Glucidex 19, Roquette Freres, Italy), hypromellose (Methocel E5LV Premium, Colorcon Ltd, UK), microcrystalline cellulose (MCC; Avicel PH 102, Avicel PH 101 (FMC International) and Avicel PH 200 (Asahi Kasei Chemicals)), magnesium stearate (FaciSpA, Italy),Aerosil[®] 200 (Aerosil, Evonik Industries, AG, Germany),talc (Imerys Talc Italia Spa), croscarmellose sodium (FMC International), and Neusilin[®] US2 (Fuji Chemical Industry) were donated by Krka, d.d., Novo mesto, Slovenia. Liquid SMEDDS was prepared by using following excipients:Miglyol[®] 812, Peceol[™], Gelucire[®] 44/14, and Solutol[®] HS 15. Peceol[™] (glycerol monooleates (type 40)) and Gelucire[®] 44/14 (lauroyl macrogol-32 glycerides) were obtained from Gattefossé, France. Miglyol[®] 812 (caprylic/capric triglyceride) was obtained from Sasol, Germany. Solutol[®] HS 15 (polyethylene

glycol (15)-hydroxystearate) was obtained from BASF, ChemTrade GmbH, Germany. Water was purified by double distillation. Other chemicals were of HPLC or analytical grade.

2.2. Solidification method selection

A comparative evaluation of various methods used for transforming liquid to solid SMEDDS was performed in order to study the impact of the method and selected solid carrier on self-(micro)emulsifying properties, the process yield, adsorption capacity, flow properties, and compressibility properties of solid SMEDDS. In addition, the morphological properties of the powders obtained were determined.

2.2.1. Preparation of SMEDDS powders

The solid SMEDDS formulations were prepared through an adsorption technique, spray-drying process, high-shear granulation, and fluid bed granulation, using method-specific solid carriers. For the solidification, previously developed liquid SMEDDS consisted of Miglyol[®] 812, Peceol[™], Gelucire[®] 44/14, and Solutol[®] HS15 (Čerpnjak et. al., 2014) were examined, whereby the solidification techniques were comparatively evaluated on drug free (placebo) liquid SMEDDS. Liquid SMEDDS were prepared by weighing oils and surfactant mixture into a glass beaker heated to ~ 50 °C and homogenized with a magnetic stirrer at ~ 50 °C for 30 minutes. Solid carriers used in our study were selected based on the literature data and our experiences. Therefore, Aerosil[®] 200 and Neusilin[®] US2 as porous and high-surface area carriers were primarily used in adsorption technique. In addition, they were also comparatively evaluated by high-shear granulation process. MCC of two particle sizes, as commonly used excipient for wet granulation, was used in fluid bed granulation and as an additive to Aerosil[®] 200 in high-shear granulation. Solidification of SMEDDS by spray-drying process is based on spraying the aqueous

1 dispersion of SMEDDS and solid carrier. Therefore, water-soluble polysaccharides MD and
2 HPMC were used for this procedure. Namely, MD is able to form true aqueous solution, while
3 HPMC is forming colloidal aqueous solution. From this point of view, they were comparatively
4 evaluated with regards to the self-microemulsifying and morphological properties of prepared
5 solid SMEDDS.

6
7 Adsorption technique: solid SMEDDS formulations were prepared by adding liquid
8 SMEDDS under gentle mixing to a known amount of various adsorbents (Aerosil[®] 200, Neusilin[®]
9 US2) to obtain a fine powder.

10 Spray-drying process: solid SMEDDS formulations were prepared by spray-drying 100
11 ml of aqueous dispersions containing liquid SMEDDS (5 g) and MD or HPMC (10 g) as a carrier,
12 using a Büchi Mini Spray Dryer B-290 (Büchi, Switzerland) with a dual-channel nozzle (0.7 mm
13 diameter) with the following process parameters: a flow rate of 4.5 ml/min, inlet temperature of
14 120 °C, outlet temperature of 37 to 42 °C for MD dispersions and 52 to 56 °C for HPMC
15 dispersions, aspiration flow of ~35 m³/h, and drying air flow of 600 l/h.

16 High-shear granulation: solid SMEDDS formulations were prepared in Mini Pro
17 (MiproProCept, Belgium) by adding liquid SMEDDS to 100 g of various adsorbents (Aerosil[®]
18 200, Neusilin[®] US2, combination of Aerosil[®] 200+MD (ratio 1:1) and Aerosil[®] 200+Avicel PH
19 101 (ratio 1:1)) under gentle mixing (impeller speed 300 rpm and chopper speed 600 rpm) to
20 obtain a fine powder.

