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The Effect of Surfactant and Suspending Agent Concentration on the Effective Particle Size of Metered-dose Inhalers

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Abstract

The aim of this study was to examine the influence of the concentrations of surfactant and suspending agent on the quantity of effective particles (size < 10 μm) delivered by metered-dose inhalers.

A 2-factor, 3-level, face-centred central composite design was used to construct a second-order polynomial model which describes the effect of formulation factors (suspending agent, surface-active ingredient) on the therapeutically important characteristic (effective particle size) delivered by metered-dose inhalers. Oleic acid was selected as the surface-active ingredient, and the suspending agent was anhydrous alcohol. A non-linear model demonstrated with good correlation the effect of the amounts of surfactant and suspending agent on the quantity of particles of effective size.

The results obtained enable determination of the correct amount of surface-active ingredient and the optimum quantity of the suspending agent, thus enabling formulation of a therapeutically effective formulation.

The bioavailability of inhalation aerosols is determined in each single dose by the particle-size distribution and the effective particle-size range of the active compound. For optimum performance of metered-dose inhalers, the drug should be delivered in a uniform dose of the correct size-range to enable penetration of the lung. The suspended drug particles must be within the respirable range of 1–10 μm for the inhaler to be effective (Clarke et al 1993; Bower et al 1995).

A stable, well-dispersed suspension or an easily dispersible suspension is required if these criteria are to be met. The adhesion between the drug substance and the carrier excipient material must be balanced to guarantee, firstly, the transport of drug-carrier agglomerates out of the inhaler device into the upper respiratory tract, and, secondly, the separation of the drug particles, which must reach the lung, from the carrier particles, which are usually swallowed (Podczek et al 1996). Non-ionic surfactants such as lecithin, oleic acid or sorbitan tri- and monooleate are, therefore, normally added to stabilize the formulation (Bower et al 1996a, b).

The main objectives of this work were to study, both experimentally and with a mathematical model, the effect of the amounts of surface-active ingredient and suspending agent on the quantity of particles of effective size delivered.

Materials and Methods

Materials

Sodium cromoglycate was obtained from EGIS (batch number 538130591), oleic acid from Croda (batch number GN106.2), 1,1,1,2-tetrafluoroethane (HFC 134a) from ICI (batch number RB 95-002) and anhydrous alcohol (USP 23) from Interkémia.

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Preparation of the samples

The oleic acid and the active compound were dispersed in anhydrous alcohol by means of an Ultra Turrax mixer (Ika-Werk, type: T45, Janke & Kunkel) at 1400 rev min^{-1}. The homogeneous suspension was poured into an aluminium can (3M Health Care) with a 20-mm neck. The metering valve (Valois DF 30/50) was placed on the can which was then closed with a crimping machine (Pamasol, type: 2002). Finally, the cans were charged with the correct amount of propellant by means of a propellant-filling machine (Pamasol, type: 2011/7).

Methods

Particle-size analysis was performed with a Malvern Master Sizer X instrument (MSX 5 unit/mount, Serial No. 6361, Malvern Instruments GmbH, Germany). Five doses of the previously well-shaken sample were fired to waste and the sixth dose was discharged through the beam path of the MSX 5 analyser 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 ensured consistent identical recording of the results.

Statistical experimental design

A 2-factor, 3-level, face-centred central composite design (Franz et al 1988) was used to construct a second-order polynomial model describing the effect of formulation factors (suspending agent, surface-active ingredient) on the product characteristic (effective particle size). The two factors and their levels are shown in Table 1, where the levels for each parameter are represented by (−) for the lower level, by (+) for the higher level and by (0) for the base level. The randomized matrix of design is shown in Table 2.

TableCurve 3D (Jandel Scientific) software was used for multiple regression analysis. The expected form of the

Table 1. Experimental design with factors and their levels.

Levels	Amount of suspending agent (x_1) (% w/w)	Amount of surface-active ingredient (x_2) (% w/w)
Lower (−)	15	0
Base (0)	20	0·5
Higher (+)	25	1

Table 2. Randomized matrix of the 2-factor, 3-level, face-centred central composite factorial design (average of six parallels ± s.d.).

	Controlled factors		Response parameter
Trial	Amount of anhydrous alcohol (x_1) (% w/w)	Amount of oleic acid (x_2) (% w/w)	Quantity of particles ≤ 10 μm (y) (% w/w)
1	+	0	24·37 ± 0·63
2	−	−	17·02 ± 0·44
3	0	−	13·72 ± 0·36
4	−	+	42·57 ± 1·10
5	0	0	31·82 ± 0·83
6	+	−	10·92 ± 0·28
7	0	+	29·97 ± 0·77
8	+	+	17·87 ± 0·46
9	−	0	39·77 ± 1·03

polynomial equation was:

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

where y is the response, x_1 and x_2 are the factors, and b parameters denote the coefficients characterizing the main (b_1, b_2), the quadratic (b_{11}, b_{22}), and the interaction (b_{12}) effects.

