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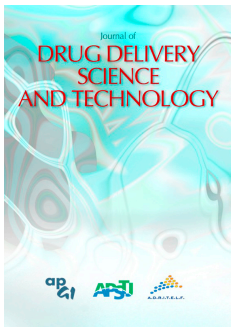

Fine powder of lipid microparticles – spray drying process development and optimization

Eliza Wolska

PII: S1773-2247(21)00320-8

DOI: https://doi.org/10.1016/j.jddst.2021.102640

Reference: JDDST 102640

To appear in: *Journal of Drug Delivery Science and Technology*

Received Date: 21 February 2021

Revised Date: 19 May 2021

Accepted Date: 31 May 2021

Please cite this article as: E. Wolska, Fine powder of lipid microparticles – spray drying process development and optimization, *Journal of Drug Delivery Science and Technology*, https://doi.org/10.1016/j.jddst.2021.102640.

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Author Contributions:

Eliza Wolska: conceptualization, methodology, investigation, writing

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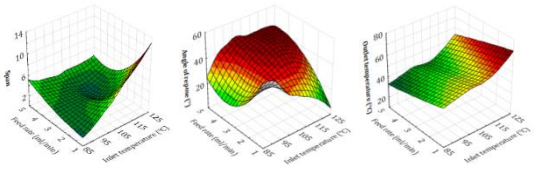
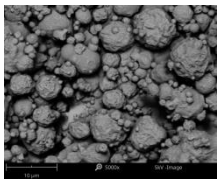
DOSAGE FORMS WITH **SOLID LIPID MICROPARTICLES:**
AQUEOUS DISPERSION OR FINE POWDER



SPRAY DRYING PROCESS OPTIMIZATION PARAMETERS



SEM image of spray-dried SLM

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Eliza Wolska

Department of Pharmaceutical Technology, Medical University of Gdansk, Hallera 107, 80-416 Gdansk, Poland
* *Corresponding author:* Tel. +48 58 3491085; fax: +48 58 3491090.
E-mail address: eliw@gumed.edu.pl (Eliza Wolska)

Abstract

Objectives: Performed studies were focused on developing spray drying technique for aqueous dispersion of solid lipid microparticles (SLM) by selecting appropriate process parameters and assessing their impact on the process and properties of the obtained dry SLM powders.

Significance: Spray drying allows to obtain SLM in a dry powder form when the liquid form does not present sufficient long-term stability (e.g. due to degradation of the active substance or aggregation of particles) or when the dosage form is to be used in a fine powder form.

Methods: In the first stage of research the experiments were designed to optimize process parameters during spray drying of the *placebo* SLM dispersions prepared with two lipids: Compritol or stearic acid. The inlet temperature and feed rate were process parameters selected for monitoring. As response values, yield and quality attributes of the final product, namely particle size, moisture content and powder flowability were chosen. The process parameters optimized in the first step were then used to dry the SLM with model active substances: cyclosporine and spironolactone.

Results: The use of 3D surface charts, developed on the basis of the results of the conducted experiments, allowed for the selection of optimal process conditions for obtaining final product with desired properties and satisfying yield. For SLM with Compritol these were: inlet temperature 90°C and feed rate 2.4 ml/min; whereas for SLM with stearic acid 80°C and 3 ml/min were optimal, respectively. Process parameters optimized for *placebo* formulations were found to be equally suitable for drying drug-loaded SLM.

Conclusions: The spray drying was found to be an effective method of obtaining dry powders from aqueous SLM dispersions. The lipid forming the SLM matrix should be considered the most important factor on which the process parameters depend. The most appropriate drying conditions selected during drying *placebo* formulations proved to be equally effective when SLM with the same composition and with model active substance were subjected to drying.

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Keywords: solid lipid microparticles, spray drying, microspheres, cyclosporine, spironolactone, powder flowability

1. Introduction

Solid lipid microparticles (SLM) are lipid-based formulation with great potential as drug delivery system. SLM were developed on the basis of SLN (solid lipid nanoparticles) studies, but they are in the micrometers size range (usually 1-100 µm, up to 1000 µm, depending on the preparation method [1-4]). Due to the particle size and the solid state of the lipid forming the matrix, SLM can provide prolonged drug release. In comparison to SLN higher drug loading is also feasible [5-8]. Similar like for SLN, the most common techniques for the preparation of SLM dispersions are: melt dispersion technique (called also hot emulsification method), solvent evaporation or diffusion method and microchannel emulsification technique [4]. Although SLM present beneficial technological and biopharmaceutical properties, they are incomparably less studied as drug carriers than SLN [9-11]. As biocompatible multicompartment carrier SLM are a good alternative to polymer microparticles and are considered for both, systemic (oral, parenteral [12-14]) and topical (dermal, ocular or even inhaled [15-18]) application.

SLM can be applied as a liquid dispersion (aqueous suspension of microspheres) or a fine powder (e.g. inhalation powders) depending on the intended administration route [3, 18, 19]. Producing SLM in the form of a dry powder is also justified in order to increase the long-term stability of the formulation (physical, chemical and microbiological) [20, 21]. Although the long-term stability studies confirmed that SLN and SLM formulations in the liquid suspension form remained stable after 2 years of storage [8, 22, 23], there is a greater risk of adverse changes in the aqueous suspensions, especially in drug loaded preparations. Unfavorable physicochemical transformations may concern both the lipid matrix and other excipients, as well as the active substance (API), which may undergo chemical degradation (e.g. hydrolysis) or premature release. Changes like degradation of the particles matrix, particle aggregation/particle fusion or unwanted increase in particle size were observed in both SLM and SLN dispersions [3, 20]. After conversion into dry powders, lipospheres could be stored over a long period, without the risk of physicochemical changes characteristic for liquid dispersions. Obtained dry formulations could be used in the form of a powder or after reconstitution, as a suspension. It is essential that the reconstituted dispersion exhibits the same properties as the original suspension.

There are few and not very well studied methods for producing SLM in the form of a dry powder: spray congealing (also called spray chilling), spray drying (from organic solution), cryogenic micronisation or particles from gas-saturated solutions technique (PGSS) [4]. However, the main problems reported are: large size of the obtained lipid particles (even up to 2000 μm) and/or the use of organic solvents (e.g. ethanol) [4, 24]. A solution to both these issues can be a two-stage process: 1/ hot emulsification technique for preparation of SLM aqueous dispersion and 2/ evaporation of water by spray drying of the resulting suspension. While it is known that spray drying process may convert various liquid feed, not only solution, but also suspension or emulsion to a dried particulate form, this approach was only used by Mezzena et al. [17] for the production of inhalable SLM from microparticulate dispersion. In other published reports, the lipid microparticles were obtained by spray drying of organic solutions – lipids were dissolved in dichloromethane, chloroform or ethanol [15, 25, 26]. The spray-drying process should certainly be considered as a more favorable alternative to the more expensive and time-consuming lyophilization process, which could also be applied as a method of transforming an aqueous dispersion into dry powder. In addition, during freeze-drying, lipospheres are exposed to freezing and desiccation stress, which may be detrimental to their further stability. Several sugars (glucose, fructose, trehalose, and sorbitol) are being used as cryoprotectants to overcome that concerns since they have shown ability to conserve lipid carrier properties after freeze-drying. Different sugars could have different cryoprotectant power at concentrations used (usually in the range from 5% to 10%), providing various protection to the SLN or SLM during freeze-drying and storage.

Drying is a one-step process often used for conversion of a liquid formulation into a dry powder. Spray drying is a simple, fast and scalable technology used widely not only in pharmaceutical but also in food and chemical industries [4, 27]. The fluid is atomized into thermal contact with a hot drying medium (usually air) with a temperature usually up to 220°C, depending on the properties of the material to be dried. Although the sprayed liquid is in contact with a hot gas, it occurs for a short time and the cooling effect of the evaporating solvent conserves the droplet temperature relatively low. Thus, even heat-sensitive products can be dried with a negligible degradation. It is also possible to dry lipid systems, such as SLN or SLM, even at temperatures above 100°C. SLN dispersions were successfully dried at the inlet temperature of 110°C [18, 19]. However, because this temperature is higher than the melting point of the lipid forming the liposphere matrix, in case of improperly selected process parameters, one should expect the phenomenon of partial melting during the process.

