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Research paper

Efficient production of solid dispersions by spray drying solutions of high solid content using a 3-fluid nozzle



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ABSTRACT

To evaluate the feasibility of producing solid dispersions with 3-fluid nozzle spray drying to improve the dissolution behavior of lipophilic drugs, 60 experiments were performed based on a Design of Experiment. Solid dispersions with mannitol as a hydrophilic matrix and diazepam as a model drug with a drug load of 20 wt-% were produced. The variables of the experiments were the water/organic solvent ratio, liquid feed flow, total solid content, atomizing airflow and type of organic solvent (ethanol or ethyl acetate). The responses measured were dissolution rate, yield, actual drug load, particle size and crystallinity of diazepam and mannitol. Increasing water/organic solvent ratio was found to be the main factor for enhancing the dissolution rate. The total solid content of the solutions to be spray dried did not affect any of the responses, which means that processing solutions of high concentrations is possible. The choice of organic solvent did not affect the responses as well, i.e. both the fully water miscible solvent ethanol and the poorly water miscible solvent ethyl acetate could be used which makes this production method highly versatile.

1. Introduction

The majority, even up to 75% [1], of new drug candidates in development pipelines belong to Biopharmaceutical Classification System (BCS) class II [2], having a low solubility in aqueous media. Due to their low solubility, bioavailability of these drugs is poor after oral administration. However, it has been shown that bioavailability can be improved by increasing the dissolution rate of the drug [3,4].

There are several formulation strategies to improve dissolution rate, one of them being formulating the drug as a solid dispersion [5]. The term solid dispersion refers to a combination of at least two different ingredients, where the drug is incorporated molecularly or as nanoparticles in a hydrophilic matrix in the solid state [6,7]. One of the techniques to produce such solid dispersions is spray drying [8,9].

Although conventional spray drying results in increased dissolution rate and therefore improved bioavailability, the technique has a major drawback. In order to produce a solid dispersion with the desired characteristics, a solvent is needed in which both drug and matrix dissolve [8]. Because of the lipophilic nature of the drug and the hydrophilic nature of the matrix finding such common solvent can be

troublesome. Often highly toxic solvents like dichloromethane are used and the choice for the matrix material is limited. In addition, usually only very low solid concentrations (typically below 0.5 wt-%) can be applied [10,11]. Thus, relative large amounts of solvent are needed, requiring more time and energy, which is not considered green [12].

We hypothesize that a technique to prevent this drawback is 3-fluid nozzle spray drying. Instead of using one common solvent, two different solvents are used to prepare two different solutions. An organic solvent can be used to dissolve the hydrophobic drug while water can be used to prepare a solution of the hydrophilic matrix material. The rationale behind this technique is that the two solutions are pumped separately through two different channels and meet at the tip of the nozzle, where they are mixed and atomized by pressurized gas (nitrogen) provided by the third channel. Subsequently, the solvents evaporate from the droplets by a stream of hot gas (nitrogen) by which a solid dispersion is formed [13]. Application of the 3 fluid nozzle might offer two advantages over the two fluid nozzle, first, the possibility to use two solvents that are not miscible, and second, the possibility of using solutions of high concentrations.

The technique of spray drying with a 3-fluid nozzle has been used

Abbreviations: CCCD, circumscribed central composite design; CQA, critical quality attribute; DOE, design of experiments; QbD, quality-by-design

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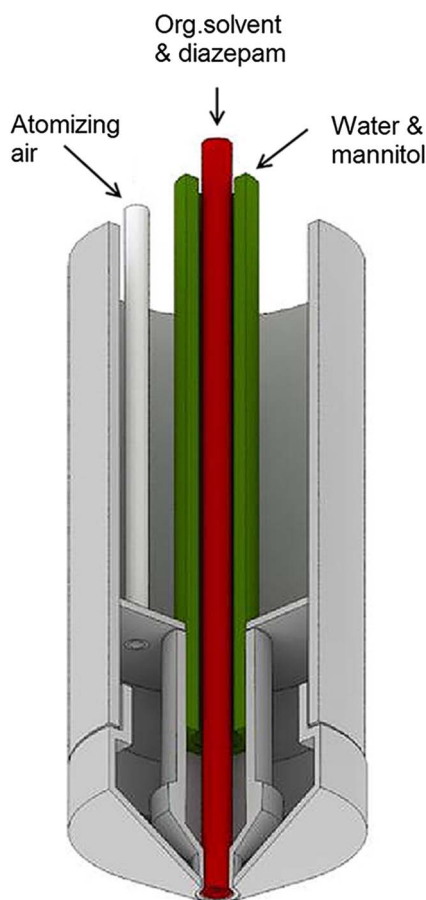


Fig. 1. Schematic diagram of the 3-fluid nozzle. Adapted with permission from [24].

Table 1
Factors and levels for the selected central composite design based on preliminary research (center values showed best results).

Factors	Levels				
	Ethanol		Ethyl acetate		
Water/org. solvent ratio [v/v]	0.5	2.0	3.5	5.0	6.5
Total solid content [mg/mL]	40	45	50	55	60
Total feed flow rate (water and organic) [mL/min]	3.0	3.8	4.5	5.3	6.0
Atomizing airflow [L_n/h]	469	536	603	670	737

for several applications. For example it has been applied to produce microcapsules of omega-3 fatty acids [14], in-situ cross-linked chitosan microparticles [15], sustained-release microcapsules [16] and pH-responsive hydrogels [17]. Furthermore, the production of solid dispersions containing lipophilic drugs by spray drying using a 3 (or 4)-fluid nozzle has also been explored before [18]. However, to our best knowledge, the effects of the process parameters on the characteristics of the final products have not been investigated in detail.

Table 2
Summary of established models.

