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Development of budesonide suspensions for use in an HFA pressurized metered dose inhaler

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ABSTRACT: The aim of this study was to develop budesonide as a suspension-based pressurized-metered dose inhaler (pMDI) using hydrofluoroalkanes (HFAs) propellants (HFA 134a, HFA 227, and HFA mixture) and stabilizing agents (oleic acid and sorbitan trioleate). A factorial design method was applied to investigate the effects of two factors (vapour pressure of the propellant system and concentration of stabilizing agents) on formulation performances. Each factor was studied in three levels. Twenty four designed formulations of budesonide suspension-based pMDI were prepared. The results indicated that the vapour pressure of the propellant system was an important factor that affected the content of the active ingredient ($p < 0.05$). The formulations containing HFA 134a (high level vapour pressure) gave drug contents above the maximum limit ($> 120\%$), whereas the formulations containing HFA 227 (low level vapour pressure) gave low budesonide contents of approximately 50%. However, when a propellant mixture with intermediate vapour pressure was used, the budesonide contents were close to the acceptable range (80–120%). Consequently, the eight formulations containing the HFA mixture together with different types and concentrations of stabilizing agent were tested for their aerosol properties. The fine particle fraction measured by a twin-stage liquid impinger ranged between 32–38%. The mass median aerodynamic diameters obtained from the Andersen cascade impactor were approximately 3 μm for all formulations. No significant difference was found among those formulations. After 3 months of storage, the aerosol properties did not change, and good physical stability was achieved. The particulate budesonide was able to readily re-disperse in the HFA mixture and a homogeneous suspension could be maintained for up to 20 min.

KEYWORDS: inhalation, glucocorticosteroid, particle size distribution

INTRODUCTION

Budesonide is a synthetic glucocorticosteroid with mainly anti-inflammatory activity. Although it is rapidly and almost completely absorbed from the gastrointestinal tract, its bioavailability is low (about 10%) due to extensive first-pass metabolism in the liver. Furthermore, the metabolites produce less than 1% of the glucocorticoid activity when compared to the unchanged budesonide[1,2]. As with other glucocorticosteroids, long-term administration of systemic budesonide may cause many adverse effects such as hypothalamic-pituitary-adrenal suppression, growth retardation, and osteoporosis[3]. Administration of glucocorticosteroids by inhalation is more advantageous for the treatment of respiratory diseases. Consequently, inhalation of current medications is now the first-line therapy for persistent asthma[4–6]. Through inhalation, drugs are directly delivered to the target site including the airways and lung. Thus a high topical anti-inflammatory effect is achieved, while the adverse systemic side effects are reduced[4,7].

The pressurized-metered dose inhaler (pMDI) is the most widely used device for delivering a drug into the airway. It is well known as a safe, convenient, and reliable delivery system used by 80% of asthmatics worldwide[8,9]. The key components of the pMDI are the container, propellant, concentrated drug formulation, metering valve, and actuator. All play roles in the formation of the aerosol cloud and delivery efficiency[10,11]. If the performance is consistent and the pMDI delivers an accurate dose from the first until the last dose it will be beneficial to patients.

Chlorofluorocarbons (CFC) were previously the most common propellants used in pMDIs due to the fact that they are non-toxic, non-flammable, and have a large enough vapour pressure[10,11]. However, their production has been phased out under the Montreal protocol due to CFCs causing a depletion of ozone in the stratosphere[9,12]. Thus two new hydrofluo-

roalkanes (HFAs), tetrafluoroethane (HFA 134a) and heptafluoropropane (HFA 227), have become the alternative propellants for use with pharmaceutical aerosols delivered in pMDIs. They have also similar advantages to CFCs for use in pMDIs and they do not damage the ozone layer[9,11,13]. However, their physicochemical properties, such as vapour pressure, polarity, and density are significantly different from CFCs[11]. Consequently, re-formulation of pMDIs for use with these new propellants is required to produce equivalent efficacy and safety profiles to the previous CFC products. Re-formulations of pMDIs with the new propellant can be developed in either a solution or suspension system. However, the HFAs are poor solvents for many of the currently available anti-asthmatic drugs including budesonide[11]. Therefore, development of inhaled asthmatic drugs as suspension formulations is a promising avenue to explore. Moreover, it is expected that bad tastes of the drug are reduced when formulated as a suspension instead of as a solution[11,14]. However, the difficulty is to stabilize the dispersion system throughout the shelf life. An unstable suspension may result in unpredictable particle size and emitted dose[11]. Hence, additives such as stabilizing agents are required to solve this problem[14].