This could result in a change, or even a significant deterioration of the properties (mainly related to powder flow, but also API distribution and the drug release behavior) of the obtained lipospheres.

The yield of the spray drying process and properties of the obtained powders are directly influenced by process parameters. Several factors are known to affect the spray drying process, e.g. inlet temperature, feed rate, outlet temperature or concentration of solids in the feed [4, 27]. With regard to lipid particle dispersions the influence of temperature during drying is especially important. The particles delivered in feed may also be adversely affected by high shear stress in the nozzle. In effect it is not so easy to maintain the size, shape and morphology of the primary particles, which is the main goal of process optimization. Although the spray drying process exhibits many applications in pharmaceutical industry, the use of this process for conversion of the aqueous dispersion of SLM into a dry powder is not sufficiently understood or well reported.

The aim of the present study was to examine and determine on a laboratory scale the best instrument parameters and working conditions to transform aqueous SLM dispersion into SLM dry powder, not losing primary size and morphology in such a way that the obtained SLM dry product can further be used directly as a dry powder or after reconstitution into a liquid dispersion before administration. A practical aspect of the work was to identify the most critical process and formulation parameters in order to achieve successful performance of the process yielding a product with the desired particle size and flowability. As drying of the drug-loaded formulation may not be as effective as for the *placebo* formulation, in the next step dispersions of SLM loaded with model APIs (cyclosporine – CsA and spironolactone – SPIR) were spray dried using the process parameters optimized during the first stage. To the best of our knowledge this is the first research paper presenting the optimization method of spray drying process of an aqueous SLM dispersion with a particle size less than 50 μm.

2. Materials and methods

2.1. Materials

Cyclosporine A (CsA) was obtained from LC Laboratories (Boston, MA, USA) and Compritol 888 ATO (glyceryl behenate) from Gattefossé (Saint-Priest, France). Spironolactone (SPIR), stearic acid and Tween 80 (polysorbate 80) were purchased from

Sigma-Aldrich (St. Louis, MO, USA); polyvinylpyrrolidone (PVP) was from BASF (Ludwigshafen, Germany). All other chemicals used were of analytical reagent grade.

2.2. Preparation of SLM dispersions

For the preparation of SLM dispersions two different lipids: Compritol and stearic acid were used as matrix-forming lipid. The lipid concentration in the dispersions was 10% (w/w) and the formulations were either prepared drug-free (*placebo* formulations) or drug-loaded with cyclosporine (F/CsA) or spironolactone (F/SPIR). The composition of all tested formulations was selected at the preliminary stage of SLM dispersion examination and is illustrated in Table 1. The drug loaded formulations contained 0.1% or 1.0% (w/w) of CsA and 0.1% or 0.5% (w/w) of SPIR, which in relation to the lipid content was 1% or 10% of CsA and 1% or 5% SPIR, respectively. The experimentally determined solubility of the active substances in the tested lipids was 100 mg/g (10%) and 330 mg/g (33%) of CsA in Compritol and stearic acid, respectively, as well as about 30 mg/g (3%) of SPIR in both tested lipids. In comparison with selected API concentration in SLM formulations, SPIR concentrations were both below (1%) and above (5%) the specified solubility, while in the case of CsA were below (1%) or equal to the determined solubility (10%).

SLM formulations were prepared using a hot emulsification method, which has been fully described in a previous paper [16]. All excipients were heated at a temperature 10°C above the lipid melting point, which was 69-74°C for glyceryl behenate and 69,6°C for stearic acid [28, 29]. Thereafter, the mixing process of the lipid phase with aqueous phase was performed at 80°C using a high-shear mixer Ultra-Turrax (T25 Janke-Kunkel, IKA Labortechnik, Germany) with dispersing tool from stainless steel (S 25N – 18 G, working range from 10 ml to 1.5 L), at the speed of 8000 rpm for 5 min. After cooling in an ice bath (30 min) the dispersions were stored in a refrigerator. The batch size was 200 g or 300 g.

Table 1

The composition (w/w %) of the investigated formulations ***placebo*** and with API

Formulation	The composition of formulations (*placebo* and with API)					
	CsA	SPIR	Compritol	Stearic acid	Tween 80	Water
F1	**-**	**-**	**10.0**	**-**	**5.0**	**85.0**
F2	**-**	**-**	**-**	**10.0**	**3.0**	**87.0**
F3	0.1	-	10.0	-	5.0	84.9
F4	1.0	-	10.0	-	5.0	84.0
F5	0.1	-	-	10.0	3.0	86.9
F6	1.0	-	-	10.0	3.0	86.0
F7	-	0.1	10.0	-	5.0	84.9
F8	-	0.5	10.0	-	5.0	84.5
F9	-	0.1	-	10.0	3.0	86.9
F10	-	0.5	-	10.0	3.0	86.5

2.3. Spray drying of SLM dispersions

Spray drying of tested formulations was performed using a laboratory Buchi Mini Spray Dryer B-290 (Buchi Labortechnik AG, Flawil, Switzerland) equipped with standard 0.7 mm nozzle. SLM dispersions immediately before spray drying were diluted with 5% (w/w) PVP solution in equal parts (1:1) and stirring on a magnetic stirrer until the drying process was completed. In the main stage of the study, *placebo* SLM were tested (Table 1). The instrument parameters such as: inlet temperature and liquid feed rate were changed within the range indicated in Table 2. The outlet temperature was evaluated because its value depended on both of these parameters. Other process parameters were maintained constant: the pressure of compressed air was 0.7 MPa, aspiration setting was 100% and the air was used as a drying gas. As response values, to determine efficiency of the process and quality of the final product, particle size (span and percentage of particles with size <50 μm), the yield, moisture content and flowability of the SLM powders were examined (Table 2).

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Table 2

Ranges in which the instrument parameters were modified and the properties of the spray dried SLM powders which were evaluated

Tested factors	Range of instrument parameters		Investigated powder properties
	Compritol	Stearic acid	
Inlet temperature	90-120°C	75-100°C	Particle size (μm)
Feed rate	1.2-6.0 ml/min	2.4-4.5 ml/min	Span
Outlet temperature*	32-62°C	32-50°C	Yield (%)
			Moisture content (%)
			Flow rate (min)
			Angle of repose (°)
			Hausner ratio (HR)

* a value that was not set at the beginning of the process, but resulted from the other two: inlet temperature and feed rate

The resulting spray dried powders were collected and stored in capped glass jars at room temperature. Tested parameters were modified based on the properties of the obtained product. The important feature assessed was the process efficiency calculated as the process yield according to Eq. (1).

$$\text{Yield (\%)} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \text{ x } 100 \qquad (1)$$

where *practical yield* is the amount of powder recovered after spray drying in the receptacle and *theoretical yield* is the amount of dry mass from the dispersion without losses.

In the spray dried powders moisture content, particle size and span (see point 2.4. and 2.6.) were also evaluated. Flow properties of the prepared dry SLM powders were tested as well (see point 2.7.). In Table 2 both equipment-related factors, as well as investigated properties of tested formulations were presented. During the process optimization, attempts were made to select drying parameters that could guarantee the best properties of the obtained dry powders. As the best properties of lipid particles (shape, morphology, size) were considered properties as close as possible to the primary particles (from SLM dispersion). Due to the different possibilities of further use of the spray dried SLM powder, its flowability was also assessed, following the pharmacopoeial criteria for determining the angle of repose and the Hausner ratio.

In the second stage of research, the inlet temperature and flow rate parameters, which have already been selected as the most appropriate for *placebo* formulations, were applied

during API loaded SLM (Table 1) spray drying. As a model drugs CsA and SPIR were chosen. In this work, the obtained API loaded dry powders were also characterized as described above. In this case, however, in addition to the physicochemical properties, such as in the case of placebo particles (shape, size, flowability), it is also important to assess the impact of spray-drying process on the biopharmaceutical properties of lipid particles. Therefore, the distribution of the active substance in the lipid matrix or the release rate of API from the dosage form has been described in detail in a separate paper [30].

