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Practical guidelines for predicting the proper conditions of high-energy mixing in a planetary ball mill towards powder flow improvement

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In this work Response Surface Methodology and Central Composite Rotatable Design were applied to find high-energy mixing process parameters enabling flow properties of highly cohesive Disulfiram powder to be improved. Experiments were conducted in a planetary ball mill. The response functions were created for an angle of repose and compressibility index as measures of powder flowability. To accomplish an optimisation procedure of mixing process parameters according to a desirability function approach, the results obtained earlier for potato starch, as another cohesive coarse powder, were also employed. Coupling these results with those achieved in a previous work, it was possible to develop some guidelines of practical importance allowing mixing conditions to be predicted towards flow improvement of fine and coarse powders.

Keywords: dry coating, powder flowability, high-energy mixing, planetary ball mill, response surface methodology

1. INTRODUCTION

Ability to flow is an important property of a powder bed, which has a significant impact on handling, storage and processing. Powders with a particle size below 100 μm are cohesive and they exhibit poor flowability due mostly to van der Waals and electrostatic forces and/or liquid bridges between particles (Wibowo and Ng, 2001). Moreover, there are a lot of difficulties with an effective flowability improvement. While admixing is the most popular method of improving powder flow properties, there is a problem with the homogeneity of mixtures, which is essential especially in the pharmaceutical industry. These difficulties induced researchers towards looking for new solutions. They proved that high-energy mixing is a more effective method of flowability improvement than admixing. During this process, the mechanical energy provided to the powder bed allows to break up the agglomerates of powder and admixture and to obtain a uniform powder bed. The final result of a high-energy mixing is a dry coating phenomenon. Particles of a modified powder (host particles) are coated by nano- or microparticles of admixture (guest particles) (Qu et al., 2015; Zhou et al., 2010; Zhou et al., 2011). High-energy mixing can be successfully conducted in many high-energy mixers widely described in the literature, but they are only laboratory devices (Pfeffer et al., 2001).

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Recently, a planetary ball mill was investigated towards a powder property improvement (e.g. dissolution improvement) via dry coating of powders (Sonoda et al., 2008). It has also turned out that mixing in a planetary ball mill is an effective method of a cohesive powder flowability improvement (Leś et al., 2015; Leś et al., 2017; Leś and Opaliński, 2021). The possibility of performing experiments in an industrial scale, even in a continuous mode, is the main advantage of this type of a high-energy mixer. For example, Fokina et al. (2004) demonstrated that milling and recycling of hard alloys based on tungsten carbide is much more effective in a planetary ball mill than in a conventional ball mill.

High-energy mixing in a planetary ball mill is an effective process, but on the other hand, it is difficult to perform due to problems concerning proper process conditions selection and the amount of additives used. Poorly selected process parameters will result in undesired caking of a powder in a mixing chamber, deterioration of process efficiency due to sticking of powder particles to grinding media and walls of the chamber, non-uniform mixture, etc.

There are plenty of operating conditions effecting processes in a planetary ball mill, which make the analysis of the process truly difficult. The mixing effect depends on the pot geometry, revolution radius, rotational speed, ratio of velocity of the basis plate and the pot, ball-filling ratio, ball to powder weight ratio, ball diameter as well as friction conditions. Taking into consideration all the above mentioned parameters during an experiment is almost impossible and needs a computational simulation. The scale-up problems based on the correlation between the specific impact energy of balls and process parameters should be also solved using Discrete Element Method (Mio et al. 2004; Rosenkranz et al. 2011; Burmeister and Kwade 2013; Broseghini et al. 2016).

The aim of this work was to find the optimal parameters of a high-energy mixing in a planetary ball mill as needed for a flow improvement of coarse and highly cohesive powder materials. Disulfiram powder was chosen, as a typical material from this group. The results obtained in this study for coarse particles (Disulfiram and potato starch) were merged with the earlier gained results for finely ground cohesive powders (given in (Leś and Opaliński, 2021)). On the basis of this, some practical guidelines regarding conditions and parameters of mixing in a planetary ball mill towards better flow quality of cohesive powders were formulated.

2. MATERIALS AND METHODS

2.1. Materials

In a high-energy mixing process, Disulfiram (*Tetraethylthiuram disulfide*, kindly donated by Polpharma, Poland), also known as Anticol, Antabuse or Esperal, was investigated as an example of a host particle. This is a common drug used in an aversive therapy of alcohol addiction (Kragh, 2008; Sandberg et al., 2008). The most popular form of the drug is a tablet but due to powder cohesiveness there is a serious problem with powder flow during dosing into a die of a tablet press.

In the process optimisation, the results of high-energy mixing obtained earlier for other coarse and highly cohesive materials such as potato starch (Chempur, Poland) (Leś et al., 2017) were also used. Particle size distribution and Carr indices for both materials are given in Table 1.

Non-toxic and biocompatible hydrophilic fumed silica, Aerosil® 200 (Evonik, Germany), with an average particle size about 12 nm (Evonik Resource Efficiency Gmbh, 2018) was used as a modifier (guest particle) required to improve Disulfiram flowability via the dry coating method. Jing et al. (2015) proved that silica addition is also beneficial for increasing powder dissolution in water.

Performing a high-energy mixing in a planetary ball mill often requires the addition of a small amount of a process control agent (PCA) to the mixing chamber. It is recommended to avoid powder caking and

Table 1. Particle size distribution and physical properties of unmodified Disulfiram and potato starch powders

Material	d_{50} [μm]	d_{10} [μm]	d_{90} [μm]	Angle of repose [deg]	Aerated bulk density [kg/m^3]	Packed bulk density [kg/m^3]	Compressibility index [%]
Disulfiram	27.014	10.263	57.181	57	336	656	48.8
Potato starch	34.377	20.275	56.385	50	666	858	22.4

sticking to the mixing device. In this work, as an anticaking agent, isopropyl alcohol (Stanlab, Poland) was used.

