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Metered-dose inhaler formulation of fluticasone-17-propionate micronized with supercritical carbon dioxide using the alternative propellant HFA-227

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Abstract

The commonly used propellants from the chlorofluorocarbon (CFC) type are known to deplete the ozone layer so that replacement by alternative propellants is required. The aim of this study was to show the feasibility to reformulate fluticasone-17-propionate, a very promising anti-inflammatory drug, using the propellant heptafluoropropane (HFA-227). The glucocorticoid was micronized by a new technique using supercritical carbon dioxide (aerosol solvent extraction system, ASES) resulting in very fine particles. Metered-dose inhaler formulations were performed using a pressure filling technique. ASES products showed a very narrow particle size distribution with slightly different crystal properties. These products were compared to metered-dose inhaler formulations with jet milled drug, the marketed Flutide™ MDI and the Flutide™ Diskus™ powder inhaler. The fine particle fractions, determined with a twin stage impinger, of CFC-free formulations with one ASES product were equivalent to the CFC-formulation Flutide™ both having a fine particle fraction of roughly 60%. A variation of actuator orifice diameter even increased the fraction of drug particles $< 6.4\ \mu$m. The study proved the feasibility of reformulating fluticasone propionate with the alternative propellant HFA-227. The processing of steroids using supercritical carbon dioxide proved to be a useful technique for the micronization and surface coating with a surfactant in one process step. © 1998 Published by Elsevier Science B.V. All rights reserved.

Keywords: Aerosol formulation; Fine particle fraction; Twin stage impinger; CFC-free; Fluticasone-17-propionate; ASES; HFA-227

1. Introduction

The therapy of lung diseases using aerosolized drugs shows certain advantages over the oral application of actives as drug dose and systemic and local side effects can be minimized (Aerosol Con-

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Table 1
Formulation parameters of all investigated fluticasone suspension MDIs (g)

Formulation	A	B	C	D	E	F	G
Fluticasone, jet-milled	0.018	—	0.018	—	0.018	—	—
Fluticasone, ASES	—	0.018	—	0.018	—	0.018	—
Pluronic L 92	0.036	0.036	—	—	—	—	—
Glycerintriacetate	—	—	0.036	0.036	—	—	—
Glycerintrioctanoate	—	—	—	—	0.036	0.036	—
Fluticasone/lecithin–ASES	—	—	—	—	—	—	0.020
Propellant R 227	ad 10.0	ad 10.0	ad 10.0	ad 10.0	ad 10.0	ad 10.0	ad 10.0

sensus Statement, 1991). Beside the nebulization of aqueous solutions and suspensions with ultrasonic or pneumatic nebulizers and the dispersion of drug as dry powder formulation (Matthys, 1990) the metered-dose inhaler (MDI) is the most utilized device in the treatment of asthma (Boyd, 1995). MDIs are pressure packed systems containing a liquefied propellant including the drug dissolved or suspended with help of certain additives, e.g. surfactants (Hickey and Evans, 1996). As the commonly used propellants from the chlorofluorocarbon (CFC) type are well known to deplete the stratospheric ozone (Molina and Rowland, 1974), reformulation efforts with non ozone depleting propellants were undertaken (Jenkins, 1995; Li and Schultz, 1996; Elvecrog, 1997). Up to now, only one CFC-product containing salbutamol sulphate has been launched on the market (Tansey, 1995). As glucocorticoids were attested to have a high value in the early treatment of asthma (Barnes, 1995) it is of value to develop CFC-free formulations with these anti-inflammatory drugs. First attempts have been reported with beclomethasone-17,21-dipropionate (BDP) so that the first marketed product can be expected in mid 1997 (Woodcock, 1997). A more promising glucocorticoid than BDP is fluticasone-17-propionate (FP) as it shows a high receptor activity (Würthwein et al., 1992) and a first pass effect of nearly 98%. Hence, side effects caused from swallowed drug are expected to be minimized (Ventresca et al., 1994). The purpose of this study was to develop CFC-free formulations using FP and the propellant heptafluoropropane, HFA-227. As previous studies showed only very poor solvency of the commonly used surfactants oleic acid, sorbitane trioleate and lecithin in the hydrofluorocarbon propellants (Byron et al., 1994) additives with differing chemical structure were used for drug dispersion and valve lubrication.