2.4. Particle size analysis

The particle size distribution was measured by laser diffraction (Beckman-Coulter LS 13 320, Indianapolis, IN, USA). When the particles were in aqueous SLM dispersion (after preparation, before spray drying) Universal Liquid Module (ULM) was used. ULM is capable of measuring particle samples in the size range 0.017 µm to 2000 µm due to additional detectors and PIDS function (*Polarization Intensity Differential Scattering*). SLM dispersion was added to the sample cell until the correct obscuration parameter (usually at the level of 40-45%) was obtained (when sizing particles with using PIDS, a PIDS obscuration level of 40% to 60% is recommended).

Spray dried powders were also measured by laser diffraction, this time using a Tornado Dry Powder System (DPS) connected to the same device (Beckman-Coulter LS 13 320) as the ULM attachment. The measurement of powder was carried out without dispersion in a liquid medium and without any other sample preparation prior to measurement. The appropriate amount of sample was placed in a sample holder and delivered to the sensing zone in the optical bench by a vacuum. The Tornado DPS provides automatic feed rate (obscuration) control to obtain the set point for the obscuration (6%). DPS is capable of measuring particle samples in the size range 0.4 µm to 2000 µm.

The obtained results were recorded in the form of a graphs and statistics presenting values e.g. d_{10}, d_{50}, d_{90}, determined as measures of maximum diameter of 10%, 50% and 90% of the detected particles, respectively. Particle size was also expressed as span calculated using the following Eq. (2).

$$\text{Span} = \frac{\mathrm{d90} - \mathrm{d10}}{\mathrm{d50}} \qquad (2)$$

Finally, the value corresponding to the percentage of particles located below the value of 50 µm in the tested formulation was also evaluated.

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2.5. Optical microscopy and scanning electron microscopy

An optical microscope (Nikon, Eclipse 50i, Nikon Corporation, Tokyo, Japan) was used for initial microscopic evaluation of *placebo* and drug-loaded SLM.

To visualize surface properties and morphology of the tested lipid microparticles a scanning electron microscope Phenom Pro (Phenom World Thermo Fisher, Eindhoven, Netherlands) was employed. Standard sample holder and a carbon adhesive tape were used to fix a sample of SLM dry powder. When the SLM dispersion was tested, water was evaporated from the sample at room conditions after the dispersion was applied to the carbon tape. Before microscopic observations tested sample was coated with a thin layer of gold. Acceleration voltage of 5 kV was applied to record images at a magnification of 5000x.

2.6. Moisture content determination

The moisture content of the spray dried SLM powders were analyzed using Moisture Analyzer type WPS 210S (Radwag, Poland). The appropriate mass of the powder samples were uniformly spread to a thin layer on a sample dish and dried to a constant weight with a heating cycle of up to 105°C. It was considered that at this temperature no degradation of any compound would occur but that all the water would be evaporated. The weight loss after complete drying reflects the initial and therefore total moisture content of the tested samples.

2.7. Flowability assessment

Flow properties of the prepared spray dried SLM powders were tested according to pharmacopoeial methods (Ph. Eur. 9.0). The flow rate and angle of repose were measured using a manual powder flow tester (Electrolab, Mumbai, India). A powder samples were placed in a funnel with 10 mm orifice and poured onto the base with diameter (*d*) of 10 cm to form a cone. The height of the cone (*h*) was measured using height gauge and the angle of repose α (°) was calculated using following Eq. (3).

$$\tan(\alpha) = \frac{h}{0.5 \text{ x d}} \qquad (3)$$

Measurements were done in triplicate, and the results were expressed as mean ± standard deviation (SD). As reported by the pharmacopoeia, although there is some variation in the qualitative description of powder flow using the angle of repose, much of the pharmaceutical

literature appears to be consistent with the classification by Carr, which is shown in European Pharmacopoeia and was used to classify our powders.

Hausner ratio (HR) was determined with the procedure in which the unsettled apparent volume (V_o) and the final tapped volume (V_f), of the powder, after tapping the material until no further volume changes occur, were measured and HR was calculated according to Eq. (4).

$$\text{Hausner Ratio} = \frac{Vo}{Vf} \quad (4)$$

The tapped volume was determined using Erweka SVM tester (Heusenstamm, Germany), by measuring the volume of the powders after 1250 taps. The results of the Hausner ratio were classified according to the generally accepted scale of flowability presented in the European Pharmacopoeia (2.9.36. Powder flow).

2.8. Statistical analysis

All the statistical analyzes were conducted and all data charts were prepared using Statistica software (StatSoft program, Version 12). The statistical significance of differences between assessed factors was tested by a one-way analysis of variance ANOVA. Differences were considered to be significant at level of $p < 0.05$.

3. Results and discussion

3.1. Selection of conditions for the spray drying process

The spray drying process is one-step method to transfer SLM from aqueous dispersion to a form of dry powder. This method requires the careful adjustment of drying conditions appropriate to the material being dried in order to obtain a product with the desired properties. This is particularly important for primary dispersion composed of lipid material with low melting point. Therefore, in our study, optimization of spray drying conditions of SLM aqueous dispersions was performed, and the aim was to obtain SLM powder composed of lipid particles, the properties of which remained unchanged after the spray-drying process.

The first attempts to spray-dry the aqueous SLM dispersions indicated numerous difficulties in obtaining SLM in the form of a dry powder with the desired properties. Due to the lack of literature reports (which concern mainly aqueous or organic solutions of active substances and polymers, and not lipid suspensions), the process was carried out under various conditions of inlet temperature, flow rate or concentration of the dried dispersion

(2.5%, 5%, 10%). The problem turned out to be not only to obtain a fine, dry powder (that can also be redispersed in water), but also the melting of the solid lipid during drying or to poorly yield of the process. Polymers (polyvinylpyrrolidone – PVP, hydroxypropylmethylcellulose and maltodextrins) were used as auxiliary substances, not only facilitating the drying process but also redispersion. The polymers in the composition of the dried mixture are also used for coating or obtaining a prolonged action. Polymers are known, that can act as an agent avoiding particle aggregation, stabilizing agent and filler [4, 31]. Among the tested polymers, the best properties were shown by PVP, which was selected for further tests as an auxiliary substance facilitating drying and subsequent redispersion.

A number of the observed problems related to the drying of the SLM dispersion indicated the need for a precise selection of the process conditions, and thus the need for its optimization. For this purpose, *placebo* SLM dispersions with Compritol or stearic acid were prepared according to the composition in Table 1. The PVP solution was added to the SLM suspensions in a 1:1 ratio prior to spray drying. Then aqueous dispersions were dried according to the process conditions shown in Table 2. Inlet temperature was investigated from 75 to 120°C and feed rate from 1.2 to 6.0 ml/min, with specific narrowing for SLM with stearic acid. At the same time, influence of outlet temperature on the powder particles features was investigated. The outlet temperature depends on inlet temperature and flow rate simultaneously, and is a factor that could be used to control the course of the entire process. The initial selection of drying process parameters and their experimental range presented in Table 2 were based on the formulation properties (lipids melting point), our previous experience and observations carried out during preliminary studies. Based on the results of preliminary experiments the primary dispersions contain 5% (w/w) and that value was maintained constant in the current studies, because the drying process also depends on the SLM concentration.

In dry SLM powders, the particle size distribution was examined, and the moisture content, yield and flowability were determined. Characterization of SLM powders was conducted at room conditions. The type of analyzed physicochemical properties of the tested powders was selected on the basis of their potential impact on the application properties, long term stability and process properties, if they were to undergo further technological processes.

3.2. Spray drying of aqueous dispersions of Compritol-SLM

For all obtained 13 batches of *placebo* SLM dispersions with Compritol (F1 in Table 1) the process was feasible in the assumed parameters ranges of the apparatus (Table 2), except for drying at 120°C and feed rate of 6 ml/min, when a too high feed rate disturbed obtaining any dry product. The collected SLM powders were weighed, in order to determine the process yield (according to Eq. 1) and they were subjected to further tests. The results were presented in the form of 3D surface charts showing the relationships between measured values and process parameters (Fig. 1). Evaluated formulation properties and instrument (spray dryer) related parameters were dependent and independent variables, respectively.