2.2. Equipment

High-energy mixing of Disulfiram was performed in a Mono Pulverisette 6 planetary ball mill (Fritsch, Germany). Both the mixing chamber (500 cm^3 volume) and milling balls (5 mm diameter) were made of zirconium oxide. The ball to powder weight ratio was kept at a constant level of 8:1 and the amount of the powder mixture was 100 g.

Particle size distribution of Disulfiram and potato starch were determined using a Mastersizer 2000E (Malvern Panalytical, United Kingdom), a particle size analyser. Potato starch particles were dispersed in isopropyl alcohol and Disulfiram particles in water. Measurements were performed after 60 s of ultrasonication.

The images of the particle surface of both powders were obtained with a scanning electron microscope (SEM) after sputter coated with carbon in the Institute of High Pressure Physics of the Polish Academy of Science.

Powder flowability was evaluated based on a static angle of repose, defined as the steepest slope of a freely heaped material without collapsing (Al-Hashemi and Baghabra Al-Amoudi, 2018) and a compressibility index (CI) value, calculated according to Eq. (1) (Jallo et al., 2012):

$$\mathrm{CI} = \frac{\rho_t - \rho_a}{\rho_t} \cdot 100\% \tag{1}$$

where ρ_t is a tapped density measured after 180 taps and ρ_a is aerated bulk density. The reduction of the angle of repose and the compressibility index indicates better flowability. All above mentioned Carr indices were measured using Powder Characteristic Tester PT-S (Hosokawa Micron, Japan).

2.3. Design of experiments

High-energy mixing in a planetary ball mill, as a multi-parametric process, was performed based on Response Surface Methodology coupled with Central Composite Rotatable Design. Four main process variables: mixing speed (x_1), mixing time (x_2), amount of Aerosil (x_3) and isopropyl alcohol as PCA (x_4) with their actual value ranges were chosen based on the pre-experiments. The variables were investigated on five coded levels $\pm\alpha$, ± 1, 0 (as is shown in Table 2) to obtain second-order polynomial equations – response functions (Eq. (2)):

$$y = (b_0 + \varepsilon) + \sum_{i=1}^{k} b_i x_i + \sum_{1 \le i \le j}^{k} b_{ij} x_i x_j + \sum_{i=1}^{k} b_{ii} x_{ii}^2 \tag{2}$$

where: b_0 – constant term, ε – residual associated with the experiments, k – number of input variables, x – process variable.

Table 2. Levels of input variables

Variable	Symbol		$-\alpha$	-1	0	$+1$	$+\alpha$
	coded	actual					
Mixing speed, rpm	x_1	z_1	140	170	200	230	260
Mixing time, min	x_2	z_2	2	5	8	11	14
Amount of Aerosil, mass fraction, %	x_3	z_3	1.0	1.5	2.0	2.5	3.0
Amount of isopropyl alcohol, ml	x_4	z_4	0.2	0.3	0.4	0.5	0.6

In this type of design, for four process variables, star value (a distance from the centre of experiment) is $\alpha = 2$ (Aslan, 2008). The obtained response functions present simultaneous influence of all variables and their interaction on the flowability indices (angle of repose or compressibility index).

The experimental design matrix created for four process factors and the results of the experiment are presented in Table 3. The proper experiment design consisted of 32 tests (including 17 standard factorial tests, 8 tests in star points and 7 centre replications).

Table 3. Experimental design matrix and responses

Group of tests	Test number	Coded levels of variables				Output variables		Group of tests	Test number	Coded levels of variables				Output variables	
		Mixing speed	Mixing time	Amount of Aerosil	Amount of propan–2–ol	Angle of repose	Compressibility index			Mixing speed	Mixing time	Amount of Aerosil	Amount of propan–2–ol	Angle of repose	Compressibility index
		x_1	x_2	x_3	x_4	y_1 deg	y_2 %			x_1	x_2	x_3	x_4	y_1 deg	y_2 %
Factorial design	**1**	–1	–1	–1	–1	39.5	46.9	Axial points	**17**	–2	0	0	0	36.7	44.8
	2	–1	–1	–1	1	38.1	46.3		**18**	2	0	0	0	37.6	49.2
	3	–1	–1	1	–1	39.2	45.0		**19**	0	–2	0	0	40.5	44.0
	4	–1	–1	1	1	45.6	46.0		**20**	0	2	0	0	39.5	50.5
	5	–1	1	–1	–1	39.6	50.7		**21**	0	0	-2	0	36.2	52.3
	6	–1	1	–1	1	34.9	48.7		**22**	0	0	2	0	48.2	47.9
	7	–1	1	1	–1	43.9	48.0		**23**	0	0	0	–2	40.9	48.7
	8	–1	1	1	1	44.6	47.4		**24**	0	0	0	2	41.2	50.0
	9	1	–1	–1	–1	38.4	49.8	Centre points	**25**	0	0	0	0	41.5	50.5
	10	1	–1	–1	1	37.7	51.2		**26**	0	0	0	0	39.9	49.2
	11	1	–1	1	–1	42.3	47.6		**27**	0	0	0	0	39.8	50.5
	12	1	–1	1	1	45.6	48.1		**28**	0	0	0	0	40.1	49.2
	13	1	1	–1	–1	39.9	50.9		**29**	0	0	0	0	39.9	49.5
	14	1	1	–1	1	34.7	49.0		**30**	0	0	0	0	41.7	50.1
	15	1	1	1	–1	39.6	50.0		**31**	0	0	0	0	41.1	49.6
	16	1	1	1	1	40.5	48.8								

Response Surface Methodology procedure with all stages of optimisation was performed using Statistica 12 software package (StatSoft).