21 Fluid-bed granulation: solid SMEDDS formulations were prepared in Mini-Glatt (Glatt
22 GmbH, Germany) by spraying liquid SMEDDS heated to 50 °C with 100 g of various carriers
23 (Avicel PH 101 and Avicel PH 200) at a flow rate of 3 g/min, pressure 0.95 bar, and flow rate 0.7
24 bar, using a 0.5 mm nozzle, to obtain a fine powder.

2.2.2. *Pharmaceutical and technological evaluation of SMEDDS powders*

The powders obtained were comparatively evaluated for flow properties, liquid retention potential, and compaction properties in order to select the optimal combination of solidification method and carrier for tablet preparation.

Flowability was measured according to the Ph.Eur. method (2.9.16 Flowability) using a Pharmatest PTG (Germany) apparatus. The results were expressed as flow time per 100 g of sample. The angle of repose of the powder was measured by the static angle of repose method. The height (h) and diameter (r) of the resulting cone were measured and the angle of repose (θ) was calculated from the equation $\tan\theta = h/r$.

Compressibility properties were evaluated according to the Ph.Eur. method (2.9.16 Flowability) using a Stempf volumeter STAV 2003 (J. Engelsmann AG, Germany). Powders were gently poured into a 10 ml graduated cylinder. The weight of 10 ml was then determined and the bulk density (BD) was calculated as the ratio of mass of untapped powder to its volume (g/ml). The tapped densities (TD) were obtained by mechanically tapping a graduated cylinder containing powder from a height of 25 mm. After observing the initial powder volume, the cylinder was tapped 100 times until achieving constant volume, the resulting reduction in volume was recorded, and then the TD was calculated from the ratio of mass of powder to constant tapped volume (g/ml). The Carr index (CI) and the Hausner ratio (HR) were calculated according to Eq. 1 and Eq. 2.

$$\text{Carr index} = 100 \times \frac{(TD - BD)}{BD} \quad (\text{Eq. 1})$$

$$\text{Hausner ratio} = \frac{TD}{BD} \quad (\text{Eq. 2})$$

1 *Liquid load capacity* was defined as the maximum amount of a liquid SMEDDS that can
2 be retained in the selected carrier while maintaining acceptable flowability, determined visually.

3 *Morphological analysis of SMEDDS powders:* The particle morphologies were examined
4 by scanning electron microscopy (SEM; Ultra Plus, Carl Zeiss, Germany) operating at 1 to 2 kV
5 accelerating voltages.

6 *Reconstitution properties:* 1 g of SMEDDS powder was dispersed in 250 ml of purified
7 water to simulate physiological conditions and incubated during constant stirring for 30 minutes
8 at 37 ± 0.5 °C. The average droplet size and PDI of the (micro)emulsions formed were determined
9 by photon correlation spectroscopy using a Zetasizer Nano series instrument (Malvern
10 Instruments Inc., Southborough, MA). All studies were repeated in duplicate and the calculated
11 average values were used.

12 *Process yield* was expressed as a percentage of the amount of solid SMEDDS ultimately
13 obtained with regard to the total amount of carrier and of liquid SMEDDS used.

15 **2.3. Design of experiments (DoE)**

16 In order to study the influence of selected process parameters on self-microemulsifying
17 properties of SMEDDS powders, DoE (Design of Experiments) of the spray-drying procedure
18 described above was performed using a three-factor two-level factorial design (2^3), with inlet air
19 temperature (A), pressure (B), and pump speed (C) as independent variables as shown in **Table 1**.
20 The level of each independent variable was set on the basis of preliminary screening experiments.
21 The Unscrambler® software (version 10.1, CAMO software, Norway) was applied to generate
22 and evaluate the statistical experimental design. All experiments were performed in randomized
23 order. The mean droplet size (after reconstitution), PDI, and yield of the process were selected as
24 response variables. Main and interaction effects, weighted regression coefficients, and PLS

ANOVA(p values) were used to determine the influence of a particular independent variable on selected responses. The significant terms ($p < 0.05$) according to analysis of variance (ANOVA) were chosen for final evaluation. A positive and negative sign of weighted regression coefficients represent a synergistic and antagonistic effect, respectively. PLS ANOVA regression was applied in order to determine the relationship able to describe the response variation inside the design.

2.4. Stability studies of SMEDDS powders

The long-term physicochemical stability of SMEDDS powders prepared by spray-drying liquid SMEDDS containing dissolved (6% w/w) and partially suspended (18% w/w) naproxen, using MD as solid carrier, was evaluated. Samples were stored in closed glass vials at room temperature (25°C, 60% RH) and protected from light. After 1 month and 2 years of storage time, representing long-term stability, the drug content, mean droplet size of microemulsions after reconstitution, and DSC analysis were performed.