The aim of this study was to develop budesonide as a suspension-based pMDI with an HFA propellant (HFA 134a, HFA 227, or HFA mixture) and stabilizing agents (oleic acid and/or sorbitan trioleate) using a factorial design method. The effects of the vapour pressure of the propellant system and concentration of stabilizing agent on formulation performances were then investigated.

MATERIALS AND METHODS

Materials

Micronized budesonide, HFA 134a, HFA 227, and HFA mixture were gifts from AeroCare Co., Ltd., Thailand. The oleic acid was purchased from Panreac Química SAU, Spain. The sorbitan trioleate was obtained from Fluka, and the 99.9% dried ethanol was obtained from Lab-Scan Analytical Sciences, Thailand. Chemicals used in analytical process were purchased from local suppliers in Thailand. All chemicals were analytical grade and used as received.

Experimental design

A three level factorial design was applied to investigate the effects of vapour pressure of propellant system and concentration of stabilizing agent on the formulation performances. The three levels of vapour pressure were obtained from the different propellant systems which were HFA134a (572 kPa), HFA mixture (535 kPa), and HFA227 (390 kPa). Oleic acid or sorbitan trioleate was chosen as the stabilizing agents. Three levels of concentration of each were studied. Combinations of those two stabilizing agents were also investigated. A high level of oleic acid was combined with a low level of sorbitan trioleate, and a low level of oleic acid was combined with a high level of sorbitan trioleate. The matrix of independent variables according to the factorial design is shown in Table 1. For each formulation, the concentration of budesonide was equivalent to 100 µg/actuation. In addition, 1% w/w of dried ethanol was used to improve the solubility of the stabilizing agents in the HFA propellant.

Table 1 Matrix of independent variables for the factorial design.

Formulation	1st variable: stabilizing agent		2nd variable: propellant system
	Oleic acid	Sorbitan trioleate	Vapour pressure
F1	0	–	0, 1, 2
F2	1	–	0, 1, 2
F3	2	–	0, 1, 2
F4	–	0	0, 1, 2
F5	–	1	0, 1, 2
F6	–	2	0, 1, 2
F7	0	2	0, 1, 2
F8	2	0	0, 1, 2

Independent variable levels: low (0), intermediate (1), high (2) concentration in case of stabilizing agents and vapour pressure in case of propellant.

Preparation of the pMDIs

The pMDI was prepared by the pressure filling method. In brief, the micronized budesonide was dispersed in dried ethanol. The stabilizing agents were added and then mixed by Vortex-2-Genie (Scientific Industries, Inc., USA) to obtain the concentrated formulation. Each aliquot was pipetted into an aluminium canister. Then 50 µl metering valves were crimp-sealed onto the canisters and the canisters were then filled with propellant. Complete dispersion of the drug powder in the propellant system was warranted by sonicating the canisters for 60 s in an ultrasonic bath (Bandelin Sonorex, Germany).

Analysis of budesonide pressurized metered dose inhaler formulations

Budesonide was analysed by high performance liquid chromatography (HPLC). The HPLC system consisted of a Spectra System SCM 1000, a Spectra System Pump P2000, plus an auto-sampler, Spectra System AS 3000 equipped with a Spectra System

SN4000 and a Spectra System UV 1000 detector (Thermo Fisher Scientific, Inc., USA). The BDS Hypersil C18 column (150 × 4.6 mm id, 5 µm) (Thermo Scientific, UK) was used in this study. The mobile phase consisted of 25 mM phosphate buffer, pH 3.2 and acetonitrile in the ratio of 65:35 (v/v). The mobile phase was set at a flow rate of 1.5 ml/min at ambient temperature. The UV detector was operated at 240 nm. The injection volume was 50 µl.

