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Examination of homogeneity with X-ray beams

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Abstract

The effects of blending time and rotation speed on the homogeneity of powder blends were examined. The concentrations of the samples were measured with an energy-dispersive X-ray fluorescence analyser, and control measurements were made with a UV spectrophotometer. The paired sample *t*-test showed that, for a large majority of the samples for which measurements were made to determine the concentrations, there was no essential difference. It may be stated, in accordance with the fitted equation, that the rotation speed and the square of the blending time exert significant effects on the distribution of the active ingredient. The energy-dispersive X-ray fluorescence analyser can be applied well for direct determination of the homogeneity of certain powder blends.
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Keywords: Powder blend; Homogeneity; Full factorial design; X-ray fluorescence analysis; UV spectrophotometric analysis

1. Introduction

One essential condition for the safe application of a medicine is a reliable dosage that can be attained with the medicine, containing the active ingredient in uniform dispersion.

Accordingly, one of the critical stages in the making of pharmaceutical dosage forms is the homogenization of the powder blend and proof of its homogeneity (Lieberman and Lachman, 1981; Johansson and Nicklasson, 1987; Davies et al., 1998). Many authors have reported about the effect of blender speed and the sampling practices (Muzzio et al., 1997, 2003; Sommier et al., 2001; Sudah et al., 2002).

The aims of this work were to investigate the effects of blending time and intensity on the homogeneity, and the suitability of an energy-dispersive X-ray fluorescence analyser for measurement of the concentrations of powder blends.

The energy dispersive spectrometer is widely used for elemental analysis. This technique is suitable for direct measurement of the element component of a drug (Reimer, 1985).

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When a material is irradiated by the beam from an X-ray tube, its constituent atoms are excited. This causes them to emit X-rays known as fluorescence. Each element in the sample emits its own uniquely characteristic fluorescent radiation, with an intensity directly related to the concentration of that element in the material. This phenomenon is the basis of X-ray fluorescence spectrometry. The fluorescence comprises discrete X-ray photons emitted at various (characteristic) energy levels. Photons of all energies are simultaneously received by the detector of the spectrometer and converted into a series of electrical signals, which are electronically amplified, processed and transformed into digital values. The digital values are stored in a multichannel analyser, which separates them according to the photon energy levels. The result is a spectrum for the sample, which is further processed by the software to deliver a result calculated directly in terms of element concentrations (Philips Analytical, 2001).

A compact table-top energy dispersive X-ray fluorescence analyser was used to measure the elemental range from sodium (Na) to uranium (U), in the concentration range from ppm to 100%.

The experimental design applied for this purpose allowed the simultaneous investigation of more than one variable with a lower expenditure of time, cost and work; additionally it was able to demonstrate possible interactions between the variables and was suitable for a search for the optimum.

2. Materials and methods

2.1. Materials

The powder blends contained the following materials: pyridoxine chloride (BASF Aktiengesellschaft, Ludwigshafen, Germany), Metolose 90SH (a hydroxypropyl methylcellulose) (Shin-Etsu Chemical Co., Ltd., Tokyo, Japan), mannitol (Ph.Eur.) and Gelcarin GP-379 NF (iota-carrageenan) (FMC Corporation, Philadelphia, USA). The same compounds were used in each run of the experiment (see Table 1).

2.2. Methods

2.2.1. Blending

Each powder blend was mixed with a Turbula mixer (W.A. Bachofen Maschinenfabrik, Switzerland). The blending time and the rotation speed were examined at three levels (see Table 2). 1.5 g samples were taken from the top, middle and bottom of the container.

Table 1
Ingredients of powder blends

Material	Quantity (g)
Pyridoxine chloride	90.0
Metolose 90SH	25.0
mannitol	132.5
Gelcarin GP-379	2.5
Sum	250.0

2.2.2. Analysis

2.2.2.1. X-ray fluorescence analysis. Measurements on the samples were made with a Philips MiniPal PW 4025 (MiniPal, Philips Analytical, Almelo, The Netherlands) energy-dispersive X-ray fluorescence analyser. During the measurements, the conditions applied were 4 kV, 1000 μA and 1 bar helium purge. The samples were measured for 10 min and the measurements were repeated in triplicate for each sample.

The concentrations of chlorine (m/m%) were calculated by means of linear calibration ($r^2 = 0.9458$) from the intensities of the K_α lines of the detected radiation.