2.5. Preparation of tablets and minitables

The spray-dried SMEDDS powders containing 6% w/w and 18% w/w naproxen in liquid SMEDDS were mixed with microcrystalline cellulose (Avicel® PH 102), colloidal silicon dioxide (Aerosil® 200), and sodium croscarmellose, and the mass was sieved through sieve with mesh no. 20 and blended in a polyethylene bag. Magnesium stearate and talc were sieved through sieve with mesh no. 20 and added to the previously obtained mixture and blended. The composition of the compression mixture is presented in **Table 2**. The final blended mixture was compressed into 500 mg tablets and 50 mg minitables using a Killian Pressima tablet press machine equipped with round punches of 11 and 5 mm diameter.

2.6. Evaluation of SMEDDS tablets and minitables

Prepared tablets and minitables were evaluated for technological properties (average weight and weight variation, thickness, hardness, friability, disintegration time), dissolution behavior, self-microemulsifying properties, and crystalline properties of incorporated naproxen.

Average weight and weight variation: The weights of 10 tablets were checked using a Mettler Toledo balance (Mettler Toledo, Switzerland), and the average weight and weight variation were determined.

Thickness and diameter: The thicknesses and diameter of 10 tablets were checked using a digital caliper with an accuracy of ± 0.01 mm, and the average thickness and diameter were reported.

Hardness: The hardness of 10 tablets was checked using a Erweka TBH125 tester (Erweka, Germany), and the average hardness was reported.

Friability: The friability of 10 tablets was checked using a Erweka TA 10 Friability tester (Erweka, Germany). Tablets were weighed (w_1) and placed in a rotating drum and allowed to rotate 100 times. After that, the tablets were reweighed (w_2) and the result (% weight loss) was reported using the following equation:

$$\frac{w_1 - w_2}{w_1} \times 100$$

Disintegration time: The disintegration time of six tablets and minitables was checked in deionized water at 37°C using a Sotax DT2 disintegration tester (Sotax, Switzerland) and the average time was reported.

Reconstitution properties: Two 500 mg tablets were dispersed in 250 ml of purified water and two 50 mg minitables were dispersed in 25 ml of purified water and incubated during constant stirring for 30 min at 37 ± 0.5 °C. After that, dispersions were filtered through the

coregrade filter in order to remove the particles of excipients. The average droplet size and PDI of the (micro)emulsions formed were determined by photon correlation spectroscopy using a ZetasizerNano series instrument (Malvern Instruments Inc, Southborough, MA). All studies were repeated in duplicate and the calculated average values were used.

In vitro dissolution studies: The in vitro dissolution test was performed using a USP Apparatus 1 (VK 7000, VanKel, USA). Dissolution studies were performed on SMEDDS tablets and minitables in comparison with liquid SMEDDS and SMEDDS powders filled in hard gelatin capsules in an amount corresponding to 6 or 18 mg of NPX. In addition to this, pure and spray-dried naproxen and a physical mixture of SMEDDS powder (without spray drying) in an amount corresponding to 6 mg of NPX were analyzed as the references. Samples were placed in a 900 ml dissolution medium of pH 1.2 and 6.8 (900 ml of 0.1 M hydrochloric acid aqueous solution with a pH of 1.2 and 900 ml phosphate buffer solution with a pH of 6.8). The dissolution study of samples was performed in triplicate (for medium pH 1.2) and in duplicate (for medium pH 6.8) at constant conditions (100 rpm and 37.0 ± 0.1 °C). At predetermined time points, 5 ml aliquots of dissolution medium were withdrawn, filtered through a 0.45 µm pore filter, and analyzed with an HPLC system (Agilent 1100 Series, Agilent, USA), using the following experimental conditions: column: Zorbax Eclipse XDB C₁₈ (4.6 mm × 150 mm; 5 µm); mobile phase: mixture of methanol, acetonitrile, and bidistilled water (20/28/52 w/w) with the addition of 0.4 ml of triethylamine per 1 l of mobile phase; flow rate: 1.5 ml/min; detection: UV-VIS detector at 270 nm.

2.7. Differential scanning calorimetry (DSC)

The physical state of the naproxen was examined in the SMEDDS powders (during stability testing), compression mixture, and SMEDDS tablets in comparison with pure naproxen and spray-dried naproxen. DSC thermograms were recorded using a DSC 1 (Mettler Toledo,

Switzerland). A 3 to 5 mg sample was weighed and sealed in an aluminum pan. The sample was heated from 0 to 180 °C at a rate of 10 °C/min under nitrogen flow 50 mL/min. An empty pan was used as a reference.

3. Results and discussion

3.1. Evaluation of solid SMEDDSs prepared using various solidification techniques

In order to evaluate various solidification techniques and identify the most promising corresponding solid carriers, samples of solid SMEDDS were formulated and characterized by their liquid load capacity (ratio carrier: liquid SMEDDS), flow properties (angle of repose), process yield, and compressibility properties (Hausner ratio and Carr index). The results are presented in Table 3. Furthermore, comparative self-microemulsifying properties (droplet size and PDI of microemulsions formed upon dilution with an aqueous phase) and morphological properties of solid SMEDDS were examined. The results are presented in Table 4.