3. RESULTS AND DISCUSSION

3.1. Statistical analysis

The second-order polynomial equation with interactions (Eq. (2)) was fitted to the results of the experiment. Coefficients which were insignificant for model solutions (probability value, $p > 0.05$) were removed and the equations were calculated again. The final response functions for coded levels of mixing speed and time, amount of Aerosil and propan–2–ol created for the angle of repose and compressibility index of Disulfiram are respectively:

$$y_1 = 40.598 - 0.446x_2 + 2.604x_3 - 0.832x_1^2 + 0.430x_3^2 - 0.619x_1x_2 - 0.994x_2x_4 + 1.456x_3x_4 \quad (3)$$

$$y_2 = 49.758 + 1.050x_1 + 1.067x_2 - 0.892x_3 - 0.700x_1^2 - 0.637x_2^2 - 0.537x_1x_2 - 0.500x_2x_4 \quad (4)$$

and those calculated for the actual levels of input variables:

$$y_1 = 37.0 + 2.32z_2 - 10.3z_3 + 4.32\cdot10^{-5}z_1^2 + 2.03z_3^2 - 0.00334z_1z_2 - 4.50z_2z_4 + 18.4z_3z_4 \quad (5)$$

$$y_2 = -1.71 + 0.394z_1 + 2.75z_2 - 1.78z_3 - 7.78\cdot10^{-4}z_1^2 - 0.0708z_2^2 - 5.97\cdot10^{-3}z_1z_2 - 0.181z_2z_4 \quad (6)$$

The correctness of the created models and significant influence of all process variables on the angle of repose and the compressibility index were proved according to a lack of fit test ($p = 0.05$) and the Analysis of Variance (ANOVA).

The good agreement of the experimental and calculated values of both responses was confirmed based on the values of the coefficient of correlation (R^2), which is 0.88 for the angle of repose and 0.86 for the compressibility index (Fig. 1).

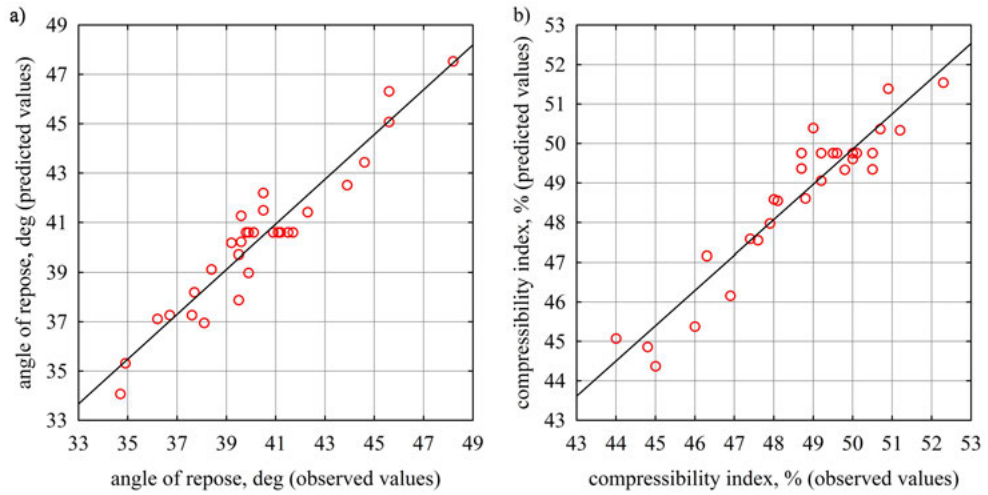

Fig. 1. Relation of experimental and predicted values of: a) angle of repose (according to Eq. (3)); b) compressibility index (according to Eq. (4))

The influence of mixing speed, time, amount of Aerosil and isopropyl alcohol on the examined Carr indices is presented in Fig. 2 and Fig. 3, while the parameters not shown on the plots are at the centre level. The analysis of the plots indicates local minima of the response functions.