2.2.2.2. UV spectrophotometric analysis. We also carried out control measurements on the same samples with a Unicam Helios Alpha S2 spectrophotometer (Spectronic Unicam, Cambridge, United Kingdom). The appropriate amount of powder blend was dissolved in artificial gastric juice and was measured at 291 nm; measurements were again made in triplicate. The pyridoxine chloride contents of the samples were calculated from the measured absorbances on the basis of linear calibration ($r^2 = 0.9999$).

Table 2
Examined variables

Variables	Levels		
	Low	Center	High
X_1: blending time (min)	10	20	30
X_2: rotation speed (rpm)	35 ± 3	50 ± 3	70 ± 3

2.2.3. Statistics

The analysis of the results and the evaluation of the experimental design were carried out with the SPSS 11.0 and Statistica for Windows 6.0 programs.

3. Results

The Kolmogorov-Smirnov test revealed that the measured concentrations exhibited normal distribution, i.e. further comparisons could be made by using the *t*-test and ANOVA.

ANOVA indicated no significant difference between the sampling sites with either measuring technique. Thus, differences between the sample concentrations at the bottom, middle and top of the container can be attributed to chance.

The results of UV and X-ray spectrometric measurements were compared by means of the paired sample *t*-test, which gave a significant difference only in the case of sample 10. This means that there was no essential difference for a large majority of the samples for which measurements were made to determine the concentrations.

The experiment was performed according to a 3^2 full factorial experimental design (Gonzalez, 1993). The settings of the experiment and the results can be seen in Table 3.

To evaluate the measurements, we used the absolute values of the difference ($|\Delta c|$) between the measured concentrations and the theoretical pyridoxine chloride content (36 m/m%). Then was fitted a quadratic polynomial according to the following equation:

$$y = b_0 + b_1x_1 + b_2x_2 + b_{11}x_1^2 + b_{22}x_2^2 + b_{12}x_1x_2,$$

where y stands for $|\Delta c|$, and b's are the regression coefficients of the factors. The values of the coefficients can be seen in Table 4.

It may be stated that the UV spectrophotometric measurements revealed that the linear component of the rotation speed and the quadratic component of the blending time exert significant effects on the distribution of the active ingredient.

Table 3
Experimental design and results

Run	Sampling place	X_1	X_2	UV		X-ray	
				$\|\Delta c\|$	Mean	$\|\Delta c\|$	Mean
1	Top	10	35	1.64	2.12	1.44	1.36
	Middle			2.79		1.83	
	Bottom			1.93		0.81	
2	Top	10	50	3.33	2.98	2.09	2.05
	Middle			2.87		2.65	
	Bottom			2.73		1.41	
3	Top	10	70	1.52	4.40	1.41	2.67
	Middle			6.00		3.08	
	Bottom			5.68		3.52	
4	Top	20	35	1.73	1.43	0.08	0.95
	Middle			0.22		2.25	
	Bottom			2.34		0.50	
5	Top	20	50	1.76	2.18	0.95	1.92
	Middle			1.09		2.72	
	Bottom			3.70		2.09	
6	Top	20	70	3.42	3.07	1.51	1.81
	Middle			3.40		2.25	
	Bottom			2.39		1.67	
7	Top	30	35	2.46	3.85	1.99	2.01
	Middle			6.29		1.26	
	Bottom			2.80		2.76	
8	Top	30	50	1.15	2.32	2.72	2.33
	Middle			2.86		2.12	
	Bottom			2.94		2.15	
9	Top	30	70	7.94	8.01	5.00	5.15
	Middle			7.95		7.02	
	Bottom			8.14		3.44	
10	Top	20	50	1.54	1.40	2.11	2.18
	Middle			0.85		1.69	
	Bottom			1.82		2.75	
11	Top	20	50	2.04	2.30	1.74	1.21
	Middle			1.59		1.67	
	Bottom			3.26		0.21	

Table 4
Regression coefficients of the fitted model

Factor	UV $\|\Delta c\|$ mean		X-ray $\|\Delta c\|$ mean	
	$r^2 = 0.9865$		$r^2 = 0.9593$	
	Coefficient	p	Coefficient	p
X_0 (=1)	3.41	0.002*	2.28	0.005*
X_1	0.80	0.056	0.59	0.103
X_1^2	−0.92	0.029*	−0.56	0.077
X_2	1.35	0.021*	0.89	0.049*
X_2^2	−0.60	0.064	−0.07	0.699
X_1X_2	0.47	0.193	0.46	0.210

X_1: blending time; X_2: rotation speed.
* Statistically significant ($p < 0.05$).