Additionally, a new micronization technique using the aerosol solvent extraction system, ASES (Müller and Fischer, 1989) was used as alternative to the jet milling. This may be of advantage as jet milled drugs are often electrically charged and show a high agglomeration tendency (Gallagher-Wetmore et al., 1994). Furthermore the micronization and a coating of drug with a surfactant is possible in a one process step in order to realize a better dispersibility of the active in the propellant (Steckel et al., 1997). The ASES process is one of the valid techniques for the precipitation of drugs in supercritical carbon dioxide. The RESS technique (rapid expansion from supercritical solutions) is a similar process which can be applied for drugs being soluble in the supercritical gas phase: this solution is then rapidly expanded to subcritical conditions and the drug precipitates (Tom and Debenedetti, 1991; Phillips and Stella, 1993). Another micronization process using supercritical carbon dioxide is the GAS (gas anti-solvent) recrystallization which is similar to the ASES process (Gallagher-Wetmore et al., 1994).

The resulting fluticasone microparticles from the ASES process were characterized with regard to their physical properties such as particle size, crystallinity and morphology. Twin impinger experiments with MDI formulations should give information about the aerodynamic behaviour of aerosol droplets. The dependence of surfactant

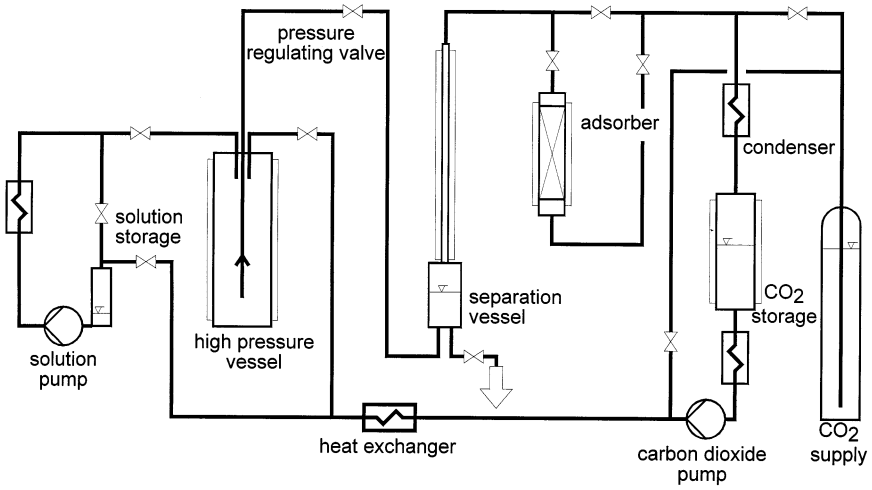

Fig. 1. Scheme of the ASES process.

Table 2
In vitro deposition of jet milled and ASES processed fluticasone MDIs formulated with different additives (% of total emitted dose[a])

Additive	Glycerintriacetate		Pluronic L 92		Glycerintrioctanoate	
	ASES	Micronized	ASES	Micronized	ASES	Micronized
Mouthpiece	5.15 (0.37)	5.38 (0.50)	6.73 (1.15)	5.15 (1.29)	5.02 (0.18)	3.94 (0.34)
Glass inlet	59.55 (4.07)	47.58 (0.21)	65.50 (0.82)	43.57 (4.40)	57.86 (0.64)	60.21 (1.70)
Upper impingement	8.34 (1.20)	7.13 (0.20)	4.55 (0.13)	4.40 (1.31)	9.68 (0.27)	8.40 (0.36)
Lower impingement	26.93 (2.49)	39.92 (0.26)	23.22 (0.20)	46.89 (1.79)	27.44 (0.55)	27.45 (1.72)
Total emitted dose (μg)	134.4 (6.0)	115.3 (2.5)	117.5 (4.0)	130.7 (4.1)	130.8 (5.6)	130.0 (15.0)
Approx. label claim (μg)	125	125	125	125	125	125

[a] Mean value (S.D.), $n = 3$.

type, micronization technique and actuator design was investigated.