Content of active ingredient delivered by actuation of the valve

The content of the active ingredient delivered by actuation of the valve was determined by discharging the pressurized container through the central hole of a stainless steel base plate [15] that was placed in a suitable vessel. The specified volume of methanol was added into the vessel. The inhaler was discharged in the inverted position under the surface of the solvent. The pressurized inhaler was shaken for 30 s prior to dose collection, and the first 2 doses were discharged to waste. Ten deliveries at the beginning (3–12), middle (76–85), and end (141–150) of the calculated number of doses were analysed for the amount of budesonide by HPLC. The result was calculated as the amount of active ingredient delivered from each actuation of the valve.

Assessment of fine particle fraction

The fine particle fraction (FPF) was assessed using a twin-stage liquid impinger (TSI), Apparatus A according to the British Pharmacopoeia [15]. Volumes of 7 ml and 30 ml of the mobile phase were introduced into the upper and lower impingement chambers, respectively. The pressurized container was shaken for 5 s, and the first 5 doses were discharged to waste. The pMDI was connected to the TSI using the actuator adapter. Five consecutive doses were discharged into the impinger at an operation flow rate of 60 ± 5 l/min. The drug deposited on the inner surface of the throat and neck was rinsed with the mobile phase into the upper impingement chamber, whereas the drug deposited in the inlet tube was rinsed into the lower impingement chamber. The amounts of budesonide collected in the upper and lower impingement chambers were analysed by HPLC. The FPF was calculated as the percentage of drug that reached the lower impingement chamber based on the emitted dose.

Assessment of aerodynamic particle size distribution

The measurement of the aerodynamic particle size distribution was performed on an eight-stage Andersen cascade impactor (ACI) given in the British Pharmacopoeia as Apparatus D [15]. The pressurized inhaler was shaken for 5 s and the first delivery was discharged to waste. The pMDI was connected to the metal inlet of the ACI using an adaptor. Air was drawn through the apparatus and the flow rate adjusted to 28.3 l/min (± 5%). Then, the inverted inhaler was discharged into the apparatus for 2 consecutive doses. A shaking time of 5 s was required between each delivery. The metal inlet and stages were washed with the mobile phase. Each fraction was adjusted to a specified volume and analysed for the amount of drug by HPLC. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were calculated according to the method described in Ref. 16.

Physical stability assessment

A physical stability assessment was performed after the formulations were stored for a short period (3 months, 25 °C or ambient conditions). The assessment of dose uniformity was used to predict the physical stability of the suspension system. The redispersibility of micronized budesonide in each propellant system was indicated by the number of inversions required to obtain a constant delivered dose. The sedimentation of the suspension was also investigated. The delivered doses were determined after the completed suspension was allowed to stand for 0, 5, 10, 15, and 20 min.

RESULTS AND DISCUSSION

Content of active ingredient delivered by actuation of the valve

The amounts of active ingredient delivered by actuation of the valve after 1 month of storage are shown in Fig. 1. The formulations containing HFA 134a gave a drug content over the maximum limit (> 120%). However, the content of active ingredient tended to decrease and was in the acceptable range (80–120%) [15] for the last ten doses. A good uniformity of delivered doses was obtained from the HFA 227 formulation, but those values were lower than those of the lower limit. The content of the active ingredient values at every interval of dosing was approximately 35–50%. In the case of formulations containing the HFA mixture, the contents of budesonide were close to the acceptable range. The ANOVA results revealed that the vapour pressure of the propellant system is an important factor that affects the content of the active ingredient. The propellant systems with three levels of vapour pressure significantly affected the content

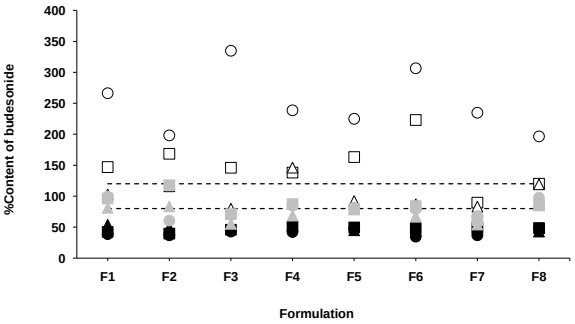

Fig. 1 Content of budesonide delivered by actuation of the valve of 24 designed formulations after 1 month storage. Dose collection was at the beginning, middle, and end of the total dose each represented as round, square, and triangle symbols, respectively, (open symbols for HFA 134a, black for HFA 227, and grey for HFA mixture). The dashed lines show the upper (120%) and lower limit (80%) of the drug content as stated in the British Pharmacopoeia, 2009.

