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A redispersible dry emulsion system with simvastatin prepared via fluid bed layering as a means of dissolution enhancement of a lipophilic drug

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ABSTRACT

The purpose of the study was to develop a redispersible dry emulsion, containing a lipophilic, poorly water soluble model drug simvastatin, by employing fluid bed coating technology. The presented dry emulsion manufacturing approach produces pellets in a way, where a layer of the dry emulsion is applied to a neutral core. In the preliminary formulation development phase 1-oleoyl-rac-glycerol was chosen as the oily lipid phase, based on the high drug solubility and potential bioavailability enhancement capability. Mannitol, HPMC and Tween 20 were selected as the solid carriers and surfactant, respectively. The design of experiments, specifically the mixture design approach, was used to obtain the optimal formulation composition. The emulsion reconstitution ability and stability were the main responses, used as the decisive parameters for formulation optimisation. Optimised formulations showed narrow droplet size distribution upon reconstitution, high stability, suitable drug loading and enhanced dissolution profile, compared to a non-lipid based tablet and the pure drug. The scanning electron microscopy, Raman spectroscopy and image analysis disclosed a uniform morphology of the applied layer with separated droplets with simvastatin and uniform size distribution and a circular shape of coated pellets. The study represents the proof of concept of designing redispersible dry emulsions using a fluid bed layering approach.

1. Introduction

In recent decades more and more newly discovered drugs are active pharmaceutical ingredients (APIs) exhibiting poor biopharmaceutical characteristics, especially low water solubility (Buckley et al., 2013). It is estimated that more than 40% of the APIs fall into this group (Vo et al., 2013). There are several formulation strategies to overcome the solubility problems, i.e. liposomes, cyclodextrins, solid dispersions, lipid based systems, etc. (Carrier et al., 2007; Herbrink et al., 2017; Ilić et al., 2009; Lim et al., 2017; Mu et al., 2013; Zecevic et al., 2014). In the recent years, lipid based systems have especially gained interest in drug formulation development, as they showed great potential for improving dissolution and solubility (Hauss, 2007). Within this group, emulsions and self-microemulsifying drug delivery systems have been the most widely used (Čerpnjak et al., 2015; Kim et al., 2014; Seljak et al., 2014). Since self-microemulsifying systems are composed of high proportion of surfactants, they might not be suitable for long term therapies due to irritation of the gastrointestinal tract (Baek et al., 2014). On the other hand, coarse disperse systems such as classic emulsion systems lack physical stability, which leads to creaming, flocculation, coalescence, and phase separation. Additionally, the presence of water can induce chemical and microbiological instability (Niederquell et al., 2017). These shortcomings can be overcome by preparing kinetically frozen dry emulsion systems – dry emulsions.

Dry emulsions are usually produced by removing the outer aqueous phase (in which one or more matrix formers in a sufficient concentration are dissolved) of a liquid oil in water (O/W) emulsion by spray-drying or the lyophilisation process (Iyer et al., 2017; Pongsamart et al., 2016). It has been demonstrated that this type of drug delivery system can significantly improve the oral bioavailability of poorly water soluble drugs (Dollo et al., 2003; Jang et al., 2006; Salama et al., 2018).

A potential alternative and new technique for the production of dry emulsion systems can be the layering process based on the fluid bed technology (FBD), where a layer of dry emulsion encapsulating the API in oil solution droplets is deposited on a neutral pellet core. Limited or no information can be found on the use of the fluid bed coating technology for producing dry emulsion-coated pellets (Luštrik et al., 2016). The general FBD coating method, in comparison to the spray-drying or lyophilisation, offers high process efficiency and yields, production of particles of a defined size and shape possessing exceptional flow

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properties, and the possibility for further processing, e.g. film-coating (Chen et al., 2017; Kazlauske et al., 2017).

In the present study, a FBD coating chamber, equipped with the novel swirl flow generator (Savic et al., 2010), is used with the aim of producing dry emulsion-coated pellets containing simvastatin as a model drug. Layered pellets should exhibit high drug loading and good droplet reconstitution ability in an aqueous medium. Simvastatin is listed to the pharmacological group of statins, and is used to treat hypercholesterolemia and hypertriglyceridemia (Stein et al., 1998). According to the BCS (biopharmaceutical classification system), simvastatin is classified as a drug with low aqueous solubility and high permeability, thus enrolled as a class II drug (Zhang et al., 2010). Nanostructured lipid carriers (Tiwari and Pathak, 2011), solid dispersions (Silva et al., 2010), self-nanoemulsifying granules (Dixit and Nagarsenker, 2008), self-microemulsifying drug delivery systems (Kang et al., 2004) and dendrimers (Kulhari et al., 2011) are the strategies that have already been used to overcome the problem of the low aqueous solubility of simvastatin. A drug's low aqueous solubility, in combination with a high first pass metabolism, has as the consequence an oral bioavailability of < 5% (Geboers et al., 2016).

Solubility and dissolution enhancement of the model drug simvastatin is in this study attempted by employing dry emulsion-coated pellets. Different oil phases were screened, and the design of experiments (DoE) approach was used to study the influence of individual formulation constituents on the reconstitution potential of the dry emulsion-coated pellets in order to form the initial liquid emulsion droplet size distribution, and on the stability of the drug in the manufactured pellets. Both physical (liquid emulsion stability, dry emulsion reconstitution ability) and chemical (chemical stability of the drug) characteristics of emulsions and dry emulsion pellets were evaluated. Moreover, within the design space, two optimal formulations for drug stability and reconstitution ability responses are produced and evaluated, and then verified by the mathematical model set obtained by the analysis of DoE experiments.

2. Materials and methods

2.1. Materials

The simvastatin was of pharmaceutical grade and a kind donation by Krka d.d., 1-oleoyl-rac-glycerol (1OG) (technical grade ~40% (TLC)), and Tween® 20 (polyethylene glycol sorbitan monolaurate) were purchased from Merck, Germany. Pharmcoat 603 (Hydroxypropyl Methycellulose – substitition type 2910 (USP), 3cP) and Miglyol® 812 (M812) were supplied by ShinEtsu, Japan and Sasol, Germany, respectively. All oils were of pharmacopeial grade. Pearlitol SD 200 (mannitol) was purchased from Roquette, France. Cellets 200 (pellets from microcrystalline cellulose) were provided by Harke Pharma GmbH, Germany. All solvents for UPLC analysis were HPLC grade. All other reagents used were of analytical grade. Water for the UPLC analysis was purified with a Milli-Q system with a 0.22 Millipak 40 filter (Millipore, Ireland).