Response	Transform	Model type	Model F value	Lack of fit F value
Dissolution rate t_{50}	Inverse sqrt	Linear	5.13 (p = .0007)	1.45 (p = .3027)
Yield	Logit (0...100)	Linear	30.50 (p < .0001)	1.67 (p = .2258)
Actual drug load	None	Quadratic	4.42 (p < .0001)	1.57 (p = .2581)
Particle size X_{50}	None	2FI	7.23 (p < .0001)	0.99 (p = .5529)
Crystallinity diazepam	None	Linear	12.12 (p < .0001)	1.12 (p = .4693)
Crystallinity mannitol	None	Quadratic	1.32 (p = .2270)	0.61 (p = .8493)

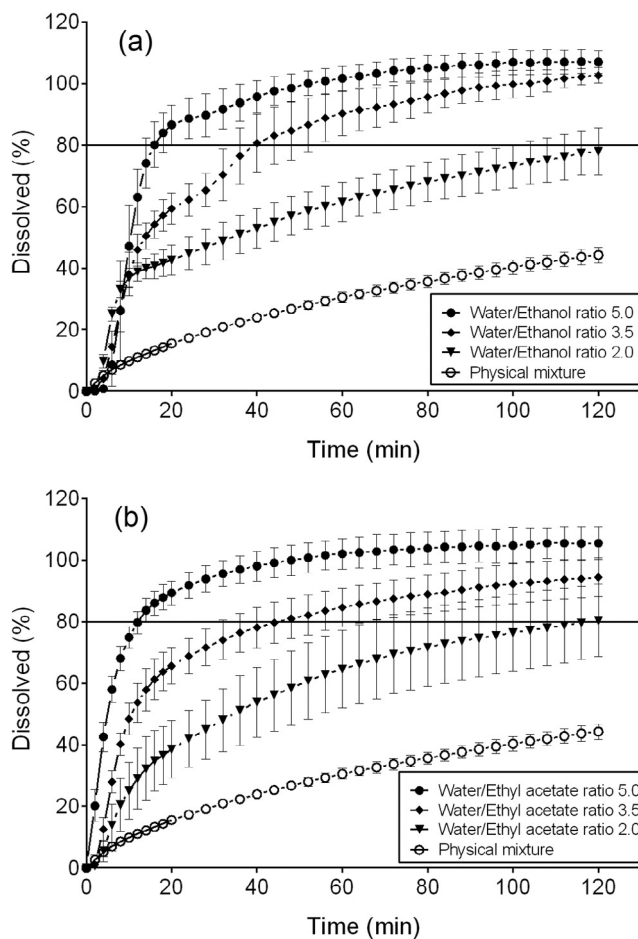


Fig. 2. Dissolution profiles of tablets with different water/organic solvent ratios and physical mixture with a drug load of 20 wt-%. Solid dispersions were prepared using (a) ethanol and (b) ethyl acetate as an organic solvent. Error bars represent standard deviation (n = 3).

With spray drying, a great variety of process parameters, such as inlet concentrations, type of solvent, throughput, inlet temperature, aspirator and atomizing airflow, can be controlled to influence the characteristics of the final product [8]. The aim of this research was to elucidate the influence of (a combination of) these parameters on the characteristics of the final product by applying a design of experiment (DOE) approach. DOE is a statistical technique that compiles experiments in structured and systematic manner. Output of the DOE is essentially empirical model that allow effective knowledge gain about variables, responses and their relationships. Finally, this information can be used to optimize processes [19,20]. It is more efficient than the one-variable-at-the-time approach, which is highly time consuming because of the large number of experiments to be done [21]. Also, the main effect of factors and their interactions cannot be calculated, as well as the relationship between the response and the factors.

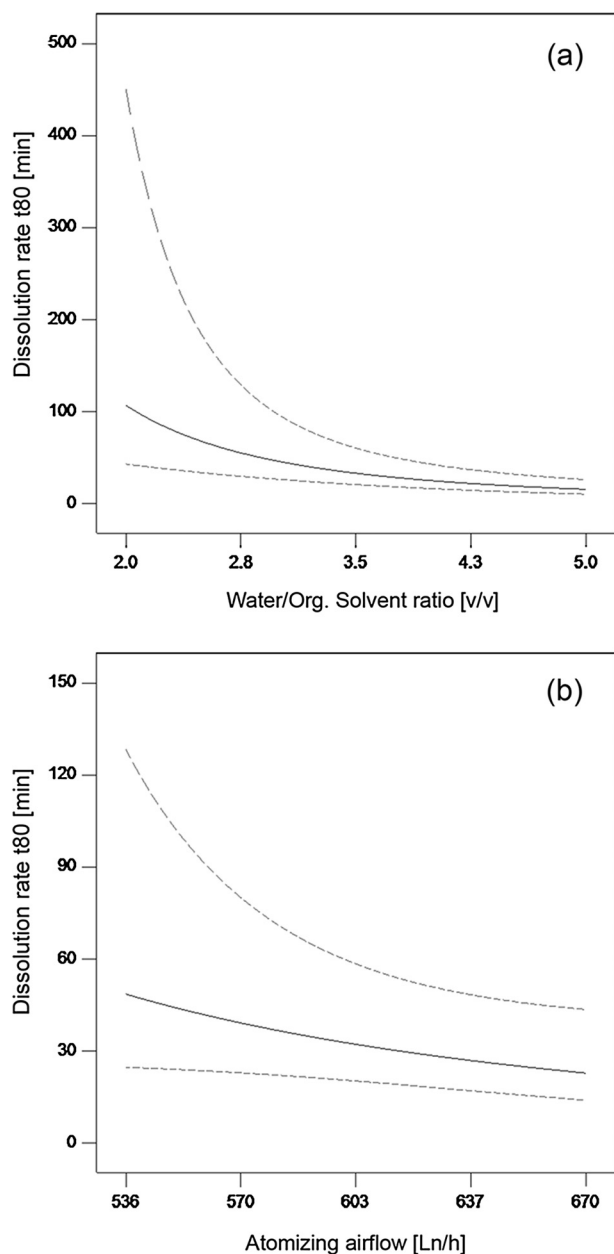


Fig. 3. Influence of (a) water/organic solvent (ethanol) ratio and (b) atomizing airflow on dissolution rate expressed as t_{80} . Dashed lines represent 95% confidence interval limits.