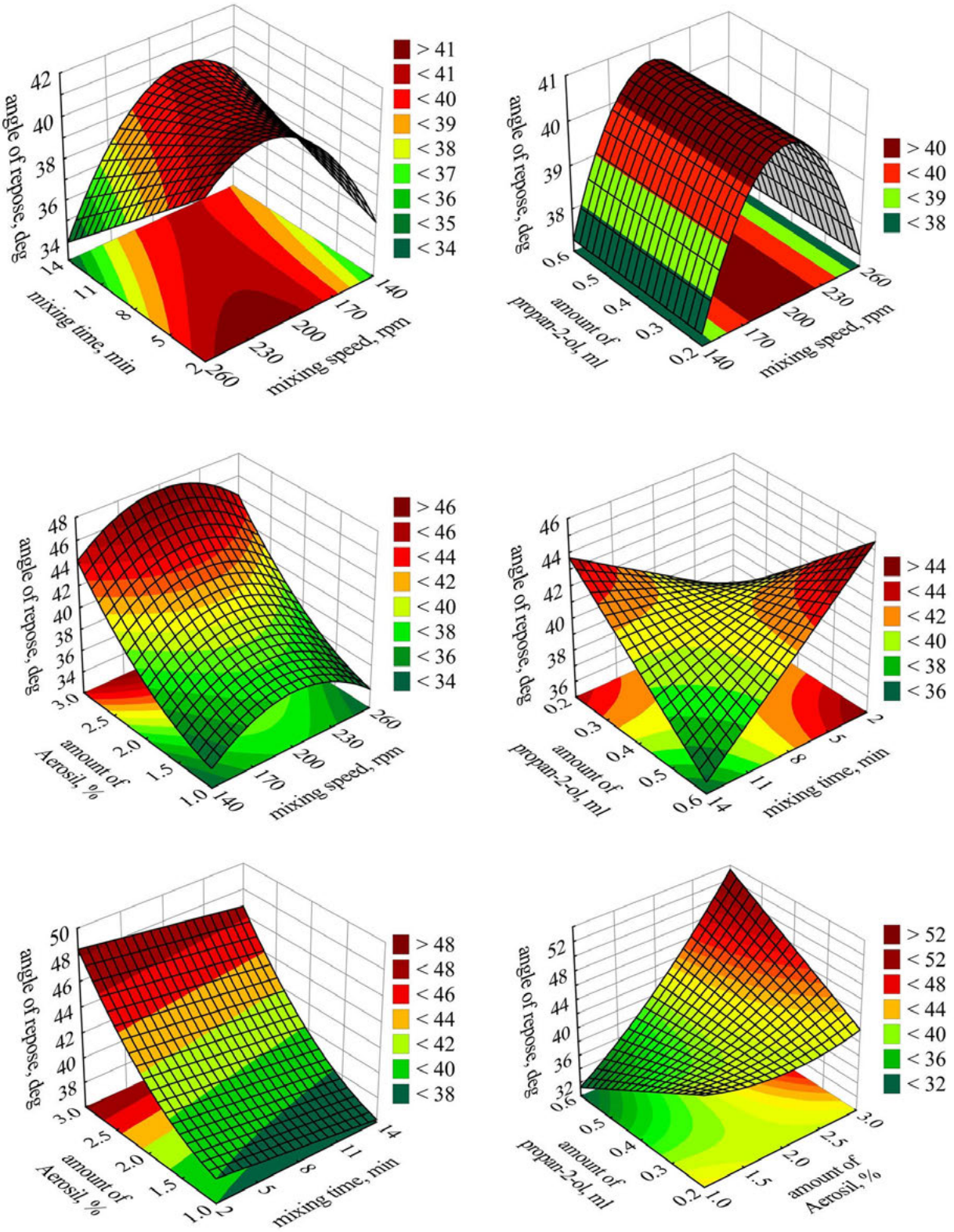

Fig. 2. The effect of process variables on angle of repose of Disulfiram (factors not shown on the plots are at the centre level)

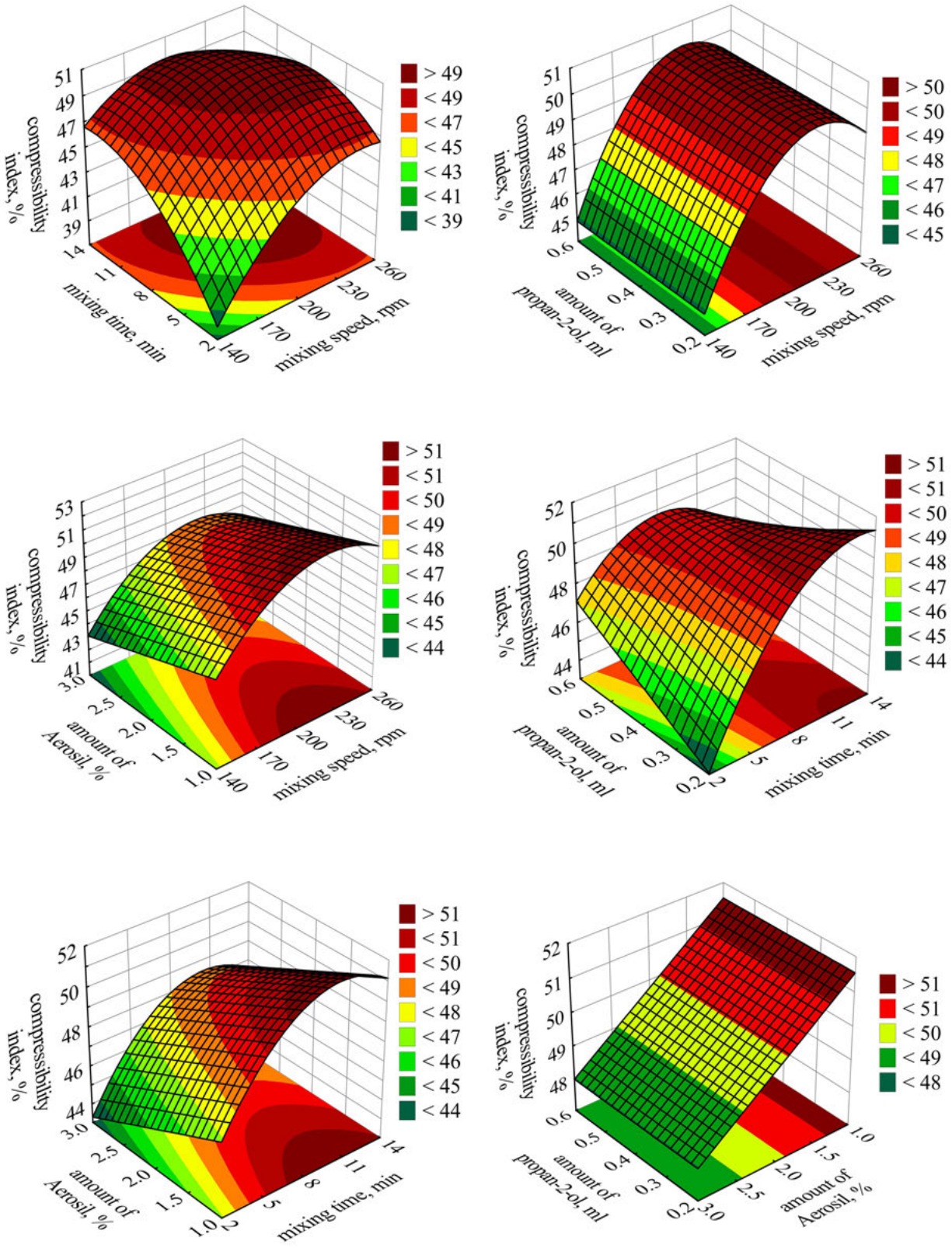

Fig. 3. The effect of process variables on compressibility index of Disulfiram (factors not shown on the plots are at the centre level)

3.2. Process optimisation

For a process optimisation, some earlier results for potato starch powder (Leś et al., 2017) were also used. On the basis of these results, the response functions for coded levels of variables (Eq. (7) for the angle of repose and Eq. (8) for the compressibility index) were created. In the case of potato starch powder, the addition of isopropyl alcohol was unnecessary because caking was not observed in the chamber after mixing in the experimental value ranges.