2.2. Methods

2.2.1. Solubility study of simvastatin

The equilibrium solubility of simvastatin was assessed by placing an excessive amount of simvastatin (500 mg) in 4500 mg of different oils (olive oil, castor oil, M812, 1OG, linseed oil and almond oil). The oils with the API were heated to 37 °C for 5 min and allowed to cool to room temperature. After 48 h of mixing with a magnetic stirrer, samples were centrifuged at 25,000 rpm for 15 min (Ultracentrifuge Sorvall® WX 100 Ultra Series, Thermo Fisher Scientific, Germany). Aliquot portions of the supernatant were collected, diluted with methanol, filtered through a 0.22 μm syringe filter and analyzed with UPLC method (described in Section 2.2.8.).

2.2.2. Preparation of liquid emulsions intended for the coating process

Liquid emulsions were prepared through different stages. Firstly, 1OG was heated up to 40 °C in order to obtain a clear liquid and further mixed with M812 in the ratio of 9:1. M812 was added to prevent 1OG recrystallisation, as it was found that with storage at room temperature, a slow recrystallisation of 1OG was seen. To the prepared mixture, Tween® 20 was added and mixed. For every gram of the 1OG/M812 oil mixture, 70 mg of simvastatin were added, heated to 37 °C and, mixed until a clear solution was obtained. The oil mixture drug solution was kept at 37 °C.

Mannitol was dissolved in ¾ and HPMC in ¼ of the water's outer phase, respectively. HPMC was prepared as an independent solution to prevent degradation of the polymer during high shear, rotor–stator homogenization. The mannitol solution was heated to 37 °C, and the oil mixture was added during stirring at 640 rpm. The resulting pre-emulsion was firstly homogenized using a high shear, rotor–stator, homogenizer (ULTRA-TURRAX® T25, IKA-WORKS, Germany) for 5 min at 8000 rpm and 3 min at 12000 rpm. The HPMC solution was added during mixing at 640 rpm for 3 min. Finally, a two-stage high pressure homogenizer (APV – 2000, SPX flow technologies, Denmark), with 200 bar for the first stage and 20 bar for the second stage was used, to obtain the final emulsion. The procedure was repeated three times.

2.2.3. Characterisation of liquid emulsions

Oil droplets size distribution was measured by laser diffraction measurements (Mastersizer S, Malvern Instruments, Ltd., UK) using the 300 RF lens and a small volume dispersion unit (at 1000 rpm) with the following parameters: 20 ± 2.5% obscuration rate; refractive index for the oil phase of 1.46. The droplet size was described by volume-based distribution parameters (d10, d50, d90 and SPAN, where SPAN is calculated as SPAN = (d90 − d10)/d50. Measurements were done in triplicate and expressed as an average ± standard deviation (SD).

2.2.4. Emulsion layering of pellets

2.2.4.1. Process parameters. To physically stabilise - kinetically freeze the homogenized emulsion, pellet coating process based on fluidized bed technology was used. Coating experiments were performed using the GPCG-1 process equipment (Glatt® GmbH, Germany) utilising a modified Wurster-type process chamber equipped with swirl generator design (Dreu et al., 2012). The two-fluid Schlick nozzle with 0.8 mm opening diameter and a 2.50 mm cap opening diameter was used. The coating process parameters were the same in all experiments: neutral cores batch size 200 g; inlet airflow rate 130 m^3/h; outlet air temperature 34 °C; spraying rate from 5 g/min (coating time: 0–5 min), 7 g/min (coating time: 5–15 min), 8 g/min (coating time: 15–25 min), 9 g/min (coating time: 25 - end min); atomizing air pressure 2.0 bars; gap between distribution/swirl generator and the Wurster insert bottom edge 17.5 mm. After 1000 g of the emulsion was sprayed onto 200 g of starting pellet cores (Cellets 200), a drying step was used. Pellets were brought to 42 °C at an inlet air temperature of 50 °C, and further dried for 3 min.

2.2.4.2. Fluid bed coating process yield. The coating yield was calculated from the drug content in layered pellets using the Eq. (1).

$$\text{Coating process yield} = \frac{\text{Mass of coated pellets (without agglomerates)} * \text{simvastatin content (UPLC analysis)}}{\text{Mass of simvastatin sprayed}} * 100\% \quad (1)$$

2.2.5. Characterisation of dry emulsion-coated pellets

2.2.5.1. Drug content. Fluid bed coated dry emulsion pellets were added to 25 ml of methanol and sonicated for 20 min in order to ensure complete release of the drug in the medium. The resulting dispersion was diluted with methanol to obtain a final theoretical API

concentration of 10 µg/ml. Finally, the dispersion was filtered through a 0.22 µm syringe filter and analysed with UPLC (method described in Section 2.2.8.).

2.2.5.2. Moisture content. The moisture content of the coated pellets was determined gravimetrically, utilising the Büchi moisture analyser (B-302, Büchi, Switzerland) by heating approx. 5 g of the pellets for 15 min at 85 °C. The moisture content was calculated using Eq. (2).

$$Moisture\ \ content\,(\%) = \frac{weight\ loss}{original\ \ sample\ \ weight} * 100\% \quad (2)$$

2.2.5.3. Coated pellet shape, size and percentage of agglomerates. The pellet size and shape distributions were determined by using the computer scanner method (Šibanc et al., 2017). In brief, for each coating experiment around 10,000 pellets were analysed after capturing images with a computer scanner (Perfection V700, Epson) in order to obtain results with high statistical confidence. The parameters evaluated by image analysis were circularity (C), pellet size and pellet size SPAN, where circularity was calculated as $C = (4 * \pi * A)/P^2$ and SPAN as SPAN = (d90 − d10)/d50.

The portion of agglomerates in the coated product was assessed by sieving the coated pellets through the sieve of pore size of 800 µm. In this way triplets and higher pellet number agglomerates could be detected. The portion of agglomerates was calculated according to Eq. (3), where the ratio of mass of particles retained on the sieve and the total mass of the product were employed.

$$\%\ \ of\ \ aggregates = \frac{mass\ \ above\ \ sieve}{total\ \ mass\ \ of\ \ pellets} \quad (3)$$

2.2.5.4. Scanning electron microscopy (SEM). Scanning electron microscopy was used to obtain the information about the morphology of the pellets. Pellet cross-sectional cuts, prepared with a scalpel, were placed on a graphite foil and examined with a 235 Supra 35VP-24-13 high-resolution scanning electron microscope (SEM) (Carl Zeiss, Germany).