The obtained SLM powders were characterized by flowability and yield, which allowed for further analysis. The mean d_{50} value in all powders (except the formulation dried at 110°C and the feed rate of 1.2 ml/min) was 14.8 ± 5.1 µm and the percentage of particles <50 µm exceeded 90.2 ± 7.9%. It can be considered that this technique is perfectly suitable for obtaining SLM powder with desirable properties, i.e. small particle size with low span (2.9 ± 22%). An example of the particle size distribution in primary dispersion and in the powder obtained as a result of spray drying (measurement carried out wet and dry, respectively) is presented in Fig. 2. The difference in the measured particle sizes is due to the addition of PVP to the SLM dispersion, which promotes particle sticking during drying (reversible process). Since the measurement was carried out using the dry method (section 2.4.), PVP did not dissolve (as during redispersion in water), thus preventing the measurement of the size of individual liposphères. In addition, the dry particles tend to agglomerate due to the sticky properties of the lipids and their tendency to adhesion. This does not mean, however, that the primary particle size increases as a result of melting during drying. The preservation of the initial size and shape of the lipid microspheres is confirmed by microscopic observations. Not only the images from the optical microscope, but above all from the high-resolution scanning electron microscope, confirm the unchanged form of the lipid microparticles after the spray drying process (sample microscopic images are presented in Fig. 2). According to the device (Beckman-Coulter LS 13 320) manufacturer's data, the system disperses coherent dry powders without grinding delicate materials. However, as it results from the comparison of the particle sizes measured in the dispersion and after the spray-drying process with the microscopic images and the morphology of the microspheres, the automatic scattering method is insufficient. This is despite the fact that the dry measurement takes place without any disturbances, for a minimum 10 second at controlled obscuration and without operator intervention. On the basis of agglomerates observed on microscopic images of SLM powders (Fig. 2b), in which single particles with preserved morphology were visible, without lumps,

without particles fused together or other fragments indicating the melting of the lipid matrix (Fig. 2B), agglomerates were found as the reason for shifting the particle size distribution towards the higher values observed in dry powders. It was found that the obtained results of particle size measurements by dry laser diffraction are similarly affected by agglomerates formed in powders in all formulations, therefore this method can be used to compare their properties. Due to the size of the measured particles, it is still the most accurate method that can be used.

The lowest variability depending on the inlet temperature and the feed rate was presented by span and the percentage of particles <50 μm (Fig. 1 A, B). Obtaining the SLM powders with similar properties in such a wide range of drying conditions means that, taking into account only these two variables, it is possible to dry the aqueous SLM dispersions in almost the entire tested range of parameters, without significantly affecting the properties crucial from the point of view of the dosage form. However, due to the economy of the process, the use of spray drying method should be justified not only by the optimal properties of the products, but also by the efficiency of the process. Determination of percentage yield is very important in the selection of the best parameters of spray drying. In the spray drying process yield of >45% is considered as acceptable [31]. The low yield in spray drying is mainly due to the small (laboratory) scale of the process. On a large scale, the yield will be greater. Losses during spray drying are usually caused by drying conditions leading to the deposition of droplet or already dried material on the walls of the drying column and cyclone or discharge of fines with the exhaust gas [32]. The yield of the process can be increased with increasing temperature. Unfortunately, too high temperature is not conducive to drying the lipid particle dispersion, which in our case also makes it difficult to achieve optimal yield. In our studies the process yield was a feature that presented the greatest variability depending on the inlet temperature and the feed rate (Fig. 1C). Thus, it is a factor that significantly differentiates formulations depending on the set drying parameters. At the same time, attention should be paid to the fact that the batch size has a large impact on the final yield of the process. The larger the batches, the easier it is to obtain higher process efficiency. The described experiments were carried out on a relatively small batches of 200 g or 300 g (drug-loaded and *placebo* formulations, respectively). However, the main goal was to check the influence of the tested parameters on changes in the drying process yield, and not the absolute amount of recovery, which would have been higher if the process had been conducted on a larger scale.

Another common technique that allows drying is the freeze-drying process. In contrast to freeze drying (which the form of the resulting product is "lyophilized cake") applied to lipid microspheres/nanospheres, spray drying gives the possibility to obtain an already finished, free flowing product, which is required for some applications (e.g. for capsules, sachets, inhalation etc.). In line with our experience, it is easier to disperse spray-dried SLM-powder than freeze-dried SLM-powder, due to the stress associated with freezing and subsequent dehydration of the SLM formulation. The freeze-drying process is also much more expensive and time-consuming, as already mentioned in the introduction, therefore spray drying is often chosen as a faster and more productive process, despite the lower yield [33].The outlet temperature is a parameter which value depends primarily on the inlet temperature and feed rate [27]. Figure 1D shows how the changes of outlet temperature depended indeed on both the inlet temperature and the feed rate in our experiment. Therefore, the use of outlet temperature as a parameter not only for spray drying control, but also as a criterion for optimizing the entire process was considered. An increase in the inlet temperature from 90°C to 100°C resulted in an increase in the outlet temperature of about 4°C, regardless of the feed rate (Fig. 3A), while in the range of inlet temperature from 100°C to 110°C, there were almost no changes in outlet temperature (average change by about 1°C). That proves the outlet temperature stability in this range (Fig. 3B). The greatest increases in outlet temperature (even by about 8°C) were observed when increasing the inlet temperature above 110°C (Fig. 3 A, B). Taking into account the above relations inlet, not outlet temperature was finally considered more appropriate to assess the impact of process parameters on powder properties.

From a technological point of view, properties such as powder flow may be of a great importance, especially if the powder is intended to be used as a final form, because in this case, one of the required steps will be to dispense the powder. The dosing process strongly depends on the flowability properties of the final SLM powders. Therefore, to assess the flow properties of obtained dry powders standard pharmacopoeial methods were applied. The results of tests (angle of repose and HR) are presented in Table 3, and their variability, depending on the inlet temperature and feed rate, is also presented in Fig. 1G, H.

The flowability expressed as flow rate through an orifice could not be determined, because the obtained SLM formulations were low-flowable powders. Although no macroscopic agglomerates were formed, the adhesive strength between the powder particles was significant. The association of the difficulty of measuring with the surface properties of the powder particles rather than the formation of agglomerates is also confirmed by the fact

that it was possible to disperse the powder particles during the particle size measurement (dry measurement technique). Since it was difficult to obtain free flow of the test dry powder through the funnel (10 or 15 mm opening), mechanical shaking was required to obtain the angle of repose cone. Consequently, the obtained cone was irregular, and therefore relatively large variations were noted with some formulations. According to the pharmacopoeial classification, the tested SLM powders could be classified into various groups: from excellent flowing to poor flowing (Table 3), while better properties (lower angle of repose) showed powders dried at lower inlet temperatures (the influence of the flow rate was inconclusive). Hausner ratio, calculated from the bulk and tapped volumes, allowed to classify powders into two categories: as fairly well or passable flowing powders (Table 3), (results slightly different from the results of the angle of repose). Although the angle of repose test showed very good properties of some SLM powders, HR did not fully confirm these results. In our opinion, due to the difficulties described above with measuring the angle of repose and thus the significant differences between the formulations (Table 3), the HR results should be considered as more reliable and representative. Although the HR results indicate slightly worse flow properties of SLM powders (generally fine powders of lipids might present inferior flowability), they still should be considered satisfactory. The European Pharmacopoeia (2.9.36. Powder flow) directly indicates that formulations with an angle of repose in the range of 40-50 degrees are manufactured satisfactorily, and only when an angle of repose exceed 50 degrees, the flow is rarely acceptable for manufacturing purpose (the mean angle of repose of the SLM powders with Compritol is 38.3 ± 8.5 degrees, neither formulation has an angle of repose greater than 50 degrees). In the case of the production process, the proper flowability of the tested formulations should be ensured by the addition of lubricating substances.

A positive effect on powder flowability might also have lower amount of water, as it can eliminate particle cohesive, tendency to form agglomerates and electrostatic charges. Most studies observe a decrease in powder flow with increasing moisture [34]. Although there is no a specific pharmacopoeial requirements or limits for residual moisture, its level should be determined also taking into account the individual properties of API and other components in dosage form. Moisture content determined in our finally obtained powders was significantly influenced by the feed rate (Fig. 1E). In the SLM powders dried at the higher feed rate (4.5 ml/min), the moisture content exceeded 5% over the entire range of inlet temperatures used (90-120°C). Lower moisture level (about 2.5-3.5%) was observed in powders dried at lower feed rate (1.2-2.4 ml/min). There was no clear correlation between

moisture content in the powder and its angle of repose, or moisture and HR. Nevertheless, the low water content was considered to be a desirable feature of the resulting powders.