$$y_1 = 42.662 + 1.839x_1 + 2.318x_2 - 1.511x_1^2 - 0.344x_3^2 + 1.987x_1x_2 + 1.037x_1x_3 \tag{7}$$

$$y_2 = 45.441 + 1.793x_1 + 3.003x_2 - 0.458x_3 - 1.234x_1^2 - 2.772x_2^2 - 1.212x_1x_2 \tag{8}$$

The optimisation of high-energy mixing of coarse powders was accomplished based on the response functions created for both Disulfiram (Eqs. (3) and (4)) and potato starch (Eqs. (7) and (8)). To determine the optimal conditions of the process and the amount of the additives, a desirability function method coupled with an optimisation in grid nodes was applied (StatSoft, 2013). The models created for both powders were converted into an individual desirability functions and then into an overall desirability function with values ranging from 0 to 1. The values of the angle of repose and compressibility index measured for unmodified powders were recognized as the least desirable responses (desirability equal to 0). The most desirable responses (desirability equal to 1) were those obtained as a result of the subtraction assumed scope of changes, which was 25 deg for the angle of repose and 25% for the compressibility index of Disulfiram and respectively 20 deg and 20% for flow indices of potato starch. These values were matched to encompass the overall change of angle of repose and compressibility index obtained as a result of the experiment and to consider that a unit change of both indices has an equivalent impact on powder flowability. According to the desirability profiles (Figs. 4d and 5d), the overall desirability function was calculated as a geometric mean of individual desirability functions of each powder.

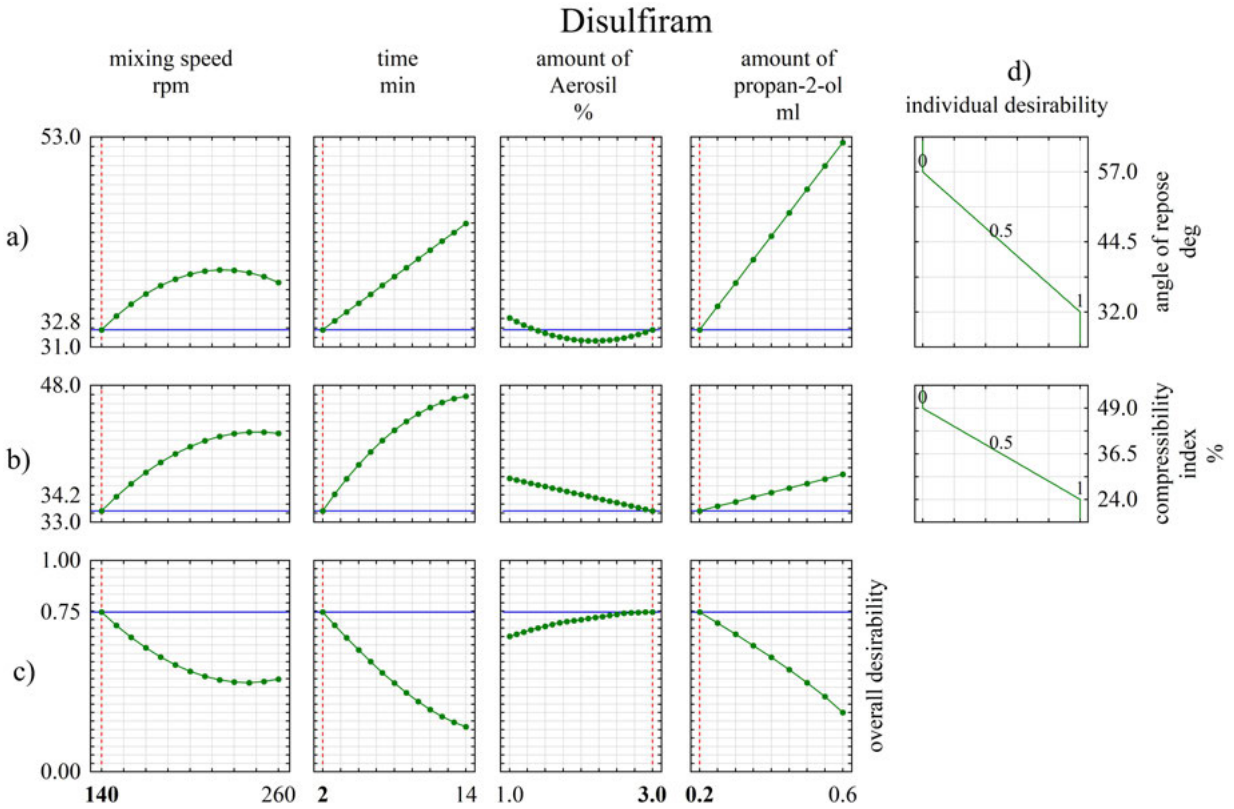

Fig. 4. Profiles of predicted values of: a) angle of repose; b) compressibility index; c) overall desirability function versus process variables and d) individual desirability profiles for Disulfiram

The optimisation of high-energy mixing in the planetary ball mill required dividing the overall value ranges into intervals to determine the grid nodes as shown in Table 4, where the step means a difference between values in the grid nodes. The values of process variables in the grid nodes were corresponding to the real test points to avoid the errors connected with optimum between the grid nodes. Optimal conditions of high-energy mixing and the amount of additives were determined between star values.

Table 4. Number of intervals of input variables in the grid nodes

		Material	
		Disulfiram	Potato starch
Input variable	Step	Number of intervals	
Mixing speed [rpm]	10	12	14
Mixing time [min]	1	12	20
Amount of Aerosil, mass fraction [%]	0.1	20	20
Amount of isopropyl alcohol [ml]	0.05	8	–

The optimisation results are presented in Table 5. Optimal values of the angle of repose and the compressibility index of Disulfiram and potato starch calculated according to Eqs. (3)–(4) and (7)–(8) were verified experimentally.