Moreover, the solution obtained by the approach does not represent the optimal conditions to obtain the desired outcome [22]. The experiments were carried out with mannitol as matrix and diazepam as model drug. The aimed drug load was 20 wt-%. Two organic solvents were used; ethanol and ethyl acetate, which are fully water miscible and poorly water miscible (solubility of ethyl acetate in water: 7.7 wt-% at 20 °C), respectively [23].

2. Materials and methods

2.1. Materials

Diazepam was obtained from Duchefa, The Netherlands. Mannitol was obtained as Pearlitol® from Roquette, France. Analytical grade ethanol (Cat. No. 20821) and ethyl acetate (Cat. No. 23882) were purchased from VWR International. Ultra-pure water (resistivity 18.2 MΩcm, filtered through 0.22 μm) was prepared using Milli-Q

Reference A + water purification system (Millipore Corporation, Billerica, USA).

2.2. Spray drying

Solid dispersions of diazepam and mannitol with the target drug load of 20 wt-% were prepared by spray drying using a Mini Spray Dryer B-290 with dehumidifier B-296 (0 °C) and inert loop B-295 for organic solvents (BÜCHI Labortechnik AG, Flawil, Switzerland) equipped with a 3-fluid nozzle (Fig. 1). The process conditions are presented in Section 2.3.

Channels of the 3-fluid nozzle were fed as follows: atomizing gas (nitrogen) through the outer channel, aqueous mannitol solution through the middle channel and solution of diazepam in organic solvent through the inner channel. Feed solutions were injected into the nozzle channels using 60 mL syringes with Luer-Lock fittings (CODAN Medizinische Geräte GmbH & Co KG, Lensahn, Germany) and NE-300 syringe perfusion pumps (ProSense B.V., Oosterhout, The Netherlands).

2.3. Experimental design

A circumscribed central composite design (CCCD) [25] was applied to optimize 3-fluid spray drying method with respect to dissolution rate, yield, actual drug load, particle size and crystallinity of diazepam and mannitol. Factors investigated were water/organic solvent ratio, total solid content of the solutions, feed flow rate, atomizing airflow and type of organic solvent. DOE factors and their respective levels are presented in Table 1. Experimental design consisted of 60 experiments in total. The detailed information of CCD is provided in Table S1 (Supplementary material). Inlet temperature (65 °C) and aspirator flow (100%) were kept constant in all experiments. Suitability of DOE process conditions was determined before actual experiments by means of predicted values of temperature and relative humidity at the outlet obtained by a spray dryer model [26].

In order to take account possible variations induced by different operator of spray dryer, DOE was divided into two blocks, namely factorial and axial block [20]. Center points of factorial and axial blocks were replicated 4 and 2 times, respectively. Prediction performance of final model was evaluated in four confirmation runs. The average response values of these runs were compared to 95% prediction interval:

$$95\%PI = \hat{y}_0 \pm t_{crit} \cdot SE_{pred}$$

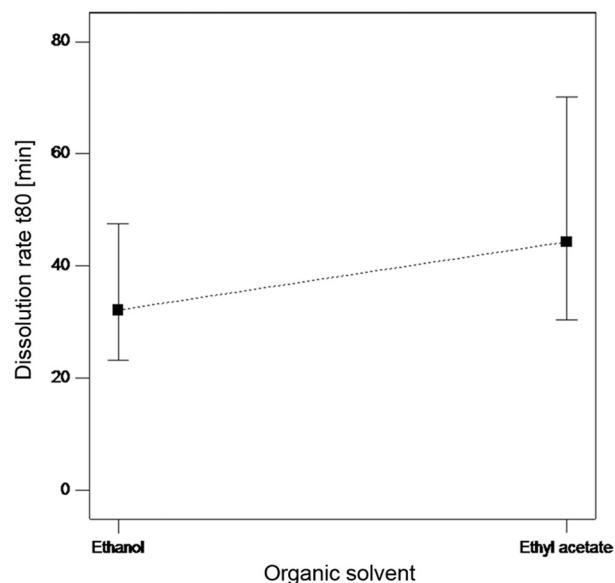


Fig. 4. The effect of organic solvent type on dissolution rate expressed as t_{80} .