Table 3

Properties of tested *placebo*-SLM (F1, F2) and API-loaded SLM dry powders depending on the conditions of spray drying, classification based on pharmacopoeial criteria (chapter 2.9.36. Powder flow, European Pharmacopoeia)

Conditions of the drying process		Values of tested parameters			
Inlet temperature [°C]	**Feed rate [ml/min]**	Angle of repose [°] ± SD	Flow property	Hausner ratio	Flow character
SLM *placebo* with Compritol					
90	**1.2**	45.8 ± 4.1	Passable	1.24	Fair
90	**2.4**	26.5 ± 1.6	Excellent	1.33	Passable
90	**4.5**	30.7 ± 1.7	Excellent	1.23	Fair
100	**1.2**	31.7 ± 0.6	Good	1.29	Passable
100	**2.4**	37.9 ± 1.1	Fair	1.19	Fair
100	**4.5**	46.2 ± 2.9	Poor	1.22	Fair
110	**1.2**	27.4 ± 0.3	Excellent	1.32	Passable
110	**2.4**	43.2 ± 1.0	Passable	1.26	Passable
110	**4.5**	47.3 ± 3.2	Poor	1.28	Passable
110	**6.0**	n.t.	n.t.	n.t.	n.t.
120	**1.2**	n.t.	n.t.	n.t.	n.t.
120	**4.5**	46.6 ± 1.2	Poor	1.24	Fair
SLM *placebo* with stearic acid					
75	**3**	34.6 ± 1.2	Good	1.23	Fair
80	**2.4**	35.2 ± 0.7	Good	1.21	Fair
80	**3**	38.0 ± 0.9	Fair	1.17	Good
API-loaded SLM with Compritol spray-dried under **inlet temp. 90°C** and **feed rate 2.4 ml/min**					
Formulation F3		29.9 ± 0.3	Excellent	1.32	Passable
Formulation F4		37.6 ± 1.2	Fair	1.30	Passable
Formulation F7		34.0 ± 1.1	Good	1.33	Passable
Formulation F8		31.5 ± 1.0	Good	1.32	Passable

n.t. – not tested

When considering the optimal powder properties, obtained formulations should be characterized by the largest percentage of particles with a size below 50 μm, the smallest span, with the best flow properties, low moisture content and with maximum yield at the same time (Fig. 1). The above criteria are best met by SLMs dried in conditions of both low inlet temperatures and low feed rates. In the tested range of parameter values, taking into account

the properties of the final powders, the optimal parameters for spray drying of the aqueous dispersion of SLM with Compritol were: 90°C inlet temperature and feed rate 2.4 ml/min (which corresponds to outlet temperature about 43°C). SLM powders dried under such conditions characterized by the following properties: excellent angle of repose (26.5°), passable value of HR (1.33), low moisture content – 3%, satisfactory yield – 59%, span – 2.5 and the percentage of particles <50 μm – 95%.

3.3. Spray drying of aqueous dispersions of stearic acid-SLM

Similar to the formulations with Compritol, SLM dispersions with stearic acid were spray dried in the range of process parameters indicated in Table 2. Although the melting point of stearic acid is similar to Compritol (69,6°C for stearic acid and 69-74°C for glyceryl behenate), more difficulties were observed when spray drying microspheres with stearic acid than with Compritol. Even slight and short-term destabilization of parameters during drying step resulted in melting of lipid particles, sticking to the elements of the dryer (mainly cyclon) and failure of the whole process. When drying SLM dispersions with stearic acid using different conditions, two batches process at the highest temperature (90°C and 100°C) and with the lowest feed rate were completely unsuccessful (no yield). All other dried formulations were weighed to determine yield and then, they were further tested as already described for Compritol powders. The collected data and test results were compiled in the form of 3D surface charts (Fig. 4) showing the relationships between powder properties and drying process parameters.

In diagrams (Fig. 4A and B), showing the relationship between span or particle size and drying parameters, for powders with stearic acid, greater variation was observed than in SLM with Compritol, and thus the area of obtaining favorable properties is narrowed down, mainly to the range of lower temperatures, with less influence of the feed rate. Similar to formulations with Compritol, in spray dried SLM powders with stearic acid the greatest variability depending on the inlet temperature and the feed rate was presented by the process yield (Fig. 4C). As indicated by Fig. 4E the residual moisture in powders with stearic acid was not as varied and dependent on the feed rate as in the case of SLM with Compritol, and its highest range was coincided, oddly enough, with the highest drying temperatures. The chart of outlet temperature dependence on inlet temperature and feed rate has a similar shape, regardless of the lipid forming the matrix of the microspheres (Fig. 1D *vs.* Fig. 4D).

The flowability of SLM with stearic acid were determined only for selected powders with the best properties, spray dried at 75-80°C inlet temperature with the feed rate 2.4 or 3 ml/min. The results of both: the angle of repose and the Hausner ratio classified the tested formulations between good and fairly good flowability (Table 3).

When considering the best powder properties, obtained dry powders with stearic acid should meet the same requirements as for SLM with Compritol. This was possible, as in SLM with Compritol, when the dispersions were dried under conditions of both low inlet temperatures and low feed rates (among the values tested for stearic acid).

In conclusion, the optimal spray drying parameters for SLM aqueous dispersion with stearic acid were: 80°C inlet temperature with feed rate 3.0 ml/min (which corresponds to outlet temperature about 36°C). SLM powders dried under such conditions characterized by the following properties: fair angle of repose (38°), good value of HR (1.17), low moisture content – 3.5%, yield – 48%, span – 2.5 and the percentage of particles <50 μm – 98%.

3.4. Optimizing the spray drying process of SLM dispersions

All the obtained results from tested *placebo* SLM formulations with different lipids were collected in the form of three-dimensional surface charts and were also subjected to statistical analysis. The conducted experiments allowed to indicate the critical factors and the best process conditions. In accordance with the adopted assumptions obtained dry SLM powder should fulfill the following requirements: good flowability, percentage share of particles <50 μm (at least 90%), span (as small as possible), acceptable yield (at least 50%), and moisture content (not more than 3%).

Appropriate ranges of process parameters, allowing to obtain a product with the indicated characteristics, can be confirmed by visual inspection of 3D charts. The analysis of the charts of preparations with Compritol (Fig. 1) and stearic acid (Fig. 4) also allows to verify the potential effects of changing the tested independent variables (process parameters) on the properties of the formulation.

Although the technology of the spray-drying process eliminates significant exposure of the spray-dried dispersion to elevated temperature, only a process that does not melt the lipid from the matrix of microspheres can be considered correctly carried out. It depends on the proper adjustment of the process input parameters (inlet temperature, feed rate).

Performed experiments showed that only selected combinations of tested parameters (inlet temperature and feed rate) resulted in obtaining final product with desired properties. In

Table 4, the various configurations of the monitored process parameters were color-coded. In the case of SLM with Compritol, the indicated range of parameters (yellow) is even quite wide (in the case of SLM with stearic acid, it is much more limited).

Table 4

Categorization of the conditions of the spray drying process depending on the properties of the obtained powder and the course of the process with the simultaneous differentiation of the lipid forming the SLM matrix.

SLM *placebo* formulations with Compritol (F1)													
Inlet temp. [°C]	n.t.		**90**	**90**	**90**	**100**	**100**	**100**	**110**	**110**	**110**	**110**	**120**	**120**
Feed rate [ml/min]			**1.2**	**2.4**	**4.5**	**1.2**	**2.4**	**4.5**	**1.2**	**2.4**	**4.5**	**6.0**	**1.2**	**4.5**
Outlet temp. [°C]			*48*	*43*	*36*	*52*	*46*	*41*	*54*	*46*	*42*	*32*	*62*	*49*
SLM *placebo* formulations with stearic acid (F2)														
Inlet temp. [°C]	**75**	**80**	**80**	**80**		**90**	**90**		**100**	**100**	n.t.			
Feed rate [ml/min]	**3.0**	**2.4**	**3.0**	**4.5**	n.t.	**2.4**	**3.0**	n.t.	**2.4**	**4.5**				
Outlet temp. [°C]	*33*	*40*	*36*	*32*		*44*	*40*		*50*	*42*				

n.t. – not tested, green color – optimal drying conditions, yellow color – acceptable drying conditions, red color – unfavorable drying conditions

During the drying of SLM with stearic acid in conditions other than those marked in green, there were fluctuations in the outlet temperature affecting the process (an increase in the outlet temperature sometimes caused a further increase in this temperature, and consequently destabilization of the entire process). The smooth course of the drying process was disturbed mainly by the deposition of a part of the dried powder in the cyclone (red in Table 4). This phenomenon could be due to partial lipid melting during drying, as this occurred mainly at higher inlet temperatures with lower feed rates (Table 4). SLMs with stearic acid were particularly susceptible to this phenomenon. Consequently, less product ended up in the dry particles collector, resulting in reduced process efficiency. In extreme situations, the drying gas flow was even obstructed and the cyclone was clogged. Moreover, in some experiments, in the final product collector single lipid lumps were observed.