2.2.5.5. Raman spectroscopy. Micro Raman spectroscopy (MRS) was used to determine the surface composition and spatial distribution of the simvastatin oil solution in the dry emulsion-coated pellets. MRS was done using a WITec Alpha 300 RS scanning confocal Raman microscope in backscattered geometry with a HeNe laser operating at a wavelength of 633 nm. The laser beam was focused through a 100×/0.9 microscope objective on an area smaller than 1 μm^2. The power of the laser at the sample surface was approximately 5.5 mW, as it was experimentally determined that this is the optimal power for the measurements, where the sample is not damaged during the evaluation. To determine the spatial distribution of the simvastatin oil solution in the coating, the coated pellet was cut using a scalpel and MRS mapping was performed on the exposed area of the coating (10x10 μm^2, divided in 900 points), where the integration time for each point was 20 s.

2.2.5.6. Dry emulsion pellet reconstitution. To evaluate the dry emulsion pellet reconstitution, conditions resembling the in-vivo situation in terms of amount of liquid were recreated. Approx. 640 mg of the sample was placed in 40 ml of distilled water within conical centrifuge tube (equivalent to proportion of 40 mg of simvastatin taken with 200 ml of water), mounted on a horizontal shaker for 15 min and shaken additionally for 1 min on a vortex shaker. The shaking procedure was repeated twice. Afterwards, the size distribution of the oil droplets was measured as described under Section 2.2.3. All experiments were done in triplicate.

2.2.5.7. Size distribution index (SDI). The oil droplet size distribution index (SDI) was developed to better represent the bimodal size distribution of droplets obtained after reconstitution. The size distribution index is calculated as follows:

$$SDI = AUC\,(1) * MAX\,(1) + AUC\,(2) * MAX\,(2) \quad (4)$$

where AUC is the area under curve of the volume-based size distribution peak (expressed in volume percentage), and MAX is the maximum of the peak (expressed as size). The delimitation between the peaks used to calculate the AUC, was the minimum value between the peaks.

2.2.6. Dissolution studies

The dissolution tests of the dry emulsion-coated pellets were conducted by a USP II dissolution apparatus. An accurately weighted amount of product equivalent to 20 mg of simvastatin was introduced in 500 ml of the dissolution medium containing citrate buffer solution with a pH = 4 (20.1 g/l citric acid, 8.0 g/l sodium hydroxide, adjusted with hydrochloric acid). The paddles were rotated at 100 rpm and the temperature was maintained at 37 °C ± 0.5 °C. At predetermined time intervals (1, 3, 5, 10, 15, 30, 60, 120 min) samples were withdrawn (without replacing the medium with fresh buffer) and diluted with methanol. Prior to analysis, samples were filtered through a 0.22 µm filter and analyzed with UPLC method (described in Section 2.2.8). All dissolution experiments were performed in triplicates.

2.2.7. Stability study

The stability of the produced pellets was evaluated by placing the samples in a desiccator at reduced humidity (< 2%), not protected from light at room temperature during one month of storage. After this period, the pellets were analyzed as described in the Section *Drug content*. The degradation of simvastatin in the pellets was calculated as the relative content of simvastatin after one month following Eq. (5).

$$Content\,(t = 1\ \ month) = \frac{drug\ \ content\,(t = 1\ \ month)}{drug\ \ content\,(t = 0)} * 100\% \quad (5)$$

2.2.8. U(H)PLC analysis

The UPLC method was developed in order to separate simvastatin from its degradation product, simvastatin acid, and from any form of blank interference. Simvastatin was determined by the chromatographic system Acquity UPLC (Waters Corp., USA). A UV–VIS photodiode array (PDA) module equipped with a high sensitivity flow cell was used for detection. The column used was a reverse phase column Acquity UPLC BEH C18 1.7 µm; 2.1 × 100 mm (Waters Corp., USA). A gradient elution was used containing mobile phase *A* (water, containing 0.1% formic acid and 10% acetonitrile) and mobile phase *B* (98% acetonitrile, 2% water). The gradient method was the following: start at 50:50 *(A:B)*; 0 – 6 min, 50:50 – 40:60; 6 – 7 min, 40:60; 7 – 8 min, 40:60 – 50:50; 8 – 10 min, 50:50. The flow rate was set at 0.3 ml/min and the column temperature was kept at 45 °C. The auto-sampler temperature was set at 10 °C. The injection volume was 5 µL and the run time was 10 min. Simvastatin and its acid form were detected at the wavelength of 238 nm. The retention times were 4 min and 6 min, for simvastatin hydroxyacid and simvastatin, respectively.

2.2.9. Statistical analysis

Statistical analysis was performed using Minitab® 17 software (Minitab Inc., PA, U.S.A.).

2.3. Experimental design

First, different emulsion formulations consisted of 1-oleoyl-rac-glycerol with Miglyol® 812 – 9:1 (oil), mannitol, Pharmacoat 603 (HPMC), and Tween 20 were tested by the coating process and limits, where the formulations were processable, were set. HPMC was added to the sugar matrix, as it has proven to be necessary for successful coating. Without

Table 1
Extreme vertices design, a subtype of mixture design, with four independent variables: 1OG, mannitol, HPMC, and Tween®20 (F1 – F15). Values of four independent variables for two optimisation experiments obtained after the models were set, F16 for SDI and F17 for stability and SDI.

	Weight proportion (%)			
Experiment	Oil	Mannitol	HPMC	Tween® 20
F1	33.17	52.00	14.21	0.62
F2	33.17	58.91	5.42	2.50
F3	33.17	60.91	5.42	0.50
F4	33.17	52.12	14.21	0.50
F5	33.17	52.00	12.33	2.50
F6	27.86	55.43	14.21	2.50
F7	30.45	58.37	9.75	1.43
F8	30.45	58.37	9.75	1.43
F9	27.86	65.15	6.49	0.50
F10	27.86	65.15	5.42	1.57
F11	27.86	57.43	14.21	0.50
F12	28.93	65.15	5.42	0.50
F13	27.86	64.22	5.42	2.50
F14	30.45	58.37	9.75	1.43
F15	31.29	52.00	14.21	2.50
F16	29.48	55.80	14.21	0.51
F17	30.90	58.38	10.22	0.50

the addition of HPMC (using only mannitol), pellet coating was/is not possible. The limits for different components were: oil from 27.86% to 33.17%, mannitol from 52% to 65.15%, HPMC from 5.42% to 14.21%, and Tween®20 from 0.5% to 2.5%. The percentage of non-water components in the emulsion, without the API, was bound to 20% as it was found out to be the optimal percentage for successful pellet coating. For the experimental design and statistical evaluation, Minitab® 17 software (Minitab Inc., PA, U.S.A.) was used. Extreme vertices design, a subtype of mixture design, with four independent variables; oil (X1), Mannitol (X2), HPMC (X3), and Tween®20 (X4), was used and three repetitions were made at the center point to estimate the repetition error. SDI (Y1) and simvastatin chemical stability (Y2) were taken as DoE responses. In total, 15 experiments were performed with three repetitions in the central point, as shown in Table 1.