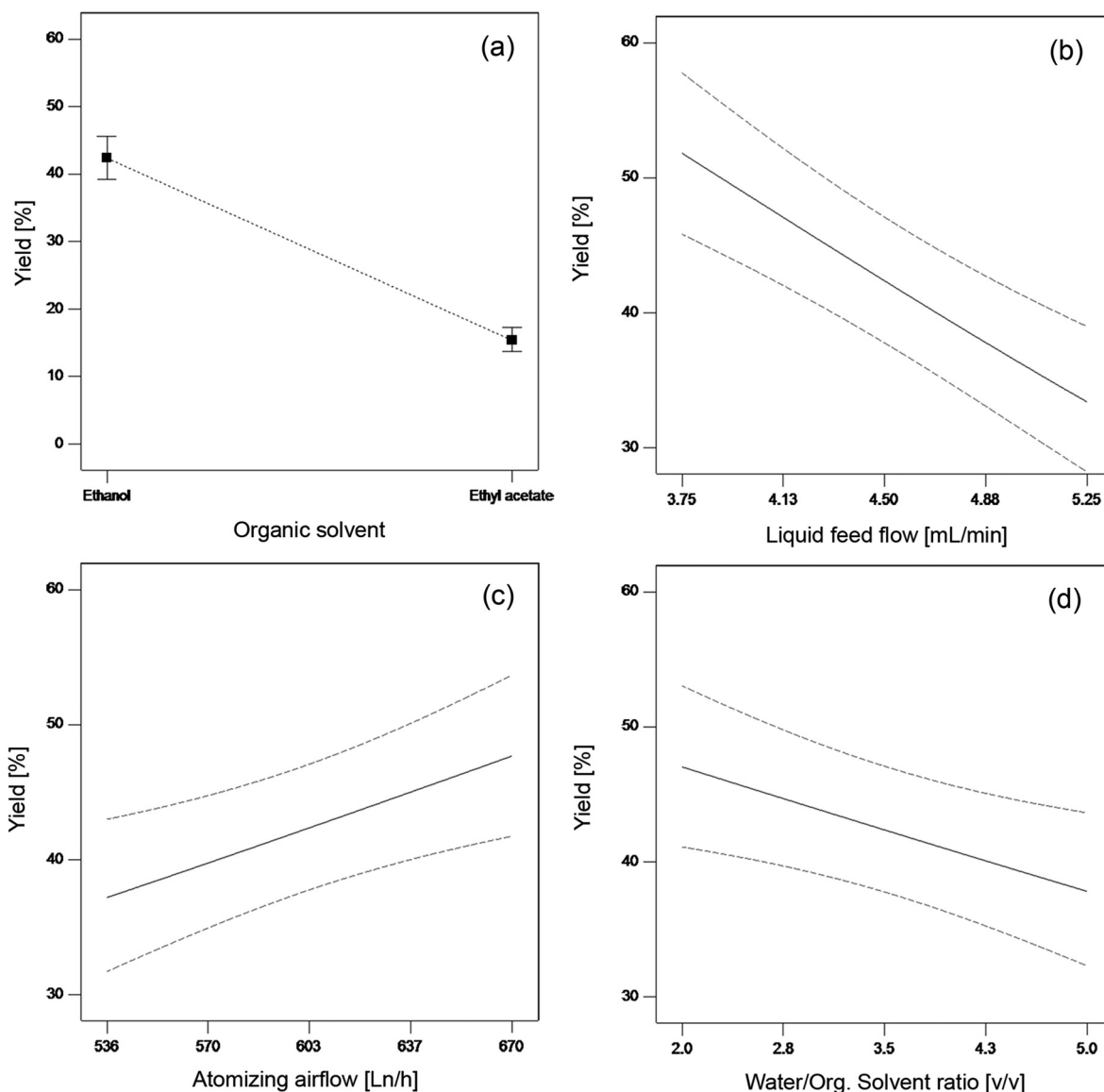


Fig. 5. Influence of type of (a) organic solvent, (b) liquid feed flow, (c) atomizing airflow and (d) water/organic solvent ratio on yield. Dashed lines represent 95% confidence interval limits.

where \hat{y}_0 is predicted value of response, t_{crit} is student's t critical value and SE_{pred} is standard error of the prediction. Design-Expert 10.0.2 software (Stat-Ease Inc., Minneapolis, USA) was used to evaluate DOE results.

2.4. Tableting

Spray dried solid dispersions were tableted using ESH compaction equipment (Hydro Mooi, Appingedam, The Netherlands). Tablets were prepared to round flat-faced symmetry with a diameter of 7 mm and a mass of approximately 50 mg. Powders were compressed at a rate of 5 kN/s with maximum compression force of 5 kN and a hold time of 0.1 s time. The die and punches were manually lubricated with magnesium stearate before tableting. Three replicate tablets were prepared for each DOE experiment. Tablets were stored at room temperature for at least 12 h prior to dissolution testing.

2.5. Dissolution rate

Dissolution behavior of solid dispersion tablets were determined using USP apparatus II AT7 smart (SOTAX, Kampenhout, Belgium) at

temperature of 37 °C with a paddle speed of 100 rpm for a period of 120 min. Demineralized and degassed water with volume of 1000 mL was used as dissolution medium. The diazepam absorbance in the medium was measured using Evolution 300 UV–VIS spectrophotometer (Thermo Scientific, Waltham, USA) and 10 mm flow-through cuvette at a wavelength of 230 nm. Sampling interval of 2 min was used for the first 10 samples and 4 min for subsequent 25 samples. A calibration curve, prepared using aqueous diazepam solutions at concentrations of 1–20 µg/mL, was used to calculate the amount of released diazepam. In data analysis, time when 80% of diazepam was dissolved (t_{80}) was used as a quantitative measure of the dissolution rate. t_{80} was calculated as an average of three tested replicate tablets of each DOE experiment. In experiments where less than 80% of diazepam was dissolved at the end of test, linear regression was fitted to dissolution graph and t_{80} was determined as an extrapolated value.

2.6. Yield

Process yield was determined as mass percentage of output and input solids. Output solid content was calculated by subtracting mass of empty product collection vial from the vial mass after spray drying.

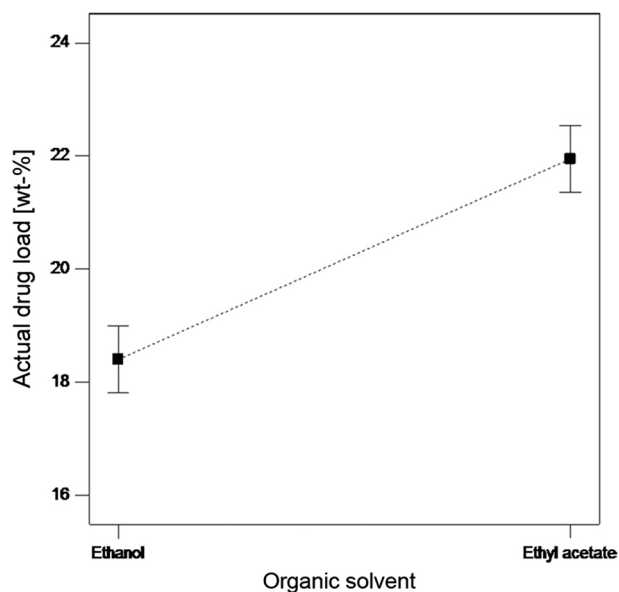


Fig. 6. Actual drug load of spray dried solid dispersions prepared using ethanol and ethyl acetate as organic solvent.

Input solids were calculated based on concentrations and consumed volumes of diazepam and mannitol solutions that were used during each experiment.