Analyzing surface charts, it was noticed that to prevent an adverse increase in outlet temperature, it is advisable that when raising the drying temperature (inlet temperature) feed rate should be also increased. During optimization of the conditions of the spray drying process of SLM with stearic acid it turned out, that despite the inlet temperature reduction

(from 90°C to 80°C), the feed rate also need to be increased (from 2.4 to 3.0 ml/min). In addition, to reduce the risk of outlet temperature increasing during drying when the feed rate is lower, conditions with higher feed rate were marked as more favorable (green color in Table 4), although the use of both parameters combinations is possible.

Comparing the behavior of SLM depending on the lipid forming the matrix of microspheres, stearic acid formulations proved to be more demanding during processing. Paradoxically, despite a similar melting point, a greater sensitivity of SLM with stearic acid than with Compritol was observed to the already described partial melting and cyclone clogging. Moreover, despite the use of a lower inlet temperature, a sufficiently high feed rate was important (Table 4). Ultimately, the parameters that allowed to obtain powders with the best properties require drying SLM with stearic acid under slightly milder conditions (lower inlet temperature and at the same time higher feed rate) compared to SML containing Compritol.

In summary, the choice of drying conditions for SLM with stearic acid is much less flexible compared to SLM with Compritol. Thus, the type of lipid used in SLM is crucial for the properties of SLM powder and can significantly affect the drying process itself.

3.5. Spray drying of drug-loaded SLM dispersions

To assess the influence of the active substances incorporation in the carrier on the drying process and the properties of the powder obtained, SLM formulations with model drug substances (CsA and SPIR, Table 1) were spray dried using the process conditions optimized for *placebo* SLM. This publication focuses solely on the possibility of API-loaded SLM spray drying using conditions that have been established and optimized using a *placebo* formulation. Therefore, dry SLM powders with API were characterized only in the same way as *placebo* formulations (particle size, yield, flowability, etc.). Important biopharmaceutical aspects, such as the influence of the spray-drying process on the release rate of the active substance or the distribution of API within the lipid microspheres, including drug substance expulsion from the lipid matrix, assessed by various instrumental techniques, are described in a separate paper [30].

API loaded dispersions with Compritol as a lipid matrix (F3-F4 with 0.1 and 1.0% of CsA, respectively as well as F7-F8 with 0.1 and 0.5% of SPIR, respectively) were drying at inlet temperature 90°C with feed spray rate 2.4 ml/min, when dispersions with stearic acid as a lipid matrix (F5-F6 with 0.1 and 1.0% of CsA, respectively as well as F9-F10 with 0.1 and

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0.5% of SPIR, respectively) were drying at inlet temperature 80°C and feed rate 3.0 ml/min. All SLM formulations with API were successfully spray dried using conditions selected as the optimal in the *placebo* formulations studies. In each case, the process ran smoothly and did not require any modification, regardless of the type and concentration of API. Obtained SLM powders with API mostly met all the criteria for the obtained dry products, assumed during optimization of the drying process parameters for *placebo* formulations. In Table 5 the yields and moisture residuals values of dry powders with CsA or SPIR are summarized.

Table 5

Characteristics of spray dried SLM powders with API

Investigated powder properties	Formulations with Compritol			Formulations with stearic acid				
	F3	**F4**	**F7**	**F8**	**F5**	**F6**	**F9**	**F10**
Yield (%)	48.0%	64.0%	52.6%	53.0%	50.1%	50.5%	47.6%	37.2%
Moisture content (%)	3.4%	3.2%	3.4%	2.6%	3.2%	2.8%	3.3%	4.1%

The F10 powder was a formulation which properties deviated the most from the accepted values. All other formulations can be considered optimally spray dried. Other criteria (span and percentage of particles below 50 μm) were also met. In Fig. 5 the particle size distributions of spray dried powder of two selected formulations (F4 – SLM with CsA and Compritol, F5 – SLM with CsA and stearic acid) were presented. The mean d_{50} value in API-loaded powders was 13 μm and 11 μm, while the percentage of particles <50 μm exceeded 95% and 98% for F4 and F5 formulations, respectively.

Moreover, tested powders demonstrated good flowability properties, as evidenced by the satisfactory values of the angle of repose, as well as the HR values, similar to the *placebo* formulations (Table 3). When the dry powders were redispersed in water, no precipitation of the active substance was observed in the microscopic image. In the previous work, no significant changes in API distribution as a result of the spray drying process were found. A detailed description of the research on spray-dried aqueous SLM dispersions loaded with API can be found in a separate publication [30].

Summing up the results of drying SLM dispersions with API, it can be concluded that the introduction of the drug substance (each of the two chosen as a model drug) into the formulation, even at a fairly significant concentration (1% in the dispersion, which

corresponds to 10% relative to the amount of lipid) did not have a significant influence on the drying process.

The results evidence that process parameters developed for *placebo* SLM formulations can be effectively used when drying SLM with different API, also in different concentrations, if the composition contains the same matrix-forming lipid.

The properties of obtained SLM powders with CsA or SPIR allow for their further use and administration in dry form or after prior reconstitution to a liquid aqueous dispersion (when the dry powders were redispersed in water, no precipitation of the API was observed in the microscopic image.). From a practical point of view, it is of a great important, that it is possible, especially at least on a laboratory scale, to optimize the spray drying process of selected formulation with API using *placebo* formulation with the same lipid forming the microparticles matrix, thus saving often expensive and available in small quantities active substances.

4. Conclusions

SLM dispersions, both *placebo* and with API (e.g. CsA and SPIR in various concentrations), can be effectively converted from aqueous dispersion to dry powder by spray drying technique. The conducted studies allowed us to optimize spray drying process of aqueous SLM dispersions containing two different lipids (Compritol and stearic acid) as microspheres matrix. Performed experiments showed that only selected combinations of tested parameters (inlet temperature and feed rate) resulted in obtaining final product with desired properties.

The use of 3D surface charts, developed on the basis of the results of experiments carried out with different values of independent variables, allows to predict the values of dependent variables depending on the conditions of the process. Flexibility in the selection of drying conditions (inlet temperature and feed rate) depends primarily on the lipid forming the matrix of microspheres. The choice of drying conditions for SLM with stearic acid is much less flexible compared to SLM with Compritol. Thus the lipid forming the matrix of microspheres is the basic factor for which the appropriate drying parameters must be selected. The results of conducted experiments and further statistical analysis of the obtained results as the most favorable conditions for conducting the spray drying process of SLM dispersions with Compritol indicated the inlet temperature of 90°C and the feed spray rate 2.4 ml/min, while for SLM with stearic acid inlet temperature was 80°C with feed spray rate 3 ml/min.

Spray drying can be carried out completely without the use of organic solvents due to the fact that the aqueous dispersion of lipid microspheres is dried. In addition, it is possible to optimize the drying process on *placebo* formulations to conditions that will then be successfully used for drying SLM with API.

Declaration of interest

The author reports no conflict of interest.