of the active ingredient, while the formulations with different types and concentrations of stabilizing agent produced no significant difference to the content of budesonide ($p > 0.05$). As a consequence, the eight formulations containing the HFA mixture were chosen for testing the full aerosol properties since they gave the most favourable results.

Fine particle fraction

The results of the FPF of eight formulations containing propellant mixture are shown in Table 2. After 1 month of storage, all formulations exhibited FPF values in the range of 32–38%. The formulations with different types and concentrations of stabilizing agent gave no significant differences on the amount of drug deposited into the lower impingement chamber ($p > 0.05$). After 3 months of storage, the FPF of all formulations were not significantly different from values obtained after 1 month of storage ($p > 0.05$).

Aerodynamic particle size distribution

After 1 month of storage, formulations prepared with the HFA mixture were assessed for particle size distribution using the ACI. Drug formulations emitted from all budesonide pMDIs could reach to the lower stage of the ACI, but approximately 50% w/w of the drug that passed through the metal inlet part was deposited on stage 3 and 4. The MMAD results are shown in Table 3. It was observed that the MMAD were around 3 µm for all formulations after 1 month of storage, and the particle size distribution did not change for up to 3 months. In addition, the GSD values were higher than 2. It could be postulated that polydispersion was obtained. The results of ANOVA revealed that the oleic acid and sorbitan trioleate present at different concentrations gave a similar MMAD.

Table 2 Fine particle fraction (FPF) of different metered dose inhaler formulations containing propellant mixture (mean $\pm$ SD, $n = 3$).

Formulations	FPF (%)	
	1 month storage	3 months storage
F1	38.3 ± 8.9	34.8 ± 5.3
F2	36.9 ± 2.2	37.4 ± 1.7
F3	33.5 ± 5.1	32.3 ± 2.8
F4	33.7 ± 6.2	36.0 ± 1.6
F5	35.4 ± 4.6	37.5 ± 0.9
F6	32.3 ± 4.8	38.1 ± 3.0
F7	33.5 ± 7.7	39.3 ± 2.9
F8	33.7 ± 3.3	34.1 ± 0.4

Table 3 The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the metered dose inhaler formulations containing propellant mixture after 1 month and 3 months storage (mean $\pm$ SD, n=3).

Formulation	1 month storage		3 months storage	
	MMAD (µm)	GSD	MMAD (µm)	GSD
F1	3.04 ± 0.01	2.23	3.04 ± 0.01	2.24
F2	3.02 ± 0.01	2.26	3.04 ± 0.01	2.25
F3	3.01 ± 0.02	2.27	3.05 ± 0.01	2.25
F4	3.04 ± 0.01	2.24	3.06 ± 0.01	2.23
F5	3.03 ± 0.01	2.25	3.06 ± 0.01	2.23
F6	3.05 ± 0.02	2.24	3.07 ± 0.01	2.23
F7	3.07 ± 0.01	2.23	3.06 ± 0.01	2.24
F8	3.02 ± 0.01	2.27	3.04 ± 0.01	2.26

Physical stability assessment

The assessments of physical stability were carried out on some formulations chosen as a representative of each propellant system and stabilizing agent. The ability to re-disperse was represented as the amount of budesonide emitted from the pMDI formulations according to the number of inversions as exhibited in Fig. 2. After the first inversion, the formulations containing HFA 134a gave a high emitted dose over the designed range (80–120%), but a lower amount of budesonide was obtained as the number of inversions increased. For formulations containing HFA 227, a different phenomenon was observed. They gave a low emitted dose (by approximately 20%) at the first inversion, but the values tended to increase when the number of inversions increased. However, the emitted