Table 5. Optimal conditions of high-energy mixing for Disulfiram and potato starch

Material	Mixing speed [rpm]	Mixing time [min]	Amount of Aerosil, mass fraction [%]	Amount of isopropyl alcohol [ml]	Angle of repose [deg]				Compressibility index [%]			
					calculated	experimental	absolute error	relative error [%]	calculated	experimental	absolute error	relative error [%]
Disulfiram	140	2	3.0	0.2	32.8	36.9	4.1	12.5	34.2	37.5	3.3	9.6
Potato starch	200	2	2.5	–	33.1	38.5	5.4	16.3	21.8	26.5	4.7	21.5

The experimental verification of the model confirmed a decrease of the flowability indices except for the compressibility index of potato starch, whose behaviour differs from typical cohesive powder. The low compressibility index measured for an unmodified material should indicate good flowability which was not observed and was in a contradiction with the angle of repose value.

The effect of process variables on the angle of repose, the compressibility index and the overall desirability function is shown in Figs. 4–5, while variables not shown on the plots are at the optimal level according to Table 5. The solid horizontal line in Figs. a)–b) defines the values of the flow indices corresponding to the highest overall desirability (determined in Fig. c)), i.e. the lowest values of the angle of repose and the compressibility index. The vertical dashed line defines the optimal conditions of high-energy mixing. The analysis of Figs. 4–5 led to the conclusion that the best flowability was observed for the lowest values of

mixing speed and time, the highest value of Aerosil addition (for both powders) and the smallest addition of isopropyl alcohol (for Disulfiram). As observed, only the amount of Aerosil can be changed in some value range, i.e. from 2.1 to 3.0% for Disulfiram and from 2.1 to 2.5% for potato starch to maintain the highest desirability. Apart from that, as observed during the pre-experiment, mixing speed and time should be as low as possible but sufficient to break up the agglomerates of Aerosil. For that reason the higher mixing speed and/or longer mixing time may be necessary.

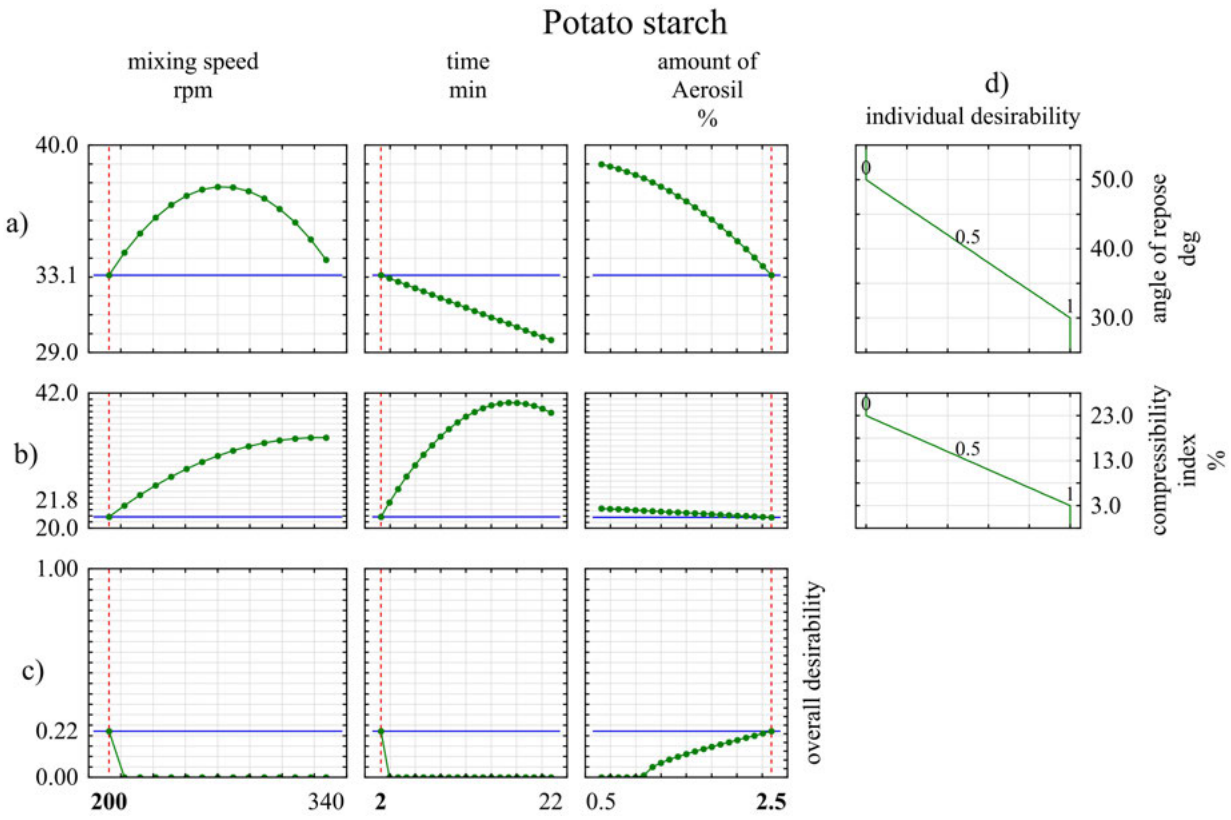

Fig. 5. Profiles of predicted values of: a) angle of repose; b) compressibility index; c) overall desirability function versus process variables and d) individual desirability profiles for potato starch

3.3. Surface morphology and particle size distribution

The surface morphology of powder particles was investigated using a scanning electron microscope. The visual analysis of SEM images of Disulfiram and potato starch particles before and after high-energy mixing in the planetary ball mill confirms the deposition of nano-silica particles on the surface of larger host particles as shown in Fig. 6. In the case of coarse powders the degree of surface covering is high and the deposition is regular in contrast to the fine powders (Leś and Opaliński, 2021).

The influence of high-energy mixing speed on the particle size of investigated powders is presented in Figs. 7–8. The increase of mixing speed results in a reduction of the particle size of potato starch and Disulfiram and it may cause an increase of the cohesiveness of the material. It should be assumed that elimination of the comminution, e.g. by using larger grinding balls or balls made of a material with lower density, could result in a greater flowability improvement of both powders.