2.7. Actual drug load

Actual diazepam content in spray dried solid dispersions were determined using Unicam UV500 spectrophotometer (Thermo Spectronic, Cambridge, UK). Accurate amount of sample (4–8 mg) was weighed and dissolved in 100 mL of 50% ethanol solution. The diazepam absorbance was measured as triplicate at a wavelength of 230 nm in 10 mm quartz cuvette. Diazepam calibration samples (1, 2, 4, 6, 8, 12, 16 and 20 µg/mL) were prepared in 50% ethanol solution as triplicate. Linear regression was used to determine diazepam content of unknown samples. Based on total mass of sample and diazepam content, actual drug load was calculated and used in data analysis.

2.8. Particle size analysis

Particle size distribution of spray dried solid dispersions were determined using HELOS BF laser diffraction apparatus equipped with RODOS dispersing unit (Sympatec, Clausthal-Zellerfeld, Germany). R3 lens with the range from 0.9 to 175 µm was used in measurements. A pressure of 3 bar was used for dispersion. Three replicate measurements were performed for each sample. Average of median particle size value (X_{50}) was used for data analysis.

2.9. Crystallinity of diazepam and mannitol

The degree of crystallinity of both diazepam and mannitol in spray dried solid dispersions were determined using differential scanning calorimeter Q2000 DSC (TA Instruments, New Castle, USA). The accurate amount of sample (2–6 mg) was placed in open aluminum pan and heated from 0 to 200 °C at 20 °C/min. The degree of crystallinity was calculated by quantifying the heat of fusion for both compounds. Diazepam and mannitol as received were assumed to be 100% crystalline and their heat of fusion were used to normalize the results.

3. Results

Mannitol was selected as matrix material because it easily crystallizes at room temperature ($T_g = 13$ °C, melting point = 168 °C) [27]. Thus, it is expected that mannitol in the solid dispersion will be highly crystalline in all cases, by which one of the responses can be kept constant. In addition, its high aqueous solubility (> 200 mg/mL) does not form a limiting factor for the dissolution of the drug. Diazepam was chosen as model drug for its poor solubility in water (65.2 mg/L at 37 °C), but high solubility in most organic solvents. Furthermore, its concentration in solutions can be easily determined by UV-spectroscopy. Finally, the degree of crystallinity of both components in the solid dispersion can be easily quantified by DSC because diazepam and mannitol have substantially different melting points (diazepam 130 °C [28] and mannitol 166 °C [29]), by which their melting endotherms are not overlapping. Experiments were conducted with both ethanol (fully miscible with water) and ethyl acetate (poorly miscible with water). Both solvents have a low toxic potential (classified ICH class 3) and their boiling points are in the same range (78 °C for ethanol and 77 °C for ethyl acetate).

The responses of the experiments were analyzed with the software to check whether the models were statistically valid (see Table 2). It was found that all the p-values of the responses were in the desired range (Model F value $p < .05$; Lack of fit F value $p > .05$), except for the crystallinity of mannitol. Although this response cannot be modelled, the crystallinity of mannitol was found to be 88.0% or higher in all cases, with an average of 94.7%. The high degree of crystallinity was expected as mentioned above.

The DOE response graphs in results section are plotted using the center points from the DOE. If not otherwise mentioned, the water/organic solvent ratio is 3.5 [v/v], total solid content 50 mg/mL, total liquid feed flow 4.50 mL/min and the atomizing airflow 603 Ln/h.

3.1. Dissolution rate

Water/organic solvent ratio was found to be the most significant factor affecting to the dissolution rate. Fig. 2 presents dissolution profiles of tablets prepared from solid dispersions with varying water/organic solvent ratio. Dissolution rate increased with increasing water/organic solvent ratio and this behavior was found to be similar for both ethanol (Fig. 2a) and ethyl acetate (Fig. 2b).

The effect of water/organic solvent ratio was confirmed by DOE response graphs. With the increasing water/organic solvent ratio, the dissolution rate significantly increased (Fig. 3a). It was also observed that the dissolution rate increased with increasing atomizing airflow (Fig. 3b).

The type of organic solvent, however, had no significant effect, although ethanol showed a slightly lower average t_{80} value than ethyl acetate as illustrated in Fig. 4. The amount of total solid content or liquid flow rate had no significant effect on the t_{80} value.

3.2. Yield

The main factors affecting to the process yield were type of organic solvent, atomizing airflow, water/organic solvent ratio and liquid feed flow (see Fig. 5).

The type of organic solvent had a significant influence on the yield: ethanol caused a higher yield than ethyl acetate (Fig. 5a). The yield increased with increasing atomizing airflow (Fig. 5c), but decreased with increasing liquid feed flow (Fig. 5b). Furthermore, a higher water/organic solvent ratio resulted in a lower yield (Fig. 5d). However, the yield did not depend on the total solid content. It is important to keep in mind that yield is a not fully reliable response. In some processes, the product was sticking to the sides of the cyclone more than in others. An increased atomizing airflow may have led to relatively dryer particles (less sticky) when they entered the cyclone while an increased liquid