2.3.1. Optimisation experiments

Two optimisation experiments (F16, F17, Table 1) were performed after the models were set. To obtain the two optimised formulations, a quadratic model was fitted on the responses (Y_1 and Y_2), and a Minitab® response optimiser (weighted desirability function) was used to find the local optimum of Y_1 (single objective) and of the combination of Y_1 and Y_2 (two-objective equally weighted optimisation), respectively.

3. Results and discussion

3.1. Solubility study of simvastatin

Two factors were considered, when deciding which oil phase to choose for the emulsion preparation. Firstly, the ability of the oil phase to dissolve simvastatin and secondly, the ability of the oil phase to promote absorption through the lymphatic system. Thus, equilibrium solubility of simvastatin in various oils was tested (Fig. 1), and literature data in terms of absorption facilitation were reviewed, which resulted in 1OG to be chosen as the oil phase.

1OG is an oil phase composed of 40% of 1-oleoylglycerol, the rest being di- and triglycerides of oleic acid in equal portions. From our solubility study, 1OG showed the greatest solubilizing potential (75.52 ± 3.0 mg/g) and a more than twofold increase compared to the second most solubilizing oil (Castor oil; 37.62 ± 1.64 mg/g). Furthermore, 1OG is composed of long chain unsaturated fatty acids, which have been shown to significantly promote lymphatic absorption, thus enhancing overall bioavailability of highly lipophilic drugs (O'Driscoll, 2002). Thereby, of the six oils tested, 1OG has demonstrated to be the most adequate oil phase for the formulation of the emulsions.

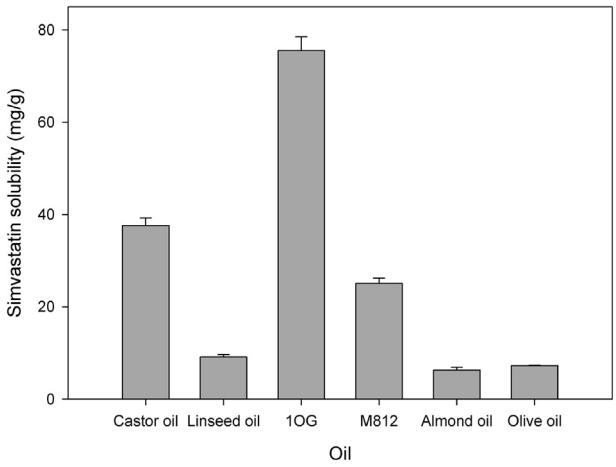

Fig. 1. Equilibrium solubility of simvastatin in various oils. Each simvastatin concentration is expressed as mean ± SD of three determinations.

3.2. Physical stability of simvastatin-loaded emulsions

Oil droplets size distribution was measured immediately after preparing the emulsions and after one month of storage. A two-sample T-Test was performed for groups of all formulations in terms of D50 and SPAN, and no significant difference was found between time 0 and time 1 month ($p > 0.05$). It can be concluded, that the prepared liquid emulsions are physically stable during the coating time period. In general, if the chemical stability due to hydrolysis of the drug in the liquid emulsion is not an issue, the coating liquid emulsion can be prepared in advance.

3.3. Characterisation of layering process and simvastatin loaded, dry emulsion-coated pellets

3.3.1. Drug content

Drug content is very important in pellet coating, as the neutral core of the pellet can represent a considerable volume of the final coated pellet. Low drug content can even lead to failure when trying to meet the required dose within limited hard capsule volume. With this in mind, drug content was assessed. Drug content is dependent on oil content in the emulsion and process yield. Thereby, formulations with the highest yield and the highest percentage of oil should have the highest drug content. The content ranged from 7.95 ± 0.09 mg/g to 10.66 ± 0.10 mg/g (Fig. 2). It should be emphasised, that a compromise was taken between prediction potential of the experiments and energy/material cost-related issues, and thus only one coating step was carried out with 1000 g of emulsion. Based on our experiences, it was estimated that this mass of coating applied was discriminating enough to distinguish between different formulations, without excessive coating material consumption. In full application, 5000 g of coating emulsion would be sprayed to 200 g of starting cores, which would finally yield product with simvastatin content of around 17 mg/g (calculated for optimisation experiment F17).

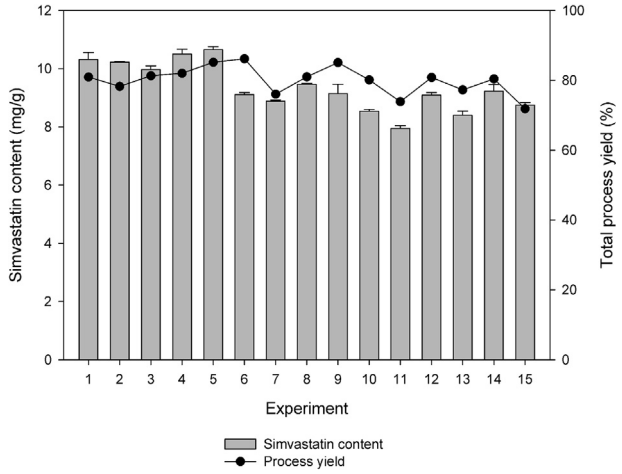

Fig. 2. Simvastatin content in dry emulsion-coated pellets and fluid bed process yield, both determined by UPLC analysis.

3.3.2. Total process yield

The total process yield ranged from 71.83% to 86.17% as illustrated in Fig. 2, for Experiment 15 and Experiment 6, respectively. The relatively modest yield can be attributed to also the stickiness of the emulsion (because of the oil components), which resulted in a considerable portion of the dry emulsion being adhered to the shaking filters and consequently lost. This was also documented with the time at which the shaking filters were blocked. Only in experiments 4 and 11, which had higher HPMC content and lower T20 content, were we able to conduct the coating experiment without cleaning the filters in between. For the other experiments, the time until the filter blockage was from 42 min to 101 min. Some losses can also be attributed to pellets being lost during removal of the product from the coating chamber.

3.3.3. Moisture content

The moisture content of the freshly prepared dry emulsion-coated pellets ranged between 1.11% for Experiment 13 and 1.51% for Experiment 12, which is shown in Table 2. Considering the low moisture content of pellets, the drying was efficient throughout the process. The low moisture content and the narrow moisture content distribution shows that regardless of the formulation used, APIs susceptible to hydrolysis and with potential stability related problems can be successfully incorporated in such system. Additionally, by achieving a low water content, potential recrystallisation of the API at the oil/water interphase, can be prevented (Luebbert and Sadowski, 2017).

Table 2
D10, D50, D90, SPAN, circularity, and water content of dry emulsion-coated and uncoated pellets.