Similar results were obtained also when the influence of mixing time on particle size distribution was investigated, while the change of the amount of additives (Aerosil, propan–2–ol) did not affect particle size.

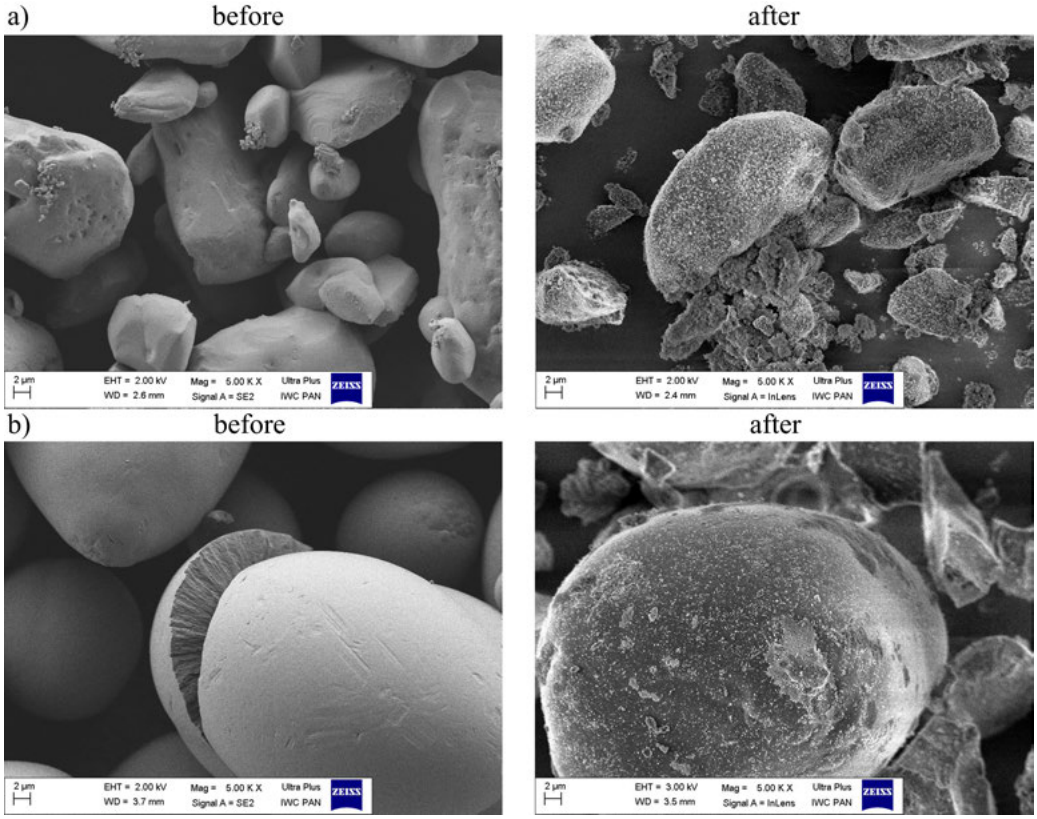

Fig. 6. SEM images of particles before and after high-energy mixing: a) Disulfiram; b) potato starch

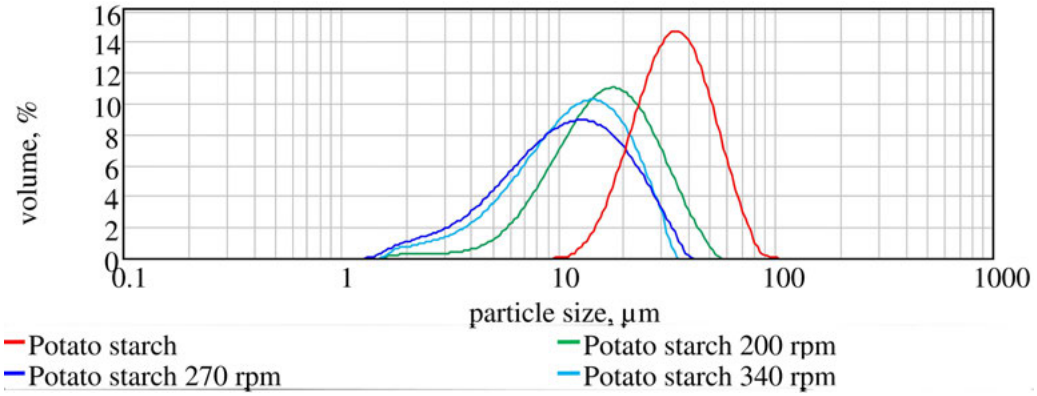

Fig. 7. Particle size distribution of potato starch before and after mixing with different rotational speed

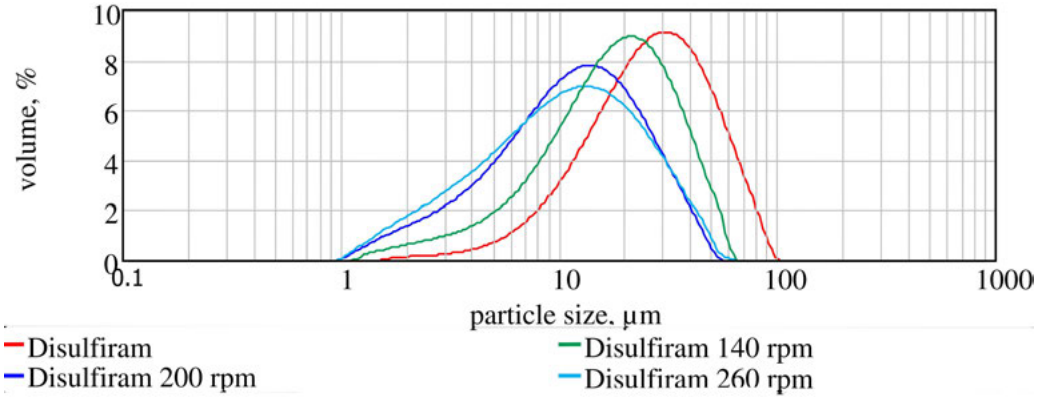

Fig. 8. Particle size distribution of Disulfiram before and after mixing with different rotational speed