The flow of different SMEDDS powders was characterized by angle of repose, and the results are presented in Table 3. Angle of repose values $< 30^\circ$ indicate “excellent” flow properties and values $> 56^\circ$ indicate “very poor” flow properties. The intermediate values indicate “good” (31–35°), “fair” (36–40°), “passable, which may hang up” (41–45°), and “poor, which must be agitated or vibrated” (46–55°) (U.S. Pharmacopeia). Among the SMEDDS powders tested, flow was rated as “good” only for powders prepared using Aerosil®200 as a solid carrier with no significant difference in adsorption or high-shear granulation technique, whereas other formulations tested exhibited fair flow properties.

The Carr index (CI, %) and the Hausner ratio (HR) were found to be lowest for Aerosil-based SMEDDS powders, and the results are in agreement with the results of the angle of repose. Namely, CI indicates powder bridge strength and stability, and HR indicates the interparticulate friction. Both factors are used to rate the flow character of the powder; namely, lower CI or HR of a powder indicates better flow properties.

The results of the liquid load capacity are in agreement with the morphological structure of the carriers. The highest liquid load capacity was observed using porous carriers (Aerosil[®], Neusilin[®] US2), whereas carriers with a fine, rectangular shape of particles (MD, MCC, HPMC) exhibited the lowest liquid load capacity.

The results presented for the process yields showed that the highest yields are obtained when using simple procedures (i.e., adsorption and granulation technique), whereas spray drying is a complex procedure, with many process parameters to regulate, and consequently the process yields are lower. In addition, solid SMEDDS prepared through spray drying consisted of nonporous MD and HPMC as solid carriers, which can also contribute to lower yields.

The self-(micro)emulsifying properties of prepared SMEDDS powders after reconstitution in aqueous media was determined in terms of mean droplet size and PDI of the microemulsions formed. The results are presented in **Table 4**.

As is evident from the results, a wide range of mean droplet size is observed (43–544 nm) upon redispersion of solid SMEDDS in aqueous media. Microemulsions (droplets < 150 nm) were formed in all samples tested except for when Neusilin[®] US2 was used, irrespective of the technique used. The best self-microemulsifying properties (the smallest droplet size) were observed when using MD as carrier and spray drying as a solidification method. In addition, a narrower size distribution (low PDI) was observed when using the spray-drying and fluid-bed method of solidification. From SEM microphotographs it is further obvious that the solidification method

influences the shape and size of the particles obtained (**Figure 1**). Namely, through adsorption and granulation techniques large, agglomerated particles with an irregular shape were obtained, whereas particles with a spherical shape that were slightly agglomerated were found after spray drying. When comparing SMEDDS powders obtained through the adsorption technique and high shear granulation using the same type of carrier (Aerosil[®] 200 and Neusilin[®] US2), it is evident that the solidification method has a considerable impact on the self-microemulsifying properties of SMEDDS powders. This is probably related to the morphological properties of SMEDDS powders. Namely, powders obtained through high-shear granulation appear as larger agglomerated and coated particles, whereas powders obtained through adsorption are less agglomerated and have a more porous surface. Due to higher specific surface area of less aggregated particles and their higher porosity the water molecules can more easily penetrate in these powders, which results in better contact with water during the reconstitution and consequently in formation of microemulsions with smaller droplet size (**Figure 2**).

Overall, the focus of our research was to find the most promising combination of solidification technique and suitable solid carrier able to form powders with the desired self-microemulsifying properties (mean droplet size < 150 nm) and adequate morphological properties (uniformly distributed and non-agglomerated SMEDDS powder). Based on the results presented above, spray drying and MD were found to be the most suitable combination. Thus, the results presented indicate justified interest among researchers in recent years in spray drying as a solidification method for liquid SMEDDS. For this reason, it was selected for further development of SMEDDS tablets and minitables.

3.2. DoE on solid SMEDDS preparation through spray drying

In this research, DoE was implemented as a key strategy to examine the influence of process parameters on self-microemulsifying properties of prepared solid SMEDDS. Based on the results of the technological and self-microemulsifying properties of SMEDDS powders obtained using various techniques, a spray-drying process using MD was selected for this evaluation. The DoE study was performed using a three-factor two-level factorial design (2^3), with inlet air temperature (A), pressure (B), and pump speed (C) as independent variables. The mean droplet size (after solid SMEDDS reconstitution), PDI, and yield of the process were selected as response variables. The 2^3 full factorial design and the observed responses for the eight experiments are shown in **Table 1**. The significant terms ($p < 0.05$) according to analysis of variance (ANOVA) were chosen for final evaluation.