Experiment	D10 (μm)	D50 (μm)	D90 (μm)	Span	Circularity	Water Content (%)
F1	298	336	412	0.17	0.93	1.19
F2	287	328	413	0.19	0.93	1.45
F3	300	330	407	0.16	0.93	1.31
F4	299	337	414	0.17	0.93	1.28
F5	299	334	413	0.17	0.93	1.21
F6	293	326	404	0.17	0.93	1.34
F7	297	337	412	0.17	0.93	1.39
F8	299	339	416	0.17	0.93	1.34
F9	298	348	422	0.18	0.93	1.16
F10	300	345	419	0.17	0.93	1.33
F11	297	337	413	0.17	0.93	1.41
F12	294	334	415	0.18	0.93	1.51
F13	293	340	416	0.18	0.93	1.11
F14	294	334	416	0.18	0.93	1.34
F15	299	338	415	0.17	0.93	1.34
UNCOATED	247	296	352	0.18	0.92	4.00

3.3.4. Coated pellet shape, size, and percent of agglomerates

Coated and uncoated pellets were tested for uniformity and size, which is shown in Table 2. As can be seen from the Table 2, the SPAN values of the coated pellets ranged from 0.162 to 0.192, which indicates a very narrow size distribution. Furthermore, SPAN value did not change significantly during coating experiments ($p > 0.05$). On the other hand, circularity of the pellets didn't only remain unchanged, but was significantly improved during coating processes ($p < 0.05$). These results show a clear advantage of the swirl flow generator equipped coater used in the experiments, compared to the conventional Wurster chamber (Luštrik et al., 2012). The more even deposition of the coating emulsion on the pellets, leads to lower drug content variability, on the other hand, improved circularity brings even better pellet flow properties.

Formation of agglomerates during fluid bed coating experiments, especially when coating small particles, represents a big problem (Nakano and Yuasa, 2001). This can be seen as mass variation in capsule-filling or tableting processes, which leads to failure when trying to meet uniformity of mass/content tests (Ali et al., 2009). In order to assure uniformity of dosage units, agglomerates are separated from the product by sieving. This step, however, further decreases total process yield. Thus, assessment of agglomerates formation was performed. The average percentage of agglomerates between all 15 experiments was 0.041%. Results of process yield, moisture content, SPAN, circularity, and the percentage of agglomerates clearly show that the coating process was conducted at an adequate performance level.

3.3.5. Morphology of applied coating layer

Fig. 3 represents SEM pictures of dry emulsion-coated pellets at different magnifications. On the picture a), a neutral core with a uniform dry emulsion coating layer can be observed. It can be seen that the core composed of microcrystalline cellulose has a very compact structure, compared to the porous structure of the dry emulsion layer. A higher magnification of the dry emulsion coating layer is illustrated in picture b), where discrete cavities, supposedly filled with oil droplets containing simvastatin, can be seen in the matrix. Difference between formulations with high or low values of SDI can be observed also by looking at the microstructure of the pellets surface. The coating layers of four different formulations with different SDIs are shown in pictures c), d), e), and f) in increasing SDI order. Picture c) represents a formulation with low SDI, having smaller, more uniform pores, compared to the picture f) taken from a pellet sample with high SDI value, having large and size non-uniform pores. As all liquid emulsions had the same droplet size distribution, the difference in the structure of the dry emulsion layer can't be attributed to the size distribution of the initial liquid emulsion. We think that the main difference in the structure of the dry emulsion layer was due to the difference in the formulations affecting the drying stage of the sprayed droplets.

3.3.6. Spatial distribution of coating layer components

The pellet coating cross-sections were analysed with Micro Raman Spectroscopy - MRS to determine the spatial distribution of the active ingredient (simvastatin) dissolved in the oil mixture. In Fig. 4 a) Raman spectra of mannitol, HPMC, and oil solution of simvastatin are shown. The spectra of pure mannitol (Fig. 4 a)-A) and HPMC (Fig. 4 a)-B) are in good agreement with the spectra from literature (Campbell Roberts et al., 2002; de Veij et al., 2009). Raman spectra in Fig. 4 a)-C represents the oil mixture that contains dissolved simvastatin, and has a characteristic peak at 1653 cm^{-1} (Graeser et al., 2008). This peak does not overlap with any other peak of the compounds used in the oil mixture. To avoid any surface roughness effects, the intensity ratio of the peaks at 651 cm^{-1} for mannitol (marked with ▼ in Fig. 4 a) and at 1653 cm^{-1} for simvastatin oil solution (marked with ▽ in Fig. 4 a)) was used to determine the local concentration of simvastatin oil solution in terms of I_{651}/I_{1653}. The results are shown in Fig. 4 b) and c), which

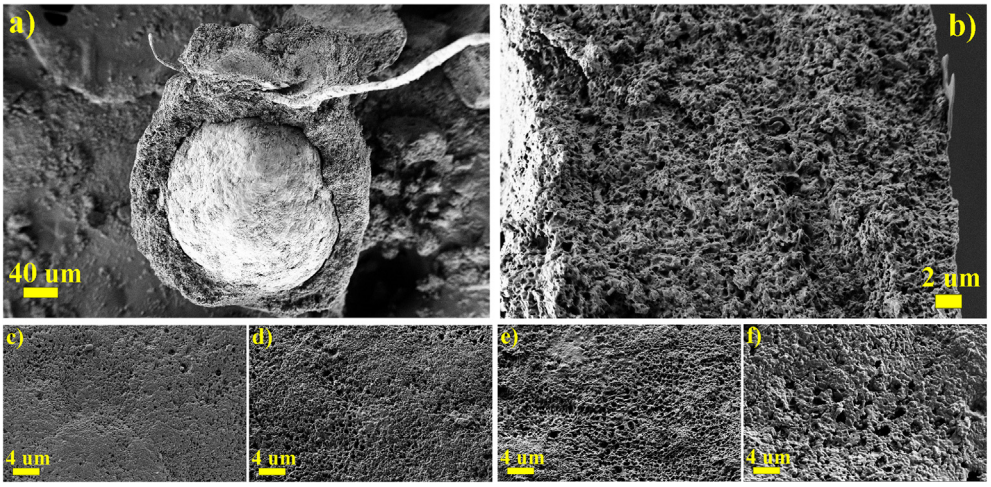

Fig. 3. SEM micrographs of dry emulsion-coated pellets using various magnifications. A cross-section of the whole pellet is shown in image a) (magnification 540 X), and a cross-section of the F16 coating is shown in image b) (magnification 8000 X). Dry emulsion-coated pellets arranged with increasing SDI (magnification 8000 X): c) F16, d) F9, e) F6, f) F2.

represent the MRS mapping of experiment F2 and F16, respectively. The intensity ratio was normalised, where 0 or black colour means high local concentration and 1 or yellow colour means low local concentration of simvastatin oil mixture solution and high concentration of the components of the matrix. Here the distinction between formulations with high/low SDI couldn't be made, because of the rough surface of cross-sections, which interfered with MRS measurements. Based on the results shown here, we can conclude that the pores seen on SEM pictures (Fig. 3) are filled with droplets of the simvastatin oil solution.