3.4. Practical guidelines for predicting proper conditions of high-energy mixing

The prediction of proper conditions of high-energy mixing in a planetary ball mill required for a satisfactory flowability improvement is difficult due to various properties of powders. For that reason, it is also impossible to generalize the obtained model equations and calculate optimal mixing conditions appropriate for all materials. Therefore, based on the experiments performed for fine powders (Apyral and calcium carbonate – given by Leś and Opaliński (2021)) as well as coarse powders (Disulfiram, potato starch) and determined optimal ranges of process variables, some practical guidelines facilitating the prediction of proper conditions and amount of additives were formulated:

1. The prediction of mixing speed and time should be based on the particle size distribution and melting point of powder. Fine powders with particle size below 10 μm should be mixed with a higher speed (280–300 rpm) and for a longer time (up to 18 min) in contrast to coarse powders for which a lower mixing speed (under 200 rpm) and the shortest time are required. For materials with a low melting point, a moderate time and speed under 260 rpm (i.e. for Disulfiram with melting point equal to 71.5 °C and mixing time of approx. 15 min) are recommended.
2. The selection of the additives should take into account application of modified powder and its purity demanded in manufacturing industry. For coarse powders, mixed under mild process conditions, to avoid excessive comminution, the amount of Aerosil addition should contain between 2–2.5% by weight due to a risk of insufficient breaking agglomerates of silica and non-uniform mixture. The addition of isopropyl alcohol is less important than other high-energy mixing factors. Preliminary experiments and the results of optimisation indicate that the amount of PCA should be as small as possible. In the case of some materials, e.g. potato starch, it can be even unnecessary.

The high-energy mixing conditions in a planetary ball mill (using grinding balls made of zirconium oxide with a diameter of 5 mm) as recommended to obtain a considerable flowability improvement of fine (under 10 μm) and coarse (over 10 μm) powders are given in Table 6.

Table 6. Guidelines for high-energy mixing performance

	Fine powders $d_p < 10$ μm	Coarse powders $d_p > 10$ μm
Mixing speed [rpm]	280–300	< 200 (the lowest as possible, sufficient to break up the agglomerates of Aerosil)
Mixing time [min]	10–18	2 (or longer, sufficient to break up the agglomerates of Aerosil)
Amount of Aerosil, mass fraction [%]	1.5–3.0	2.0–2.5
Amount of isopropyl alcohol [ml]	0.5–1.0	< 0.5 or unnecessary

For some powders, problems such as caking, significant efficiency reduction, excessive comminution or lack of uniformity of obtained mixture may occur during high-energy mixing. In such cases, the proposed ranges of the process variables should be changed according to the solutions presented in Table 7.

Table 7. Problems during high-energy mixing

No.	Problem	Solution
1.	Caking at the beginning of mixing	• ball movement trajectory change by mixing speed increase • isopropyl alcohol addition or the amount change according to the rule: – addition of less than 0.5 ml – the amount increase – addition of more than 1 ml – the amount reduction • amount of Aerosil increase
2.	Low efficiency	• mixing time reduction • mixing speed reduction • isopropyl alcohol addition or the amount change (see point 1)
3.	Non-uniform mixture	• mixing speed increasing • mixing time extension • amount of Aerosil addition reduction
4.	Excessive comminution	• mixing speed reduction • mixing time reduction • mixing balls with larger size or lower density using

3.4.1. Experimental verification of the mixing guidelines

The presented guidelines were verified experimentally for cohesive Naproxen powder mixed with Aerosil (2% mass fraction). The series of experiments showed that the high-energy mixing in the planetary ball mill with rotational speed of 180 rpm for 5 min without PCA allowed to decrease the angle of repose from more than 60 deg (over measurement scale of Powder Characteristic Tester PT-S) to about 40 deg and the compressibility index from 55.5% to about 47%. Mixing with a lower speed and/or a shorter time was ineffective because it was not possible to break up the agglomerates of Aerosil.

4. CONCLUSIONS

- Significant flowability improvement of highly cohesive Disulfiram powder is possible via high-energy mixing in a planetary ball mill. The angle of repose and compressibility index values as measures of powder ability to flow were decreased respectively from 57 to 37 deg and from 49 to 37%. The positive effect was also obtained for potato starch powder.
- The optimal high-energy mixing parameters as determined for Disulfiram using Response Surface Methodology and the optimisation in the grid nodes are as follows: mixing speed 140 rpm, time 2 min and amount of additives: Aerosil 2.1–3%, isopropyl alcohol 0.2 ml. The same appropriate variables for potato starch (excluding propan–2–ol addition) are: 200 rpm, 2 min and 2.1–2.5% respectively.
- Scanning electron microscope images confirmed the high degree of surface covering of Disulfiram and potato starch particles by Aerosil nanoparticles.
- According to the results of optimisation, some practical guidelines useful for predicting the high-energy mixing conditions towards the flowability improvement were developed. The guidelines are believed to be applicable for most powders of industrial importance.
- The accuracy and reliability of the proposed procedure were verified experimentally for Naproxen mixed with Aerosil.

SYMBOLS

b_0	constant term
b_i, b_{ii}, b_{ij}	regression coefficients
CI	compressibility index
PCA	process control agent
SEM	scanning electron microscope
x_1, x_2, x_3, x_4	coded variables: mixing speed; mixing time; amount of Aerosil; amount of isopropyl alcohol
y_1, y_2	responses: angle of repose, deg; compressibility index, %
z_1, z_2, z_3, z_4	actual variables: mixing speed, rpm; mixing time, min; amount of Aerosil, mass fraction, %; amount of isopropyl alcohol, ml

Greek symbols

α	axial, coded distance from the centre of experiment
ε	residual associated with the experiment
ρ_a	aerated bulk density, kg/m^3
ρ_t	tapped density, kg/m^3

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