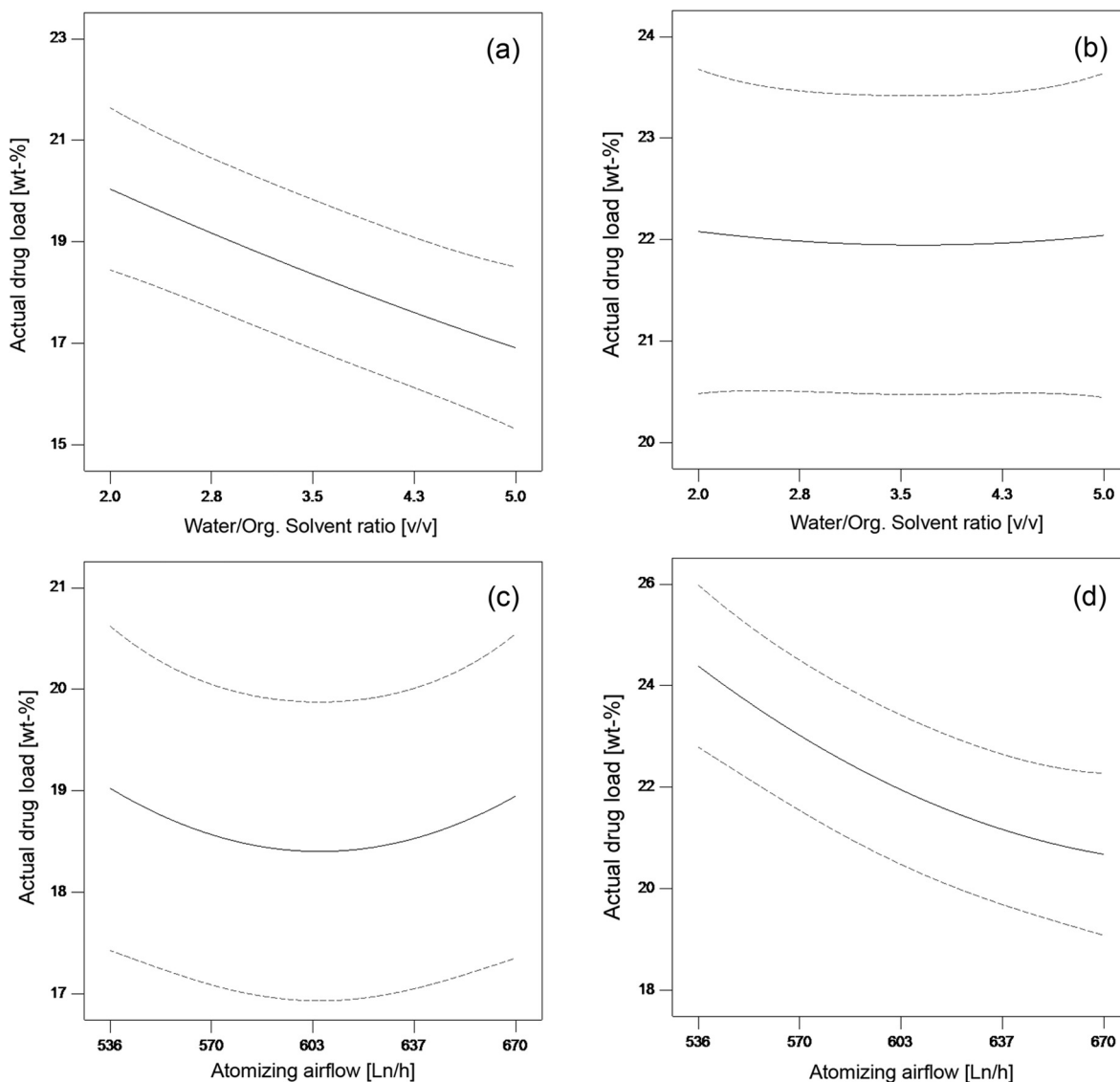


Fig. 7. The effect of water/organic solvent ratio and atomizing airflow on actual drug load. Graphs (a) and (c) correspond to solid dispersions prepared using ethanol. Respective graphs for ethyl acetate are (b) and (d). Dashed lines represent 95% confidence interval limits.

feed flow may have led to less dry particles (more sticky). In some processes, however, the produced powder fell from the cyclone into the collection vessel when a substantial amount was stuck to the cyclone, influencing the yield positively. Nevertheless, the yield was not completely random (trends are shown). External parameters that could influence the yield, like vibration or external forces, were kept to a minimum by handling the product the same way when the production process was completed.

3.3. Actual drug load

The average drug load was lower than the expected 20 wt-% when ethanol was used as solvent, but higher with ethyl acetate (see Fig. 6). Along with the type of organic solvent, water/organic solvent ratio and atomizing airflow were also found to be significant factors affecting the actual drug load (see Fig. 7).

When ethanol was used as solvent, the actual drug load increased when the water/organic solvent ratio decreases (Fig. 7a). When ethyl acetate was used, the actual drug load was not influenced by the water/organic solvent ratio (Fig. 7b). This might also be explained by the fact that ethanol mixes well with water. When ethyl acetate is used, the

actual drug load increased when the atomizing airflow decreased (Fig. 7d). Instead, when ethanol was used, the atomizing airflow did not affect the actual drug load (Fig. 7c). The actual drug load did not depend on the total solid content.

3.4. Particle size

The significant DOE factors affecting particle size X50 are illustrated in Fig. 8. Particle size decreased with increasing atomizing airflow (Fig. 8a), water/organic solvent ratio (Fig. 8b) and liquid feed flow increased (Fig. 8c).

3.5. Crystallinity of diazepam

The crystallinity of diazepam was higher when ethyl acetate was used as solvent instead of ethanol (Fig. 9a). The crystallinity of diazepam decreased when the water/organic solvent ratio increased (Fig. 9b). Neither total solid content, feed flow rate or atomizing airflow rate had a significant effect on crystallinity of diazepam.