3.3.7. Droplet size distribution index (SDI)

The great importance of oil droplet size for oil dissolved drug

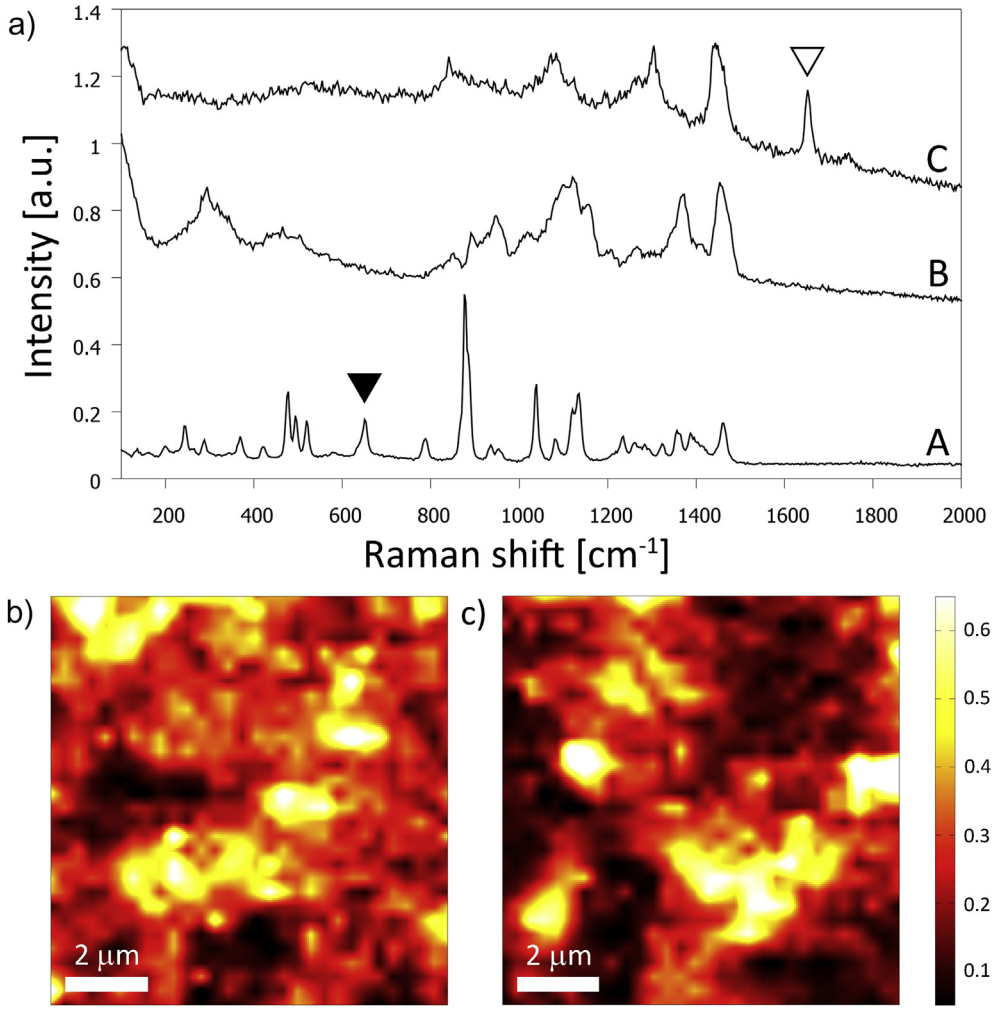

Fig. 4. MRS results – a) Raman spectra of A) mannitol, B) HPMC, and C) simvastatin oil solution. The peaks used in the MRS mapping are marked: the 1653 cm^{-1} peak, characteristic for simvastatin oil solution, is marked with ▽, the 651 cm^{-1} peak, characteristic for mannitol, is marked with ▼. b) and c) are representations of the spatial distributions of high (black area), and low (yellow area) concentrations of simvastatin oil solution for samples F2 and F16, respectively.

absorption has been described in the literature (Porter et al., 1996; Tarr and Yalkowsky, 1989), thus reconstitution of dry emulsion pellets was studied, as a surrogate marker for the possible extent of drug absorption. Table 3 shows the significant difference in the SDI across 15 experiments of the DoE. The different droplet size distributions, showing great heterogeneity for three formulations with low, medium, and high SDI, are illustrated in Fig. 5 a). SDI, as an index, was developed because it provides single value information that takes into account both the width of the volume based size distribution and the size of the droplets. As all initial emulsions had similar size distributions (Fig. 5 a)) with low SDI value, we are able to say that the lower is the SDI, the better the reconstituted dry emulsion resembles the initial emulsion, and vice-versa.

Table 3
Size distribution index (SDI) across 15 experiments of the DoE with the additional optimization Experiment (F16).

Experiment	SDI	Experiment	SDI
F1	2.12	F9	1.99
F2	15.86	F10	11.44
F3	1.69	F11	1.76
F4	2.50	F12	2.32
F5	12.40	F13	7.00
F6	10.38	F14	6.69
F7	7.56	F15	10.54
F8	7.53	**F16**	**1.50**

Based on SDI, a quadratic model, with 95% confidence the interval was fitted to the data and a good correlation was found (R^2 = 0.9681, R^2 (adjusted) = 0.9106). However, the model had a relatively low R^2 (predicted) = 0.1591). Additionally, the repetition error was assessed and a 6.82% relative standard deviation (RSD) is reported. A contour plot for the SDI response was generated to show how the formulation variables affect the SDI, as shown in Fig. 5 b). Oil, mannitol, and HPMC are expressed as proportions and Tween® 20 proportion is bound at 0.0075. The grey line in the contour plot shows the area where DoE experiments were conducted at the selected level of Tween 20. The area outside the grey line has not been validated, and the results outside the grey line should be taken with caution. From the contour plot it can be seen, that with increasing concentrations of oil or HPMC, dry emulsions with high SDI are produced. A similar pattern between the matrix polymer concentration and median droplet size was also found by Basha and co-workers (Basha et al., 2017), who demonstrated that with increasing polymer concentration and hence the viscosity, bigger oil droplets are obtained after reconstitution of dry emulsion. We think that this could be due to the bigger size of sprayed emulsion droplets, which results from the higher viscosity of the emulsion. An analogous pattern can be seen with Tween® 20, as for our dry emulsions, increasing its concentration led to higher SDI. The possible explanation for this phenomenon could be that high surfactant concentration lowers the inter-phase tension in such a way, that oil droplets have the tendency to merge during the coating atomization, wetting, and drying