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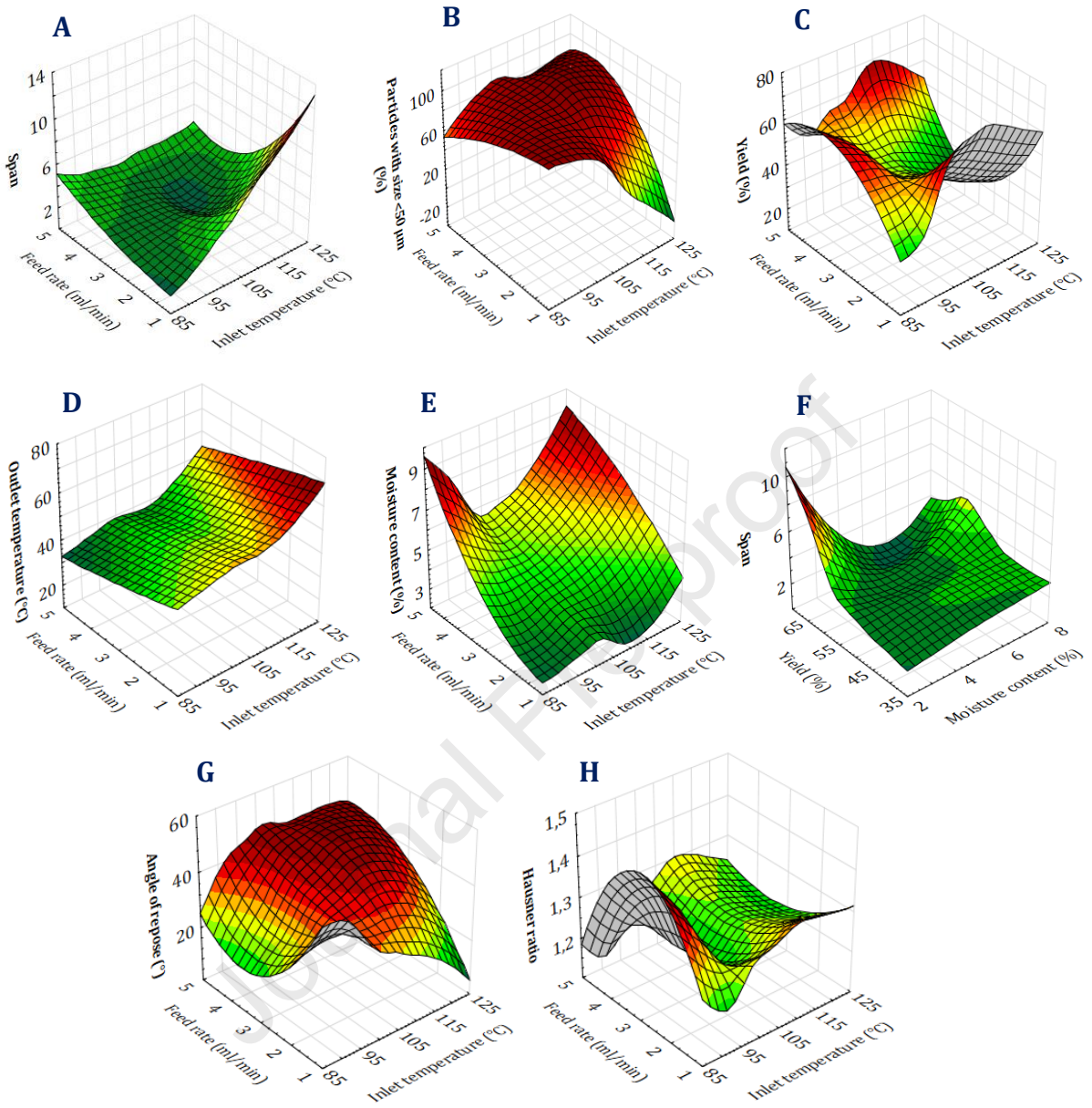

Figure 1. Surface plots 3D presenting the impact of investigated factors on the properties of spray dried SLM powders with Compritol. The dependence of (**A**) span, (**B**) particle size <50 µm, (**C**) yield, (**D**) outlet temperature, (**E**) moisture content, (**G**) angle of repose, (**H**) Hausner ratio on inlet temperature and feed rate; and dependence of (**F**) span on yield and moisture content is presented. Brown color corresponds to the highest values and dark green corresponds to the lowest values.

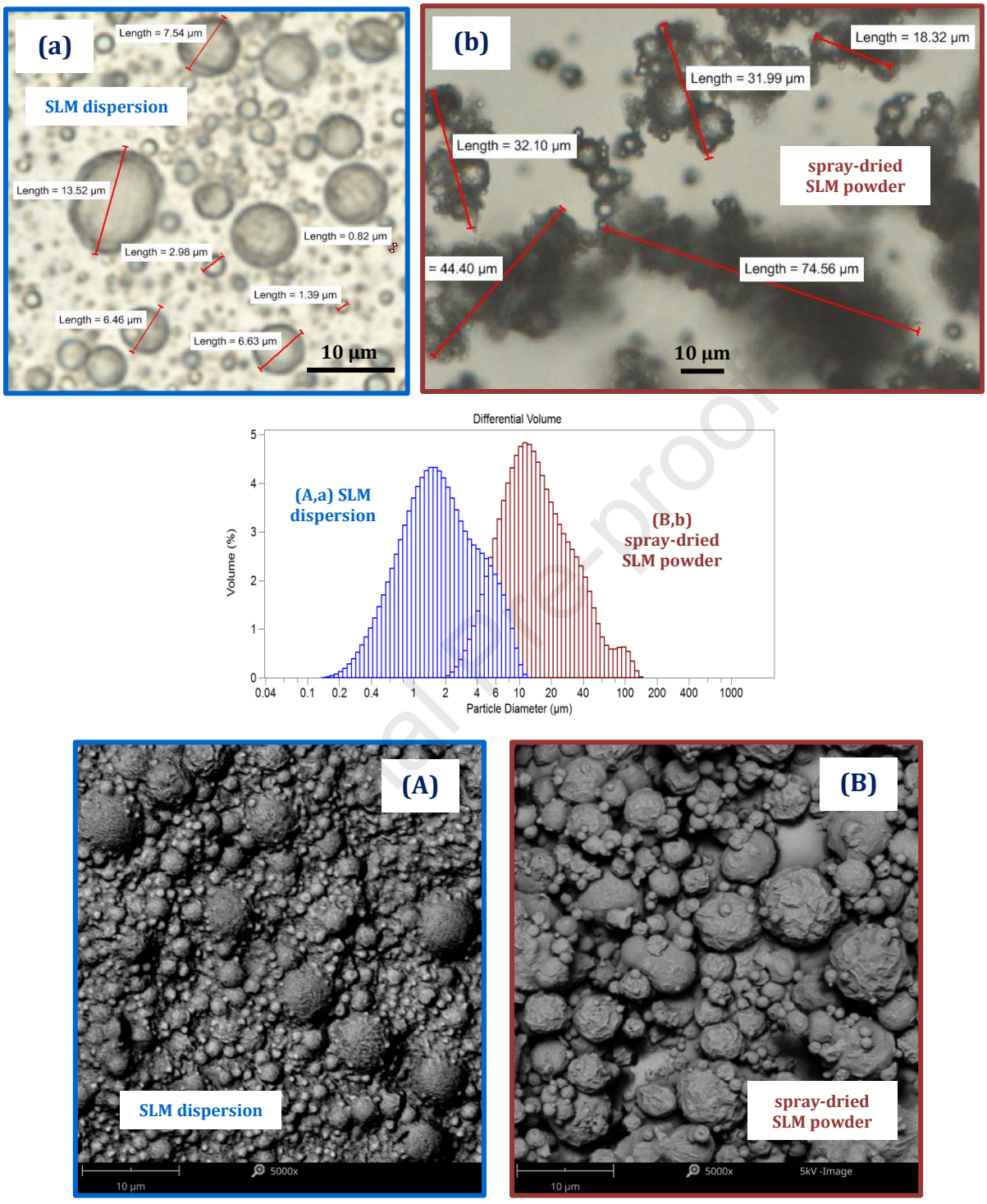

Figure 2. Particle size distribution profiles of selected *placebo* SLM with Compritol: before spray drying (aqueous dispersion) and after spray drying (SLM powder), as well as optical microscopic picture (**a, b**) and scanning electron micrographs (**A, B**) of SLM dispersion (**A, a**) and spray-dried SLM powder (**B, b**).