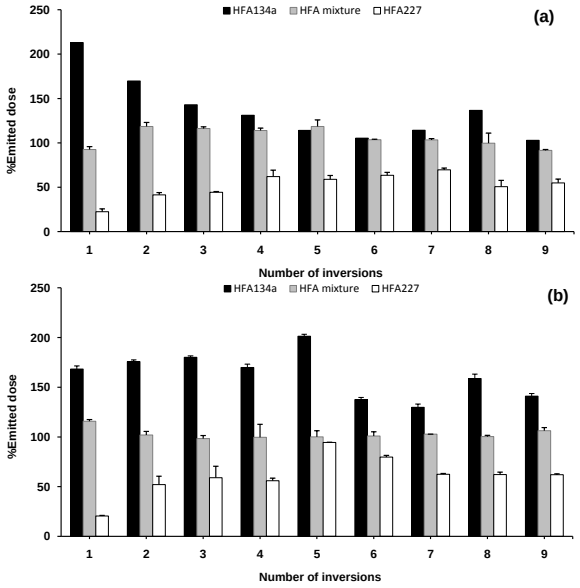

Fig. 2 Number of inversions and percentage emitted dose from metered dose inhaler containing (a) oleic acid and (b) sorbitan trioleate as a stabilizing agent in different propellant systems (mean $\pm$ SD, $n = 3$).

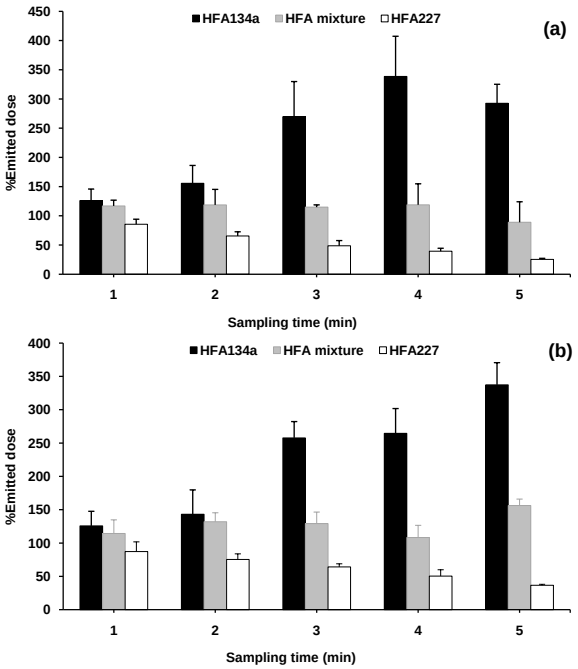

Fig. 3 Sedimentation of budesonide particles (sampling time) and percentage emitted dose from metered dose inhaler containing (a) oleic acid and (b) sorbitan trioleate as a stabilizing agent in different propellant systems (mean $\pm$ SD, $n = 3$).

doses were rather constant after inverting more than 5 times for both propellant systems. Unlike the pure HFA 134a and HFA 227, the formulations containing HFA mixture gave uniform emitted doses. The results reveal that the delivered dose was in the target range (80–120%) at the first inversion.

For testing sedimentation, the formulations showing complete dispersion were left to sediment under the gravity, and the doses were sampled at intervals over 20 min. Fig. 3 shows the sedimentation behaviour of particulate budesonide in each propellant system with the addition of either oleic acid or sorbitan trioleate. Formulations that contained HFA134a gave a high emitted dose of around 120% initially, but the doses increased to twice the target dose ($>$ 250%) after the formulations were left to sediment for 5 min. Lower emitted doses were obtained from the formulations containing the HFA mixture and HFA 227. The propellant mixture provided consistent emitted doses over the observed time, while the formulations containing HFA 227 gave emitted doses that were approximately 80% initially, and then tended to decrease when the sampling times increased.

Twenty-four designed formulations of budesonide suspension-based pMDI were assessed during this factorial experiment. The results indicated that the vapour pressure of the propellant system significantly affected the content of the active ingredient delivered by actuation of the valve ($p < 0.05$). When HFA 134a, which has the highest vapour pressure, was used as propellant, the budesonide contents were higher than the acceptable range (80–120%). The formulations used with HFA 227, which had the lowest vapour pressure, gave low budesonide contents of approximately 50%. However, the drug contents were close to the acceptable range when those two propellants were used as a mixture. It appears that the propellant mixture gave a suitable vapour pressure for generating the aerosol cloud and provided an appropriate density for suspended particles.