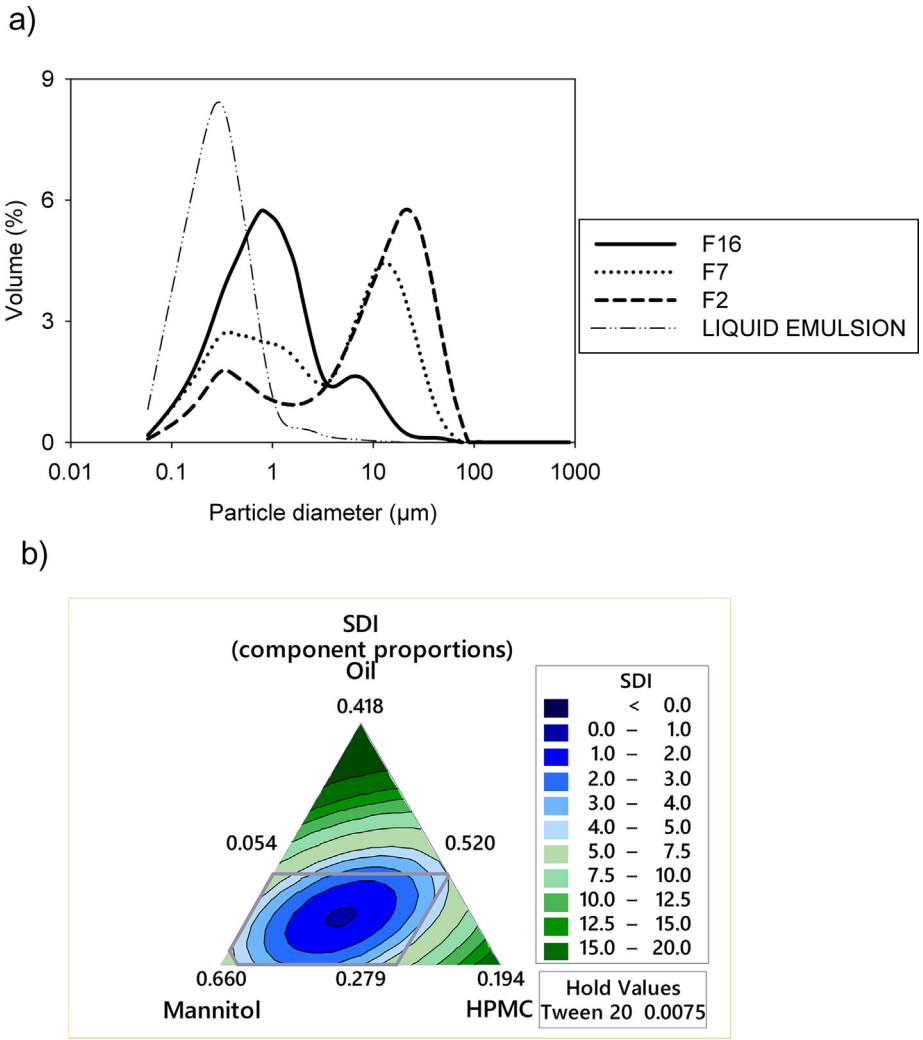

Fig. 5. a) Size distribution of oil droplets of three formulations with different SDIs (low SDI = F16, medium SDI = F7, high SDI = F2) and a representative liquid coating emulsion (Formulation F15); b) Contour plot of SDI, obtained after the model was set. Tween® 20 proportion is bound to 0.0075.

processes. The fitted model for the SDI has the following equation with uncoded factors – component proportions (oil (X1), Mannitol (X2), HPMC (X3), and Tween®20 (X4)):

$$Y1 = 1390.85*X1 + 284.904*X2 + 1701.90*X3 - 57751.2*X4 - 2909.98*X1*X2 - 4875.28*X1*X3 + 62158.6*X1*X4 - 1676.32*X2*X3 + 57977.4*X2*X3 + 57409.2*X3*X4 \quad (6)$$

Using the model and the response optimiser (goal: minimize), the local minimum of the SDI, within the design space was predicted and the model proposed formulation (F16) was prepared and coated onto neutral pellets. The predicted optimal formulation F16 was composed of the highest proportion of HPMC, the medium proportions of the oil and mannitol components, and from the lowest proportion of the surfactant. The highest proportion of HPMC was selected prior to optimisation, as it was found that formulations with more HPMC have less agglomerates and have a lower degree of adhesiveness to the shaking filters. Simultaneously, the lowest value of Tween® 20 was chosen as higher percentage of surfactants were to avoid due to GIT tissue inflammation potential of the surfactants. F16 had the lowest SDI (1.497 versus the average value of 6.786 from the 15 experiments), which proved the satisfactoriness of the presented model. The model was further improved when results of experiment F16 were added to it. This is shown by improving of all parameters showing the correlation (R^2 = 0.9692, R^2 (adjusted) = 0.9230, R^2 (predicted) = 0.3446).

3.3.8. Stability study

Simvastatin is a prodrug in the form of a cyclic ester. In the presence of water, simvastatin hydrolyses to its biologically active form, simvastatin hydroxyacid. For many prodrugs (e.g. simvastatin) it is known that conversion into the active form leads to poorer absorption (Geboers et al., 2016). Thereby, the stability of simvastatin in dry emulsion-coated pellets was monitored after pellets manufacture and the results are shown in Fig. 6. The average relative one-month stability of the 15 DoE experiments is 93.77%.