The average droplet size of spray-dried SMEDDS powders, as a major quality attribute of self-microemulsifying formulations, was examined. Based on the weighted regression coefficients (**Fig. 3**), pressure (B) is identified as the most critical process parameter for the mean droplet size and is the only one that shows significant influence ($p\text{-value} = 0.0025$) with a negative sign (i.e., higher pressure results in a lower mean droplet size, or an antagonistic effect).

In correlation with mean droplet size, PDI (polydispersity index) was also evaluated. From the calculated regression coefficients (**Fig. 4**), a major and significant impact of pump speed (C; $p\text{-value} = 0.0204$) and interaction of all three variables tested (ABC; $p\text{-value} = 0.0137$) was observed. The pump speed (C) exhibited a negative influence (i.e., lower speed, higher PDI) and the interaction of all three variables had a positive influence, representing a synergistic effect. On the other hand, the influence of interactions on process yield is evident, but is not significant ($p\text{-value} > 0.05$) (**Fig. 5**).

Considering the DoE results presented, a combination of the following process parameters was selected as the most suitable combination of process parameters for further development of SMEDDS powders for tablets and minitables: inlet temperature 120°C, pressure 50 mmHg, and pump speed 15 ml/min. Subsequently, various ratios of solid carrier and liquid SMEDDS at preselected process parameters were tested with regard to mean droplet size, PDI, process yield, and powder appearance in order to select the combination with highest liquid load capacity and best self-microemulsifying properties. The results are presented in **Table 5**.

Among the formulations tested, appearing as free-flowing powder, F2 exhibited the lowest process yield. However, with this formulation the best self-microemulsifying properties and liquid load capacity were observed. Concluding from this, formulation F2 was selected for further development of SMEDDS powders for tablet and minitab preparation.

3.3. Stability studies of spray-dried solid SMEDDS

The physicochemical stability of the spray-dried SMEDDS powders containing 6% w/w and 18% w/w of naproxen in liquid SMEDDS was evaluated. Samples were stored in closed glass vials at room temperature (25°C, 60% RH) and protected from light. After 1 month and 2 years of storage time representing long-term stability, the drug content, mean droplet size of microemulsions after reconstitution, and DSC analysis were performed. The results are presented in **Table 6** and **Figure 6**.

According to the results presented in **Table 6**, after 1 month of storage time the drug content and mean droplet size of microemulsions obtained after reconstitution practically did not change, whereas after 2 years of storage time the drug content slightly decreased and the mean droplet size slightly increased. However, the self-microemulsifying properties of aged samples were preserved. To further verify the crystalline state of incorporated naproxen during a storage

time of 2 years, DSC analyses were performed and compared with pure naproxen and initial results. The results of 2 years of storage time are presented in **Figure 6**. From the results presented it can be concluded that even after long-term storage of solid SMEDDS, irrespective of the drug loading, no endothermic effect representing a crystalline state of naproxen was observed. However, the results of XRD analysis confirmed the presence of the crystalline form of naproxen in the case of 18% w/w drug loading (data not shown). Overall, the results are comparable with the initial results already reported (Čerpnjak et. al., 2015).

3.4. Evaluation of self-(micro)emulsifying tablets and minitables

As the most acceptable traditional solid dosage form, tablets have several advantages that can contribute to assisting with patient compliance and, ultimately, effective disease treatment. Minitablets represent new trends in solid dosage forms, offering some therapeutic benefits such as dose flexibility and combined release patterns and making it possible to overcome some therapeutic obstacles such as impaired swallowing and polypharmacy therapy (Aleksevski et. al., 2015; Hadi et. al., 2012; Hiorth et. al., 2014; Keerthi et al., 2014; Moosa et. al., 2013; Tissen et. al., 2011).

Therefore, the focus of this research was to prepare tablets and minitables from previously developed spray-dried solid SMEDDS based on MD, containing dissolved (6% w/w) and partially suspended (18% w/w) naproxen in liquid SMEDDS (Čerpnjak et. al., 2015). The compression mixture for tablet preparation consisted of naproxen-loaded solid SMEDDS, microcrystalline cellulose type 102 (Avicel PH102) (diluent), croscarmellose sodium (disintegrant), colloidal silicone dioxide (Aerosil® 200), talc, and magnesium stearate. The composition of compression mixture, which was the same for tablets and minitables, is presented

in **Table 2**. Prepared tablets and minitables were evaluated with regard to technological and self-(micro)emulsifying properties. The results are presented in **Table 7**.

