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COMMUNICATION

Comparative Evaluation of Surfactant and Hydrophobizing Agent Concentration in Relation to the Optimal Particle Size of Metered-Dose Inhalers

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ABSTRACT

The aim of the present study was to formulate stabilized suspension-type metered-dose inhalation aerosols, and to examine the connection between the stabilizing additives and the optimal particle size. For the stabilization of the suspended particles, hydrophilic- and hydrophobic-type additives were applied. Oleil oleate was selected as a hydrophilic anionic surfactant, and the hydrophobizing agent was dimethyl siloxane polymer. The effect of the amount of the applied hydrophilic and hydrophobic additives on the optimal particle size was modeled by a second-order polynomial equation fitted to the data gathered by a face-centered central composite statistical design. We found that if the proper type and amount of additives are selected, it is possible to acquire the therapeutically best composition.

INTRODUCTION

The bioavailability of inhalation aerosols is basically determined by the particle size range of the active compound in each single dose. Potential areas of research in inhalation therapy, aimed at reducing particle size of inhaled drugs and increasing lung deposition, were discussed by several authors (1–3).

For optimum metered-dose inhalers (MDIs) performance, the drug should be delivered in a uniform dose

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of the correct size range to allow penetration of the lung. Davis and Bubb proved that the particle size is dependent on relative humidity; the greater the humidity, the larger the measured size (4). The suspended drug particles have to be within the respirable range of 1–10 μm for the inhaler to be effective (5,6).

A stable, well-dispersed suspension or an easily dispersible suspension is required to meet these criteria. Surfactants such as lecithin, oleic acid, or sorbitan tri- and mono-oleate are therefore normally added to stabilize the formulation (7,8).

The main objectives of the present work were to examine the connection, both experimentally and with mathematical model, between the additives of various types and the optimal particle size of MDIs.

MATERIALS AND METHODS

Materials

Sodium cromoglycate (EGIS, Hungary, batch number 538130591), oleil oleate (Select Chemie AG, Germany, batch number 30/287), dimethyl siloxane polymer DC 200/1000 (Dow Corning, France, WCO 35305), 1,1,1,2-tetrafluoroethane (HFC 134a, ICI, Belgium, batch number RB 95-002), and dehydrated alcohol (USP 23, Merck Ltd., Germany, batch number 23666986) were used.

Sample Preparation

The given amount of oleil oleate, dimethyl siloxane polymer DC 200/1000, and the active compound were dispersed in dehydrated alcohol by Ultra turrax mixer (Ika-Werk, type: T45, Janke & Kunkel) at 1400 rpm. The homogeneous suspension was poured into an aluminum can (3M Health Care, U.K.) with a 20-mm neck finish. The metering valve (Valois, France, DF 30/50) was placed on the can and was closed with a crimping machine (Pamasol, Switzerland, type 2002). Finally, the proper amount of propellant was pressed into the cans with a propellant filling machine (Pamasol, type 2011/7).

Particle Size Analysis

A Malvern Master Sizer X particle size analyzer (MSX 5 unit/mount, serial no. 6361, Malvern Instruments GmbH, Germany) was applied for the particle size analysis of the samples. Five doses of the previously well-shaken sample were fired to waste and the sixth dose was discharged through the beam path to the MSX 5 analyzer to measure its particle size distribution. The results of five measurements were averaged. The MSX 5 mount was installed in three directions. The three precise mechanical locations ensure the identical registration of each result.

Table 1

Experimental Design with Factors and Their Levels

Levels	x_1 Surface-Active Ingredient (% w/w)	x_2 Hydrophobizing Agent (% w/w)
Lower (−)	0	0.07
Base (0)	0.1	0.14
Higher (+)	0.2	0.21

Statistical Experimental Design

A two-factor, three-level face-centered central composite design (9) was applied to construct a second-order polynomial model describing the effect of formulation factors (surface active ingredient, hydrophobizing agent) on the product characteristic (proportion of the effective particle size). The two factors as well as their levels are shown in Table 1. The levels for each parameters are represented by a (−) sign for the lower level, a (+) sign for the higher level, and by (0) for the base level.

TableCurve 3D (Jandel Scientific) software was applied for the multiple regression analysis. The expected form of the polynomial equation is as follows:

$$y = b_0 + b_1x_1 + b_2x_2 + b_{11}x_1^2 + b_{22}x_2^2 + b_{12}x_1x_2 \quad (1)$$

where y is the response, x are the factors, and b parameters denote the coefficients characterizing the main (b_1, b_2), quadratic (b_{11}, b_{22}), and interaction (b_{12}) effects.

RESULTS AND DISCUSSION

Figure 1 indicates the percent amount of the particles of optimal size (≤10 μm) as a function of the concentration of the hydrophobizing agent. The measured values of the effective particles as a function of the hydrophobizing agent formed a maximum curve. The profiles of the three curves are similar to each other, and are independent of the applied amount of surfactant. The highest percent values of the effective particles were attained when the aerosol was prepared without surfactant. In this case the hy-