Results and Discussion

Fig. 1 compares the cumulative frequency–distribution curves of the various compositions measured with the Malvern particle-size analyser. The proportion of therapeutically effective particles increased when the amount of the suspending agent was reduced.

Fig. 2 demonstrates the effect of the concentrations of oleic acid and anhydrous alcohol on the quantity of effective particles. The connection between the amount of the suspending 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 the significance test at 95% confidence level, represents the effect of formulation factors (x_1, x_2) on the quantity of effective particles (size < 10 μm) measured with the Malvern particle-size analyser.

$$y = 29{\cdot}92 - 1{\cdot}01x_1 + 93{\cdot}36x_2 + 0{\cdot}01x_1^2 - 39{\cdot}91x_2^2 - 1{\cdot}86x_1x_2 \quad (2)$$

Coefficients of positive sign are indicative of an increasing effect on the corresponding response whereas while a negative sign indicates a decreasing effect.

The greater the amount of the suspending agent (anhydrous alcohol) in the system, the smaller becomes the proportion of effective particles (Fig. 2). The negative value ($b_1 = -1{\cdot}01$) indicates the dominant main effect of the suspending agent (x_1), because the positive quadratic effect ($b_{11} = 0{\cdot}01$) of the same factor is negligible. The more polar the solid dispersed material, the more unfavourable the liquid–surface interaction, so flocculation is increasingly favoured (Bower et al 1996b). When more suspending agent was used, flocculation of the polar sodium cromoglycate resulted in an increase in particle size.

The positive value ($b_2 = 93{\cdot}36$) refers to the main effect of the surfactant coefficient (X_2), which is less dominant because of the negative quadratic effect ($b_{22} = -39{\cdot}91$) of the same factor. The addition of surfactant modifies inter-particle forces and stabilizes the suspension; this might be because of better charge stabilization or steric stabilization of the solid particles (Pugh et al 1983). Consequently, the proportion of effective particles increases. The negative value ($b_{12} = -1{\cdot}86$) of the interaction between the oleic acid and anhydrous alcohol reduces the quantity of particles of effective size.

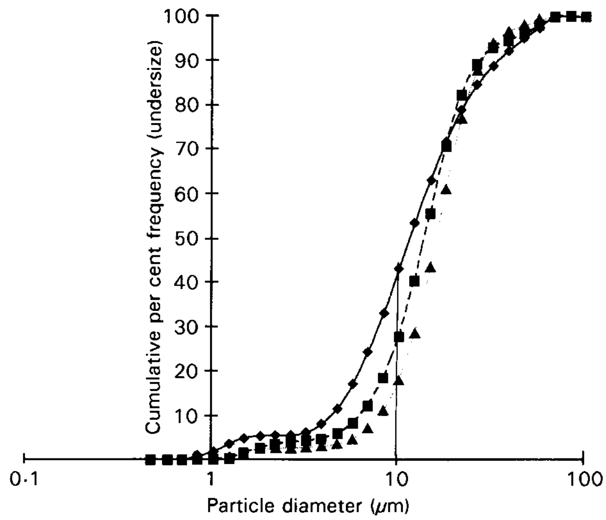

FIG. 1. Cumulative frequency–distribution curves of the various samples in the presence of 0·5% w/w oleic acid. Concentration of suspending agent: ◆ 15% w/w, ■ 20% w/w, ▲ 25% w/w.

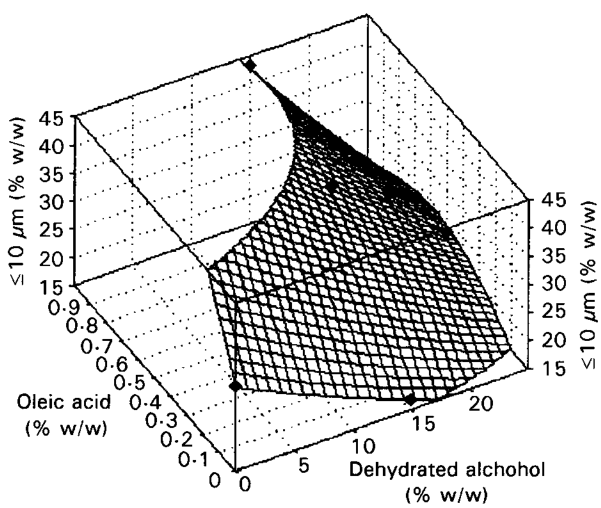

FIG. 2. Effect of the concentrations of the oleic acid and anhydrous alcohol on the quantity of effective particles delivered by metered-dose inhalers.

Conclusions

A non-linear model has been used to describe the effect of the amounts of surfactant and suspending agent on the quantity of particles of effective size delivered by metered-dose inhalers. On the basis of these results it is possible to find the therapeutically best composition by selecting the proper amount of surface-active ingredients and the optimum quantity of suspending agent.

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