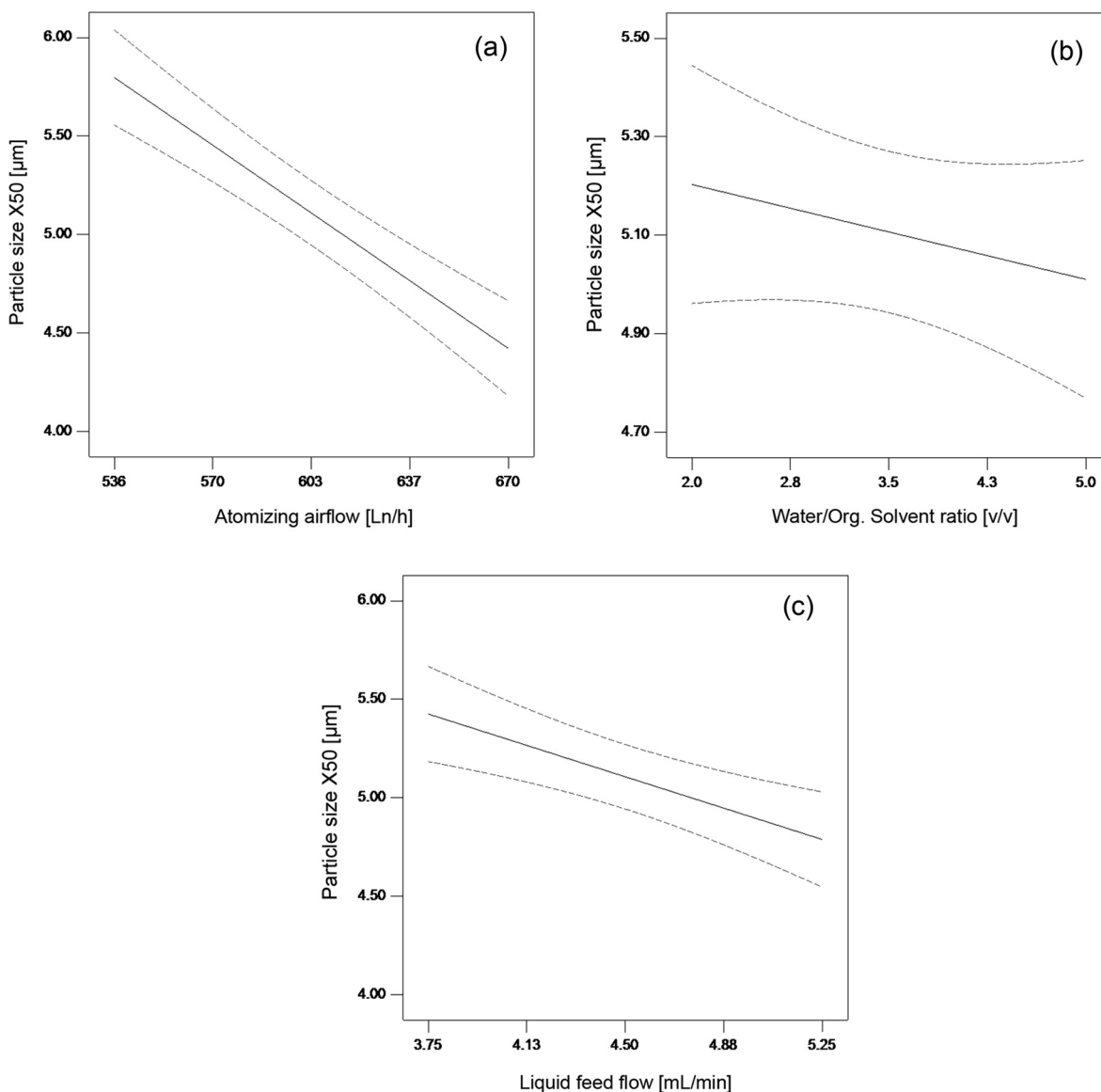


Fig. 8. Influence of (a) atomizing airflow, (b) water/organic solvent ratio and (c) liquid feed flow on particle size. Dashed lines represent 95% confidence interval limits.

3.6. Model confirmation and optimization

In order to evaluate performance of the model, four additional confirmation runs were performed. Criteria for confirmation runs was to maximize dissolution rate (thus minimize t_{80}), maximize process yield and target actual drug load within range 17.5–22.5 wt-%. The following parameters were used for confirmation: water/organic solvent volume ratio 4.1, total solid content 50 mg/mL, liquid feed flow 3.86 mL/min, atomizing airflow 670 L_n/h and ethanol as organic solvent. The model was confirmed if the average value of response falls within the prediction interval. The results of confirmation runs are presented in Table 3.

The model predictions for dissolution rate, actual drug load, particle size, crystallinity of diazepam and outlet temperature were confirmed. Only the observed mean of yield lies outside of the predicted interval (28 < 39%). As mentioned earlier, the yield can be regarded as a not very reliable response, while with some processes the product that was stuck to the cyclone wall fell down in the collection vessel just before the end of the experiment.

The dissolution rate is less than predicted (t_{80} value of 12 vs.

20 min), the crystallinity of diazepam is at the upper limit of the prediction interval (71%), the particle size is almost as predicted (4.77 vs. 4.79 µm) and the observed outlet temperature is at the lower limit of the prediction interval (37 °C).

3.7. Overview of results

All the results of the different parameters on the responses are shown in Table 4.

4. Discussion

In this study, it was found that a spray drier equipped with a three way nozzle can be used for the production of solid dispersion to improve the dissolution behavior of lipophilic drugs. The total solid content of the solutions to be spray dried did not have an influence on the yield, drug load, dissolution rate, and particle size. This means that the process can be carried out at relatively high initial concentrations. Therefore, less solvent needs to be used and fast and efficient production is facilitated. The saturation concentration of the drugs in the