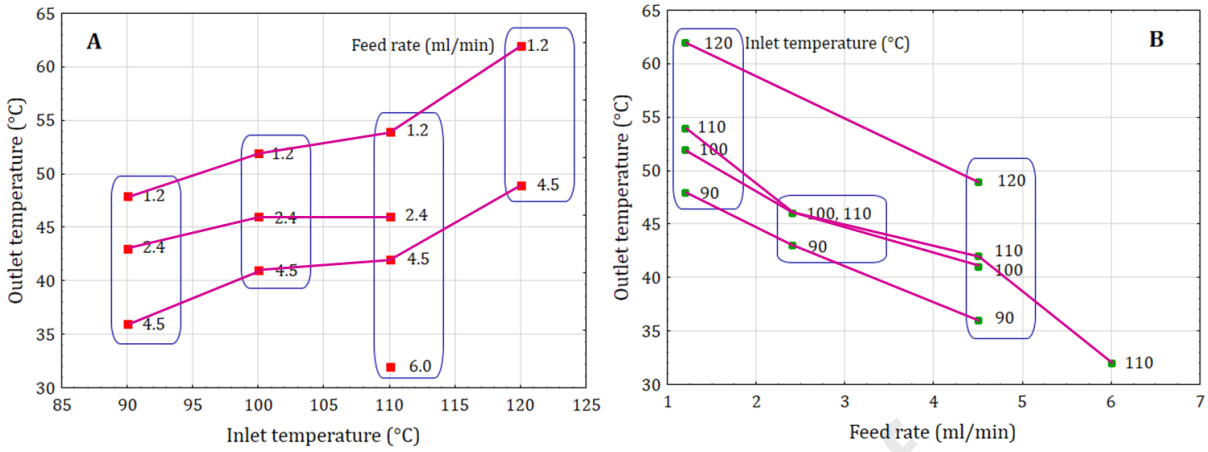

Figure 3. Graphs showing the relationship between (**A**) inlet temperature, (**B**) feed rate and outlet temperature.

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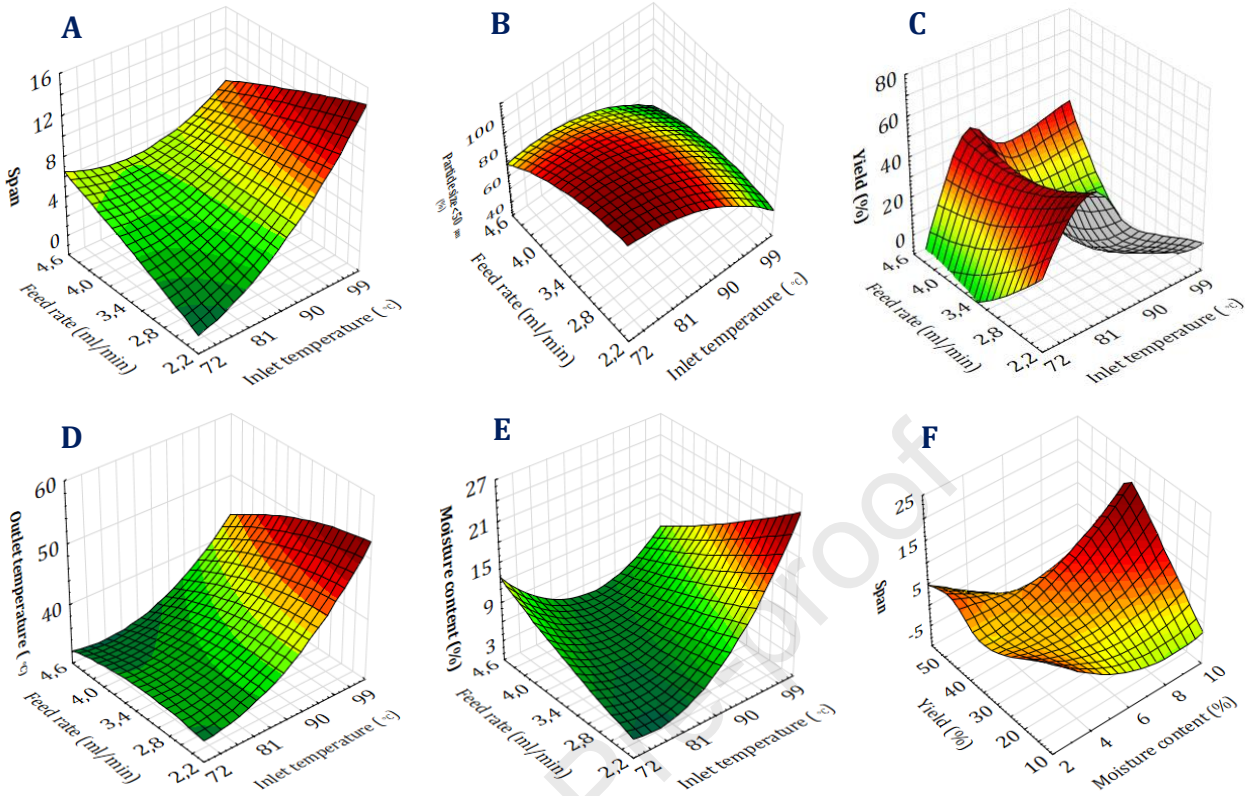

Figure 4. Surface plots 3D presenting the impact of investigated factors on the properties of spray dried SLM powders with stearic acid. The dependence of (**A**) span, (**B**) particle size <50 µm, (**C**) yield, (**D**) outlet temperature, (**E**) moisture content on inlet temperature and feed rate; and dependence of (**F**) span on yield and moisture content is presented. Brown color correspond to the highest values and dark green correspond to the lowest values.

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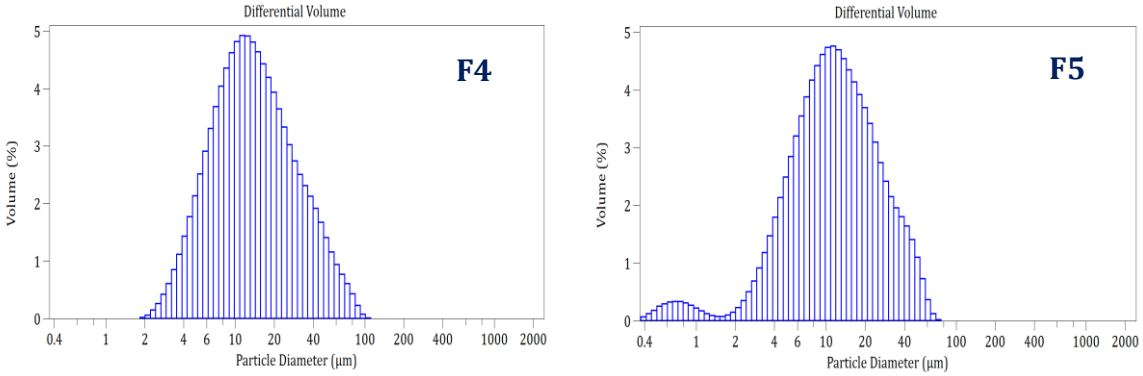

Figure 5. Particle size distribution profiles of selected CsA-loaded spray dried SLM powders.

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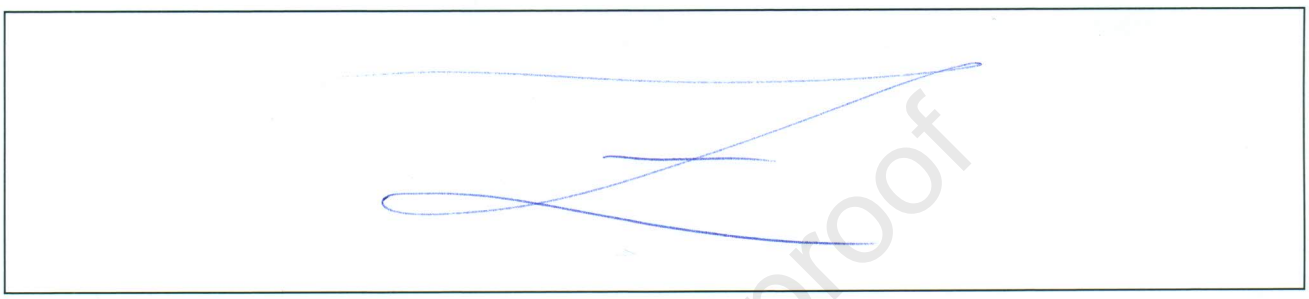
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following ~~financial interests/personal relationships~~ which may be considered as potential competing interests: ——



E. Wdowko

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