Based on the results, it is evident that the technological properties of tablets of the same size, irrespective of the drug loading, are almost the same. It may be pointed out that the tablet mass (e.g., tablets vs. minitables) has an impact on disintegration time; namely, a higher mass of a tablet resulted in a prolonged disintegration time at almost the same hardness of the tablets. Furthermore, the SMEDDS tablets and minitables were characterized in terms of ME droplet size and polydispersity index (PDI) after reconstitution, which are important quality and physical attributes influencing the stability of the emulsion, as well as determining the rate and extent of drug release. Comparing the droplet size and PDI of SMEDDS tablets with SMEDDS spray-dried powders, it was found that compression of solid SMEDDS significantly increased the droplet size after reconstitution by 11.6 to 14.2 times in the case of 6% w/w naproxen loading and by 7.7 to 11.4 times in the case of 18% w/w naproxen loading. Before compression, MD-based solid SMEDDS prepared through spray drying exhibited a droplet size of 36.5 nm (sample with 6% w/w naproxen loading) and 41.2 nm (sample with 18% w/w naproxen loading) (Čerpnjak et al., 2015). This suggested that excipients used for compression mixture preparation in combination with the compression process considerably affected the droplet size in comparison with the spray-drying solidification technique, where the droplet size remained almost unchanged in comparison with liquid SMEDDS (Čerpnjak et al., 2015). This can be explained by water-insoluble excipients used in the compression mixture (i.e., MCC, magnesium stearate, talc) affecting the droplet size and consequently also the PDI due to formation of large particles/aggregates, which is in agreement with the results presented by Li et al. (Li et al., 2013). In addition, the forces during the compression process may affect the stability of the (micro)emulsion formed, resulting in increased droplet size.

To further study the effect of additional processing of solid SMEDDS powders on the physical state of incorporated naproxen, DSC analysis of compression mixtures and tablets was performed. From the results presented in **Figure 6**, it can be concluded that additional processing did not affect the physical state of incorporated naproxen; namely, no naproxen melting effect was observed. On the other hand, the spray-drying process cannot be selected as the method for amorphous naproxen preparation because the spray-dried naproxen exhibited the same DSC thermogram as pure naproxen; namely, an endothermic peak at 156.2°C, corresponding to its melting point and indicating its crystalline nature. These results are in agreement with the literature data presented by Paudel et al. (Paudel et. al., 2013) and Mahlin et al. (Mahlin et. al., 2011), in which they explained that amorphization of naproxen by spray drying is not profitable due to its poor ability for glass formation. Thus, the data presented supported our previous explanation that naproxen is molecularly dissolved within solid SMEDDS (at 6% w/w), whereas at an 18% w/w concentration it also exists in crystalline form, as detected by XRD analysis in our previous study (Čerpnjak et. al., 2015). With respect to these results, comparable dissolution profiles of pure and spray-dried naproxen are expected.

3.5. *In vitro* dissolution studies

Dissolution studies of an incorporated drug from all SMEDDS formulations prepared are an important tool in differentiating delivery system performance. Naproxen dissolution experiments on liquid SMEDDS, MD-based SMEDDS powders, tablets, and minitables with 6% w/w and 18% w/w drug loading in liquid SMEDDS in comparison with pure naproxen, spray-dried naproxen, and physical mixture were conducted in pH 1.2 and pH 6.8. Due to the good solubility of naproxen at pH 6.8, hydrochloric acid solution is shown to be a more discriminating dissolution medium; therefore these results were used to provide a more detailed interpretation of the dissolution properties.

1 The results of the *in vitro* naproxen dissolution profile in pH 1.2 presented in **Fig. 7**
2 showed that all SMEDDS formulations exhibited considerably enhanced *in vitro* dissolution
3 profiles in comparison with pure naproxen. Furthermore, dissolution of naproxen is influenced by
4 the nature of SMEDDS formulation and naproxen concentration. As expected, naproxen release
5 is the fastest from the liquid SMEDDS formulation containing naproxen in completely dissolved
6 form (at 6% w/w drug loading); namely 91.7% within 15 minutes. This is in agreement with the
7 SMEDDS ability to circumvent the drug dissolution step in the gastrointestinal tract by delivering
8 drugs in dissolved form (Porter et. al., 2007; Neslihan and Benita, 2004).

9 The solidification process and drug loading in supersaturated concentration (at 18% w/w
10 drug loading) resulted in a slightly slower dissolution profile (~76% within 15 minutes), where
11 the naproxen release was limited by dissolving the MD carrier and by dissolution of the
12 suspended drug.

13 Furthermore, the naproxen dissolution profile was also influenced by the compression
14 process, where ~90% of drug released from SMEDDS tablets and minitables with 6% drug
15 loading was achieved after barely 90 minutes. This can be explained by larger droplet size
16 obtained upon reconstitution of tablets and minitables, in comparison with liquid SMEDDS and
17 SMEDDS powder exhibiting good self-microemulsifying properties. Based on these results, we
18 can conclude that excipients for tablet preparation and compression process affected the self-
19 (micro)emulsifying properties of spray-dried SMEDDS powders, and consequently slower drug
20 release from tablets and minitables was observed. However, drug release was indeed slightly
21 enhanced with minitables compared with tablets, which maybe associated with the specific
22 surface area of minitables. The same effect was observed when comparing minitables to tablets
23 with 18% w/w drug loading, where further incomplete naproxen release was observed (~65%
24 within 90 minutes). Because the concentration of drug dissolved after 120 minutes was

1 significantly below the saturated solubility of naproxen in pH 1.2, we proposed that the naproxen
2 release from these formulations is limited by the dissolution of the suspended drug, promoted by
3 components of the SMEDDS formulation.