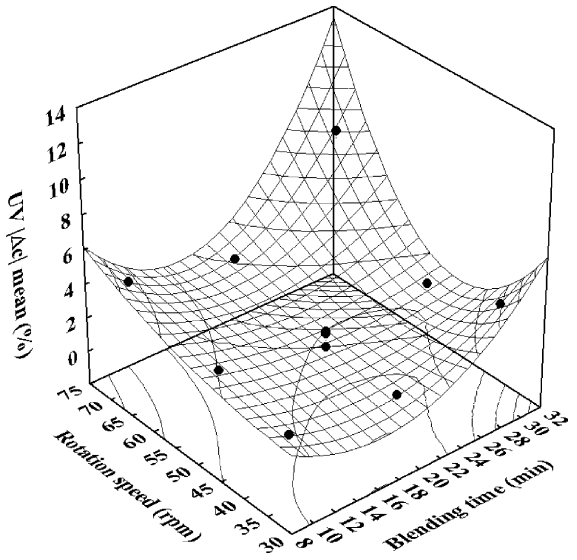

Fig. 1. Response–surface graph of UV spectrophotometric measurements.

The response–surface graph (Fig. 1) shows that, with decrease of the rotation speed, the deviation from the theoretical mean decreases, the target function displaying a local minimum near by the blending time of 20 min.

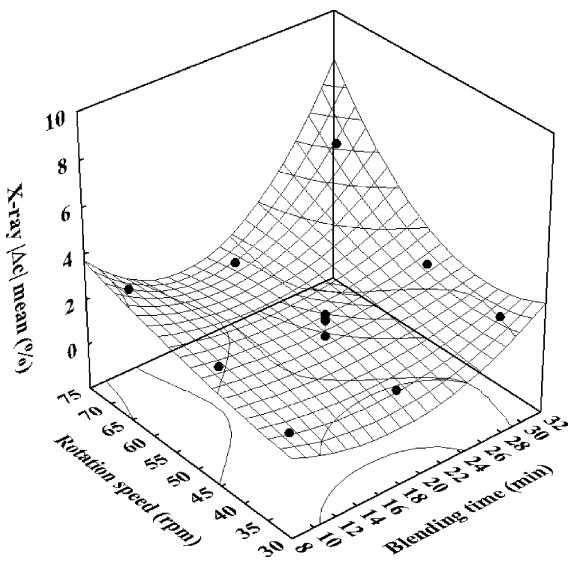

Fig. 2. Response–surface graph of X-ray spectrometric measurements.

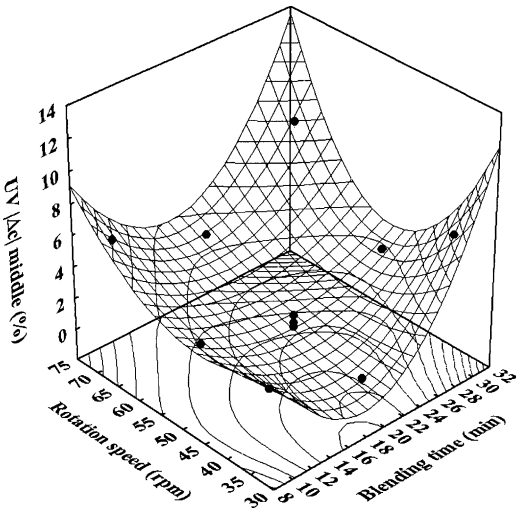

Fig. 3. Response–surface graph of middle samples measured with the UV spectrophotometer.

The X-ray spectrometric measurements indicate that only the linear component of the rotation speed has a significant effect (Fig. 2).

For the above conclusions, we used the mean of the concentrations at the three sampling sites; the response–surface graph of the UV spectrophotometrically measured middle samples is also shown, which demonstrates the effects of the variables and the optimum range of the target function most exactly (Fig. 3).

4. Conclusion

Both the blending time and the rotation speed have significant effects on the homogeneity of the powder blend. To reach the best distribution, a blending time of 20 min and a rotation speed of 35 rpm in the examined factor space are suggested.

The energy-dispersive X-ray fluorescence analyser can be applied well for in-process determination of the homogeneity of powder blends. The measurement is fast and does not require any special sample preparation. Thus, this method can be suggested for control of the homogeneity, which is one of the critical points of medicine production.

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