The optimal vapour pressure is expected to provide both a satisfactory MMAD and FPF. Among the three propellant systems, the highest vapour pressure (572 kPa) was obtained from HFA 134a. Although the high vapour pressure provided a fine aerosol due to rapid propellant evaporation, the velocity of the plume discharge resulted in a large amount of drug impacting initially in the oropharynx region[13]. In contrast, the HFA 227 exhibited the lowest vapour pressure (390 kPa) compared to the other two propellant systems. This may result in insufficient vapour pressure for generating a respirable fraction.

In a suspension-based formulation, the difference in density between liquefied propellant and suspended drug affects the content and uniformity of the delivered doses according to Stoke's law[11],

$$\nu = \frac{2gr^2(d_2 - d_1)}{9\eta},$$

where ν is the sedimentation rate of a spherical particle, g is acceleration due to gravity, r is particle radius, d_1 and d_2 are the densities of the continuous and dispersed phases, respectively, and the η is the viscosity of the continuous phase. Based on this equation, the particle size, density difference between drug particles and liquefied propellant, and viscosity of propellant are crucial factors for reducing sedimentation rates. In this study, the particle size of micronized budesonide and the viscosity of the propellant were constant. Hence the density should be a major factor influencing sedimentation rate. As clearly seen in the formulations containing HFA 134a as the single propellant, poor uniformity was observed (80–330%). This may result from the sedimentation of the micronized drug in the HFA 134a system since the density of the micronized budesonide (1.270 g/ml) was higher than the liquefied propellant (1.205 g/ml). The drug particles therefore settled under gravity. Hence a high amount of drug was loaded into the metering system. As a consequence, the drug content was higher than 80–120% at the beginning of the dosing, but the delivered doses became significantly less for the last 10 doses. For the propellant system of HFA 227, phase separation could also occur because the density of micronized budesonide (1.270 g/ml) was lower than that of the propellant (1.385 g/ml). Thus particulate budesonide tended to float to the surface of the liquefied propellant, resulting in a small amount of drug filling into the metering valve. However the HFA mixture used in this study provided a density of 1.254 g/ml that closely matched the density of the micronized budesonide (1.270 g/ml). Consequently, a stable suspension was obtained that resulted in a reproducible dosing, and an accurate delivered dose was repeatedly obtained.

Eight formulations containing the HFA mixture were chosen for full testing of the aerosol properties. All formulations exhibited a FPF that ranged between 32–38%, and the MMADs were around 3 μm which was suitable for delivery to the pulmonary area. All eight formulations containing different types and concentrations of stabilizing agent showed no significant differences in aerosol properties ($p > 0.05$). Thus the results suggest that both oleic acid and sorbitan trioleate are suitable for use as stabilizing agents in the suspension-base pMDI of budesonide, and only a small amount of stabilizing agent is required to stabilize the particles of the micronized drug in the liquefied propellant. The results also revealed that there was no synergistic effect between the oleic acid and sorbitan trioleate. Moreover, the developed formulations exhibited good stability since the aerosol properties, both FPF and MMAD, were maintained over a 3 month period of storage. This proves that the storage would not affect the performance of pMDI and the eventual clinical outcome.

Further assessments of physical stability indicated that particulate budesonide could re-disperse in the three liquefied propellants used in this study. Uniform delivered doses were achieved after 5 inversions when micronized budesonide was suspended in HFA 134a and HFA 227, whereas the HFA mixture gave an accurate delivered dose at the first inversion and uniformity was retained during further inversions. Thus we can postulate that the budesonide particles were easy to redisperse in the HFA mixture.

CONCLUSIONS

The HFA mixture was a suitable propellant for use in a budesonide suspension-based pMDI. When the vapour pressure and density of propellant matched the density of the drug particles, the formulation of pMDI provided satisfactory aerosol properties and physical stability.

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