4 Moreover, a dissolution study of spray-dried naproxen was performed in order to verify
5 the potential influence of the spray-drying process—as the technique for amorphization
6 (Hendriksen et. al., 1995; Moran and Buckton, 2007; Patel et. al., 2009) and consequently
7 solubility improvement of the drug—on the dissolution behavior of naproxen. As shown in **Fig.**
8 **7**, only a slightly enhanced dissolution profile of spray-dried naproxen compared with pure
9 naproxen was observed. This was not attributed to the amorphization of the drug as confirmed by
10 DSC(**Fig.6**), but is most likely due to the particle size reduction of the drug during the spray-
11 drying process. Overall, concluding from the results presented, only SMEDDS formulation has a
12 major and main effect on the dissolution profile and solubility enhancement of naproxen, which
13 is also supported by the dissolution results of the physical mixture.

14 On the other hand, at pH 6.8 the influence of SMEDDS formulations on the dissolution
15 improvement of naproxen is lower, due to significantly better solubility of naproxen at this pH
16 (**Fig. 8**). Nevertheless, considerable improvement of initial drug release rate (within the first 15
17 minutes) is evident in SMEDDS formulations.

18 19 **4. Conclusions**

20 Based on the results presented, it can be concluded that self-(micro)emulsifying properties
21 of prepared solid SMEDDS are influenced by the solidification technique and the solid carrier
22 used. Among the combinations tested, the spray-drying process and maltodextrin (MD) exhibited
23 the best self-microemulsifying properties, comparable with liquid SMEDDS. Thus, spray drying
24 was selected as a method of choice. The results of DoE on the spray-drying process showed that

self-microemulsifying properties of solid SMEDDS are also affected by process parameters; namely, pressure and pump speed had a major and significant influence on mean droplet size and PDI; and therefore DoE can be successfully used for method optimization. Prepared tablets and minitables of spray-dried solid SMEDDS form an emulsion with a droplet size between 300 and 600 nm upon reconstitution, exhibiting self-emulsifying properties. They both show slower drug release to some extent than liquid SMEDDS; nevertheless, it was still significantly enhanced in comparison with pure NPX and its physical mixtures.

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15 **Table 1. Three-factor two-level factorial design and responses for the spray-drying process**

Run Order	Independent variables			Responses		
	A inlet T (°C)	B Pressure (mbar)	C Pump (ml/min)	mean droplet size (nm)	PDI	Yield (%)
6	120	40	5	141.3	0.223	82.7
8	120	40	15	137.7	0.205	82.2
1	120	50	5	52.1	0.120	76.7
4	120	50	15	52.6	0.119	72.0
2	150	40	5	144.2	0.256	79.8
5	150	40	15	158.6	0.278	80.3
3	150	50	5	56.5	0.145	75.2
7	150	50	15	59.4	0.189	70.3

1

2 **Table 2. Composition of compression mixture for tablet preparation**

Spray dried solid SMEDDS (6% w/w or 18% w/w naproxen loaded in liquid SMEDDS)	60.4%
Cellulose microcrystalline(Avicel® PH 102),	28.6%
Colloidal silicone dioxide(Aerosil® 200)	1%
Croscarmellose sodium	5%
Talc	2%
Magnesium stearate	3%

3

4 **Table 3. Technological properties of SMEDDS powders**

Technique	Carrier	Ratio Carrier: SMEDDS (liquid load capacity)	Angle of repose (°)	Hausner R	Carr I	Process yield (%)
Adsorption	Aerosil® 200	1:3	33.4	1.14	12.3	94
	Neusilin® US2	1:1	38.0	1.22	18.0	93
High-shear granulation	Aerosil® 200	1:3	33.0	1.33	24.8	95
	Neusilin® US2	1:1	37.8	1.38	28.0	95
	Aerosil® 200+MCC tip101 (1:1)	1:2	36.2	1.19	15.6	93
Fluid bed granulation	MCC type 200	2:1	38.6	1.44	30.6	92
	MCC type 100	2:1	38.2	1.23	18.7	93
Spray drying	MD	2:1	37.4	1.27	21.3	72
	HPMC	2:1	38.3	1.24	19.4	78