From the response values (Y2), a quadratic model was fitted (R^2 = 0.8816, R^2 (adjusted) = 0.6685), giving the following equation (oil (X1), Mannitol (X2), HPMC (X3), and Tween®20 (X4))

$$Y2 = -1737.74*X1 - 267.237*X2 - 1201.24*X3 + 18339.7*X4 + 3796.11*X1*X2 + 4984.63*X1*X3 - 13212.8*X1*X4 + 1190.44*X2*X3 - 19628.9*X2*X3 - 23752.4*X3*X4 \quad (7)$$

Again, the repetition error was assessed (RSD = 1.83%) and the response optimiser was used and this time not only stability (Y2), but the combination of both responses, i.e. Y1 (SDI) and Y2, were chosen to optimise the results of both factors. The goal was to minimise the response Y1 and to maximise the response Y2. Based on the formulation optimisation results, F17 was produced. The product demonstrated the highest relative one-month stability among coated pellets samples (i.e. 97.18%) and a very low SDI value. The SDI value was not the lowest of the previously analysed formulations (F17 value of 2.16 in comparison to 1.50 of F16), but this can be attributed to the weighted desirability function, which took into account both the stability and the SDI. The results from the stability study showed that within the design space, raising proportions of HPMC, mannitol, and especially Tween® 20 led to lower stability. The last is expected, as it has been demonstrated many times that surfactants and especially their degradation products act detrimentally on the stability of drugs (Krishna et al., 2018; Marothu et al., 2015). Polysorbates, to which Tween® 20 belongs, are known to undergo peroxidation and hydrolysis, which can cause drug instability, thus large quantities of surfactants should be avoided or adequately stabilized with the addition of antioxidants and/or suitable pH modifiers (Kishore et al., 2011). To exclude the possibility, that the coating process has produced simvastatin hydroxyacid, which could act as an instability promotor, the acid concentration at time = 0 (after the process) was assessed. For the optimization experiment F17 it was found a small absolute increase of the ratio simvastatin hydroxyacid/simvastatin of 0.36% in comparison to the ratio within starting drug powder. This shows that process does not lead to significant simvastatin degradation via increase of simvastatin hydroxyacid.

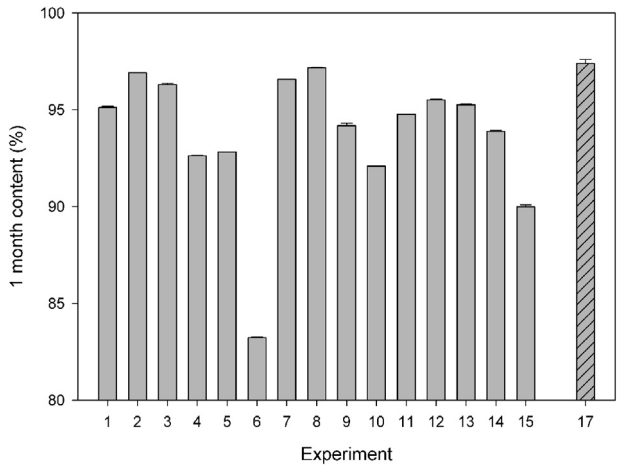

Fig. 6. One-month relative simvastatin content across 15 experiments of the DoE and the result of the additional optimisation Experiment (F17). The results are expressed as average ± SD.

3.3.9. Dissolution studies

When dealing with poorly soluble drugs, the first important step in drug absorption is the release of the drug from the dosage form into the medium. Thus, improving the dissolution profile could lead to better absorption and consequently to higher bioavailability. Dry emulsions have many times proved themselves as a viable options to improve dissolution profiles and bioavailability (Baek et al., 2014; Jang et al., 2006; Onoue et al., 2012). Furthermore, formulating dry emulsions into multiple-unit dosage forms (e.g. layered pellets) leads to higher surface area in comparison to tablets and potentially to faster dissolution (Bechgaard and Nielsen, 1978). To assess the improvement/deterioration of the dissolution profile in comparison to the reference systems, dissolution studies were conducted on the optimized formulations (F16, F17), simvastatin powder and non-lipid based tablets with 20 mg of simvastatin (Fig. 7). From the Fig. 7 it can be clearly seen that after 120 min (time relevant for drug absorption), only 1.93% of powdered simvastatin was dissolved in the dissolution medium, followed by 4.83% of dissolved drug from the simvastatin tablet. The low dissolution profiles can be attributed to the highly lipophilic character of simvastatin, which results in poor wetting and low water solubility of the drug. The release profile is just slightly improved in simvastatin tablet, probably because of the presence of surfactants in it. F16 and F17, the two optimized formulations, on the other hand, exhibited a more than 18 fold and 20 fold increase in drug dissolution after 120 min, even if a very low amount of surfactant was present. To verify that, in the case of dry emulsions dissolution tests, simvastatin was incorporated in oil droplets and not solubilized in water, because of the presence of surfactants, an additional dissolution study was performed on F17. After withdrawing samples, they were ultra-centrifuged, thus separating oil and water phase. Concentration in the water phase was measured and for the 120 min sample, only 3.72% of simvastatin was

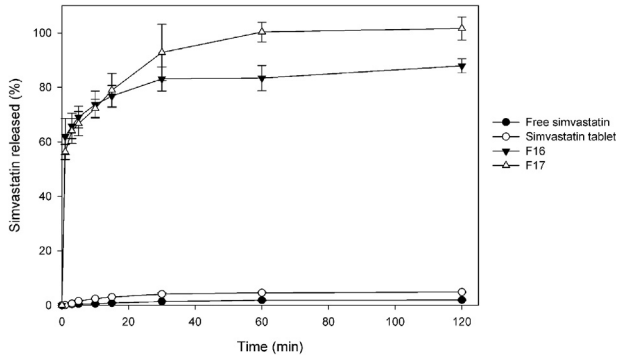

Fig. 7. The dissolution profiles of simvastatin in dissolution medium pH = 4 from powdered simvastatin, simvastatin tablets, dry emulsion-coated pellets F16, and dry emulsion-coated pellets F17. Each data point is expressed as the mean percentage ± SD of three determinations.

found in water phase, which confirms our hypothesis.

4. Conclusions

In the present study, the fluid bed coating technology, as a novel technique for preparing the dry emulsion systems, is successfully employed to produce simvastatin loaded dry emulsion layered pellets composed of 1-oleoyl-rac-glycerol and Miglyol® 812 9:1 mixture, as the oil phase, mannitol and HPMC, as the hydrophilic matrix formers and Tween® 20, as a non-ionic, non-irritating surfactant in low quantity. In total, 15 experiments were performed based on the extreme vertices mixture experimental design, and two additional optimized formulations were produced to meet criteria for droplet size distribution and stability response. Models, describing both responses, have appropriate correlation coefficients. The optimized formulations show acceptable drug loading, good coating yield, substantial improvement in dissolution profile, very low droplet size distribution index and satisfactory stability. Additionally, the optimized formulations have very low surfactant content, which makes them suitable for prolonged drug administration. Excellent flow properties of pellets and the suitability for additional film-coating process makes the presented drug delivery technology platform a viable alternative to the commonly used spray drying technique. The latter usually yields dry emulsion powders with poor flow properties, not suitable for further processing (capsule filling or tableting) and leading to a possible reason for the rejection of dry emulsion drug delivery systems from the portfolio used in pharmaceutical industry. The obtained results suggest that the fluid bed coated dry emulsions systems could be a promising approach for drug dissolution enhancement and hence drug bioavailability improvement of poorly water soluble, highly lipophilic drugs.

5. Conflict of interest

The author(s) confirm that this article content has no conflict of interest.

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