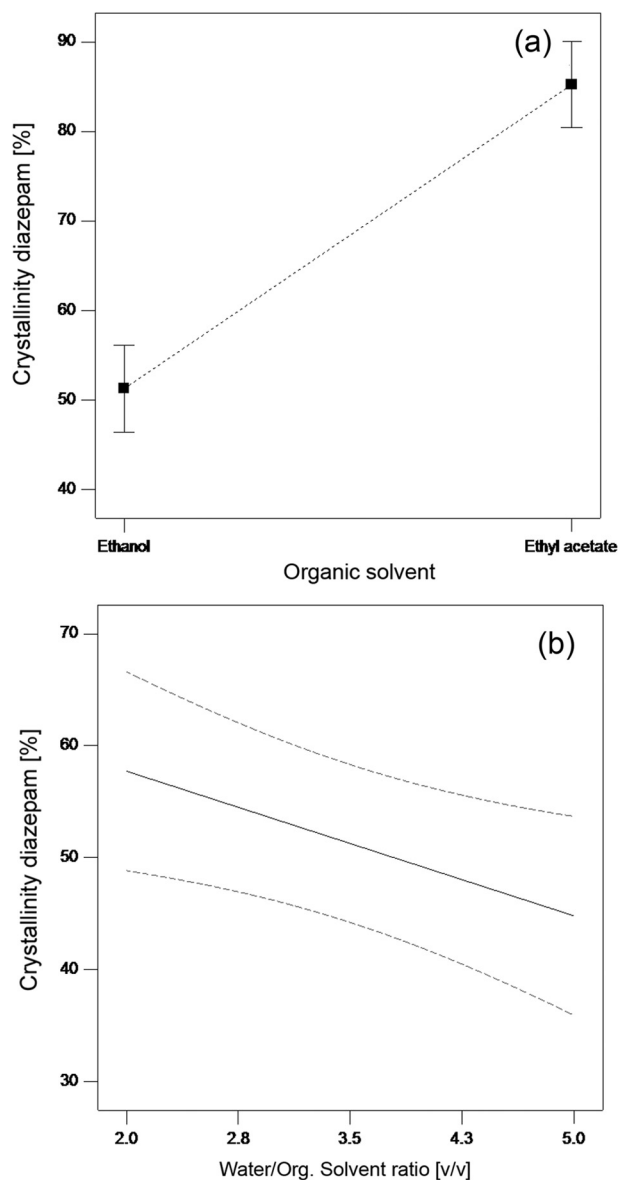


Fig. 9. The influence of (a) the type of organic solvent and (b) water/organic solvent ratio on the crystallinity of diazepam. Dashed lines represent 95% confidence interval limits.

Table 3

Confirmation of model. Observed mean was compared to the prediction interval for a sample size of 4.

Response	Optimization criteria	Mean		95% prediction interval	
		Obs.	Pred.	95% PI low	95% PI high
Dissolution rate t_{80} (min)	Minimize	12	20	6	46
Yield (%)	Maximize	28	54	39	69
Actual drug load (wt. %)	20 ± 2.5	16.7	18.1	15.1	21.1
Particle size X_{50} (μm)	None	4.8	4.8	4.3	5.3
Crystallinity of diazepam (%)	None	71	49	28	71

organic solvent may be the limiting factor. However, it was also found that the dissolution rate was not dependent on the type of organic solvent. This might imply that a solvent can be selected in which the drug dissolves well. Furthermore, it was found that even a solvent that is poorly miscible with water (ethyl acetate) can be used, which indicates the versatility of the technique. However, it should be realized that only organic solvents with a high vapor pressure can be used for spray drying to guarantee sufficient solvent evaporation before the product enters the cyclone. Obviously, to confirm the versatility of this technique to produce solid dispersion for other drug types should be evaluated case by case.

Remarkably, it was found that with increasing water/organic solvent ratio the dissolution rate increased independent whether a fully water miscible or a poorly water miscible organic solvent was used, i.e. ethanol and ethyl acetate, respectively. Obviously, using less organic solvent is advantageous as it reduces the costs and waste of the process. The increased dissolution rate with increasing water/organic solvent ratio was related with a decreased particle size and crystallinity of diazepam. Although significant, the decrease in particle size and crystallinity of diazepam was only minor and may not fully explain the increased dissolution rate. Another possible reason for the observed effects could be that with increasing water organic solvent ratios, the diazepam molecules form smaller and thus faster dissolving clusters within the spray dried particles. The formation of these smaller clusters may be explained as follows. At a higher water/organic solvent ratio, the initial diazepam concentration in the organic solvent is also higher. Therefore, during spray drying, the solution will be rapidly supersaturated resulting in a high nucleation rate for diazepam precipitation and thus in the formation of small diazepam clusters. However, more research is warranted to confirm this hypothesis.

Another notable aspect is the fact that the crystallinity of diazepam is lower when using ethanol instead of ethyl acetate. A possible explanation of this phenomenon is that when diazepam is dissolved in a fully water miscible solvent, it will mix with the aqueous mannitol solution when exiting the nozzle. When ethanol and water are combined they will mix fast, and diazepam will become supersaturated and thus precipitate very fast. Due to this fast process, the diazepam molecules were less able to arrange in a crystalline lattice and therefore become amorphous. When ethyl acetate and water are combined, only minor mixing will occur and the diazepam will stay in the organic solvent where it dissolves well. There is more time to form a crystalline lattice.

The fact that the yield could not be modelled can be attributed to product sticking to the cyclone of the lab scale spray dryer we used. With industrial spray dryers usually higher yields are obtained, because higher volumes are produced. Consequently, relatively less product sticks to the walls of the drying chamber or cyclone.

5. Conclusions

The results of this study show that spray drying using a 3-fluid nozzle is an excellent technique for fast and efficient production of solid dispersions. The DOE setting allowed screening of method characteristics and limitations. With the established model it was possible to optimize the process parameters in respect of dissolution rate and yield. With the proposed method, the dissolution rate of a poorly water soluble lipophilic drug can be enhanced drastically in particular when a high water/organic solvent ratio is used. The experiments showed that both fully water miscible (ethanol) and poorly water miscible (ethyl acetate) solvents can be used indicating the versatility of the method. However, its applicability for other drugs should be confirmed.

Acknowledgements

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Table 4

Overview of factors and responses of the experiments. Direction of arrow represents factor influence on the response. Number of arrows represents significance of the factor on the response.

	Dissolution rate		Yield	Actual drug load		Particle size X ₅₀	Crystallinity diazepam
				Ethanol	Ethyl Acetate		
Water/Organic solvent ratio	↑	↑↑↑	↓	↓	–	↓	↓
Total solid content	↑	–	–	–	–	–	–
Feed flow rate	↑	–	↓↓↓	–	–	↓↓	–
Atomizing airflow	↑	↑	↑↑	–	↓↓	↓↓↓	–
Organic solvent	–	–	***EtOH > EA	*** < 20	*** > 20	–	***EtOH < EA

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ejpb.2017.11.009>.

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