5

6 **Table 4. Comparison of reconstitution properties of SMEDDS powders.**

Technique	Carrier	Mean droplet size (nm)	PDI
Adsorption	Aerosil® 200	85.8 ± 3.9	0.483 ± 0.023
	Neusilin® US2	192.4 ± 9.5	0.527 ± 0.081
High-shear granulation	Aerosil® 200	101.2 ± 2.7	0.586 ± 0.025
	Neusilin® US2	544.0 ± 45.1	0.749 ± 0.042
	Aerosil® 200+MCC tip101 (1:1)	81.9 ± 1.4	0.406 ± 0.010
	Aerosil® 200+MD (1:1)	115.9 ± 2.8	0.452 ± 0.002
Fluid bed granulation	MCC type 200	53.4 ± 0.2	0.134 ± 0.005

	MCC type 101	68.7 ± 0.3	0.090 ± 0.007
Spray drying	MD	49.9 ± 1.3	0.247 ± 0.011
	HPMC	127.3 ± 0.8	0.188 ± 0.008

Table 5. Selection of the carrier :liquid SMEDDS ratio

	Ratio Carrier:liquid SMEDDS	mean droplet size (nm)	PDI	Yield (%)	appearance
F1	1:1	56.3	0.192	56.2	creamy product
F2	2:1	52.6	0.119	72.0	Free-flowing powder
F3	3:1	69.3	0.223	76.7	Free-flowing powder
F4	4:1	93.5	0.242	75.3	Free-flowing powder

Table 6. Stability studies of spray-dried solid SMEDDS containing 6% w/w and 18% w/w

naproxen in liquid SMEDDS

Property	Spray dried solid SMEDDS prepared by using MD as carrier					
Drug loading in liquid SMEDDS	6% w/w loading			18% w/w loading		
Time points	t_0	$t_{1\text{month}}$	$t_{2\text{years}}$	t_0	$t_{1\text{month}}$	$t_{2\text{years}}$
Drug content (%)	1.95	1.95	1.90	4.9	4.8	4.3
Reconstitution properties						
- Mean droplet size (nm)	36.5 ± 0.2	39.8 ± 0.5	58.3 ± 0.4	41.2 ± 0.2	45.8 ± 0.2	62.8 ± 1.2
- PDI	0.147 ± 0.006	0.162 ± 0.010	0.145 ± 0.019	0.108 ± 0.013	0.128 ± 0.02	0.278 ± 0.028

Table 7. Technological and self-(micro)emulsifying properties of SMEDDS tablets and minitables

Property	Tablets		Minitables	
Drug loading in liquid SMEDDS	6% w/w	18% w/w	6% w/w	18% w/w
Weight variation (mg)	523.4±6.2	524.2±5.9	50.8±1.3	50.5±1.2
Thickness (mm)	5.26	5.27	2.78	2.77
Diameter (mm)	10.98	10.96	5.10	5.12
Hardness (N)	25.8	27.2	19.8	20.3
Friability (%)	0.6	0.6	0.8	0.8
Disintegration time (min)	7	7	2	2
Reconstitution properties				
- Mean droplet size (nm)	424.3±36.7	468.9±74.2	516.7±85.6	316.2±72.8
- PDI	0.624±0.105	0.652±0.091	0.695±0.083	0.660±0.042

Figure 1. Comparison of morphological properties of SMEDDS powders at magnification 1000×. **A1** = adsorption technique using Aerosil® 200; **A2**= adsorption technique using Neusilin® US2; **B1** = high-shear granulation using Aerosil® 200; **B2** = high-shear granulation using Neusilin® US2; **B3**= high-shear granulation using Aerosil® 200 + MD (1:1); **B4**= high-shear granulation using Aerosil® 200 + MCC type 101 (Avicel PH 101) (1:1); **C1** = fluid bed granulation using MCC type 200 (Avicel PH 200); **C2** = fluid bed granulation using MCC type 101 (Avicel PH 101); **D1** = spray drying using MD; **D2** = spray drying using HPMC.

Figure 2. SEM micrograph of solid SMEDDS based on Neusilin[®] US2 (1) and Aerosil[®] 200 (2), prepared through high-shear granulation (a) and adsorption technique (b). Magnification 10,000×.

Figure 3. Regression coefficients of variables and their interactions influencing mean droplet size.

Figure 4. Regression coefficients of variables and their interactions influencing PDI.

Figure 5. Regression coefficients of variables and their interactions influencing process yield.

Figure 6. DSC thermograms of MD-based solid SMEDDS formulations with 6% w/w and 18% w/w drug loading in liquid SMEDDS: solid SMEDDS powders after 2 years of storage time, compression mixture, and tablets in comparison with pure and spray-dried naproxen.

Figure 7: Comparison of the *in vitro* dissolution profile of naproxen in pH 1.2 ($n=3$)

Figure 8: Comparison of the *in vitro* dissolution profile of naproxen in pH 6.8 ($n=2$)

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