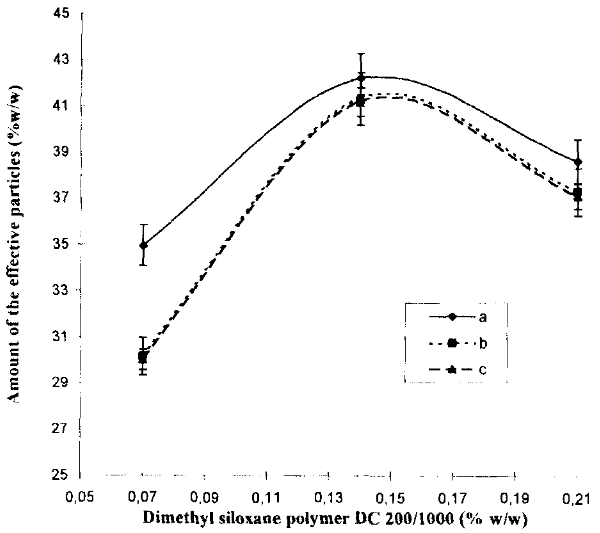

Figure 1. Percent amount of the effective particles (≤10 μm) as a function of the concentration of the hydrophobizing agent. (a) Without surfactant; (b) 0.1% w/w surfactant (oleil oleate); (c) 0.2% w/w surfactant (oleil oleate).

drophobic additives of various amounts were exclusively applied for the hydrophobization of the active compound, whereas in the presence of surfactant, the utilized additive hydrophobized all of the compounds of the system.

Figure 2 demonstrates the effect of the concentration of oleil oleate and dimethyl siloxane polymer on the quantity of the effective particles. The connection between the amount of the hydrophobizing agent, the surfactant concentration, and the quantity of the effective particles can be described by a second-order polynomial model. The resultant equation obtained after significance test at 95% confidence level, represents the effect of formulation factors (x_1, x_2) on the optimal particle size (smaller than 10 μm) measured by the particle size analyzer.

$$y = 11.41 - 51.53x_1 + 423.18x_2 + 109.5x_1^2 - 1402.04x_2^2 + 122.5x_1x_2 \quad (2)$$

The positive sign of the coefficients refers to an increasing effect, whereas the negative sign indicates a decreasing effect on the corresponding response. Table 2 summarizes the measured and the predicted values of the particles smaller than 10 μm diameter.

The more polar the solid material, the more unfavorable the liquid–surface interaction becomes; thus flocculation is increasingly favored (6). The increased flocculation of the polar active compound (sodium cromoglycate) resulted in a decrease in the proportion of the effective particle size, when the applied additive was only the surface-active anionic oleil oleate. The hydrophobizing agent and the surfactant added to the system modify interparticle forces and stabilize the suspension. Because of the increased charge stabilization or steric stabilization of solid particles (10), the proportion of the effective particles increases. The positive value of the interaction coefficient (b_{12} = 122.5) refers to the stabilizing effect of

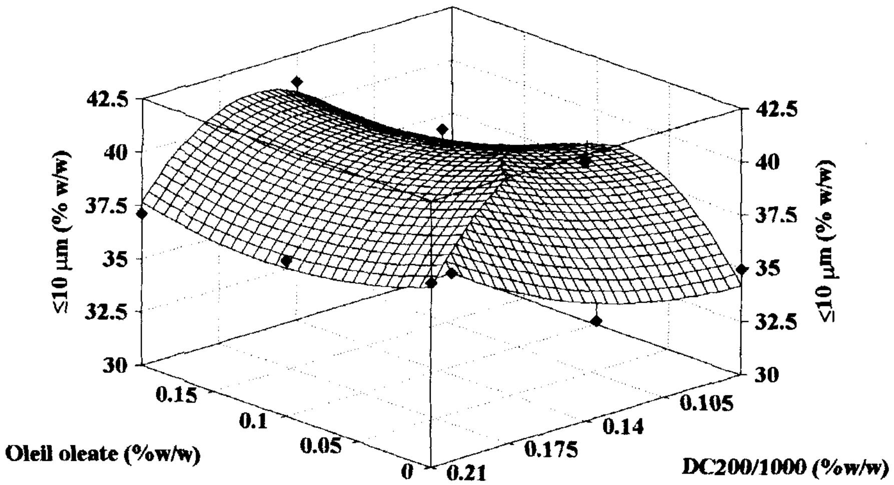

Figure 2. Effect of the hydrophilic surface-active ingredient and the hydrophobizing agent on the effective particle size.

Table 2

Randomized Matrix of the Two-Factor, Three-Level Face-Centered Central Composite Factorial Design (Average of Six Parallels)

	Controlled Factors		Response Parameter		
Trial	x_1	x_2	Measured	Predicted	±Residual (%)
1	+	0	41.17	40.68	1.19
2	−	−	34.94	34.16	2.22
3	0	−	30.14	30.96	2.73
4	−	+	38.64	38.45	0.49
5	0	0	41.31	40.83	1.15
6	+	−	30.00	29.95	0.16
7	0	+	37.31	36.96	0.93
8	+	+	37.13	37.67	1.45
9	−	0	42.21	43.18	2.29

the two interacting additives. As a result of this effect, the proportion of the effective particle size increases along with the positive quadratic effect (b_{11} = 109.5) of the surface-active ingredient.

The positive value (b_2 = 423.18) of the hydrophobizing agent coefficient (x_2) refers to the main effect of the agent, because the negative quadratic effect (b_{22} = −1402.04) of the same factor is not so dominant within the selected concentration range (Table 1). The higher the concentration of the hydrophobizing siloxane polymer, the smaller the proportion of the effective particle size. The negative value (b_1 = −51.53) of the polar surface-active ingredient (x_1) indicates the decreased amount of the particles of optimal particle size.

CONCLUSIONS

A nonlinear model was found to describe the effect of the amount of surfactant and that of the hydrophobizing agent on the quantity of the effective particle size.

For the stabilization of the examined suspension-type aerosols, it is more favorable to apply hydrophobic additive rather than conventional surfactant to obtain the therapeutically best composition.

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