2. Materials and methods

2.1. Microparticle production

The microparticle production is illustrated in Fig. 1. A solution of FP (with the optional addition of 5% lecithin) in dichloromethane was sprayed by means of a diaphragm pump (solution pump) through a nozzle into the high pressure vessel filled with supercritical carbon dioxide using another diaphragm pump (CO_2 pump). The organic solvent is soluble in the supercritical gas phase and will be extracted while the insoluble drug precipitates. The particle formation at the adjusted extraction conditions ($T = 40$°C and $p = 8.5$ MPa) can be described as a precipitation and not as a spray drying process (Dixon et al., 1993; Steckel et al., 1997). The experiments were carried out with a steroid concentration of 1% by weight and a pump rate of 63 ml/min. A nozzle (Schlick, Coburg, Germany) with a diameter of 0.3 mm and a spraying angle of 30° was applied.

The microparticles were dried by keeping them in the supercritical carbon dioxide for a total production time of 3 h. The residual solvent con-

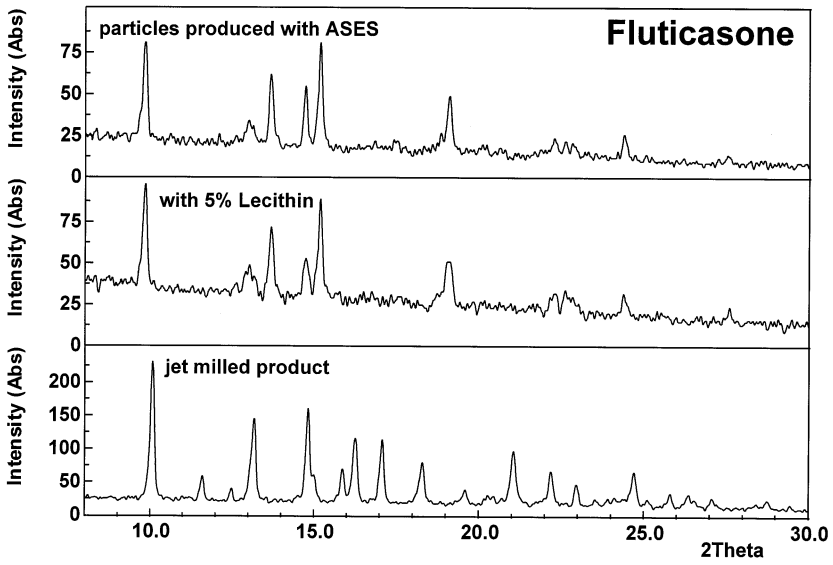

Fig. 2. X-ray patterns of FP.

tent was found to be less than 250 ppm (Steckel et al., 1997).

2.2. Sample preparation

The micronized FP was dispersed in the liquid surfactant using a pestle and a mortar. The resulting suspension was weighed into glass vials, bought from Glashüttenwerk (Kipfenberg, Germany). Afterwards a 50 μl valve (Seaquist, Dortmund, Germany) was crimped onto the glass bottle and the liquid propellant HFA-227 (Solvay, Hannover, Germany) was added through the nozzle. The last two steps were performed using a Pamasol P 2016 aerosol filling station (Pamasol, Pfäffikon, Switzerland). A 60 s period of ultrasonication in a Sonorex RK 514 transistor (Bandelin, Berlin, Germany) followed. The different actuators supplied by Seaquist (Dortmund, Germany) were connected to the MDI in a last step. In the case of the surface coated ASES product the FP was directly weighed into the glass bottles, crimped and, after adding the propellant, sonicated for 60 s, too. Table 1 gives information about the quantitative composition of all metered dose inhaler preparations.

2.3. Aerodynamic particle size analysis

A twin stage impinger (Apparatus A) (British Pharmacopeia, 1993) was used for the determination of in vitro fine particle fraction (particles < 6.4 μm) at a continuous flow of 60 l/min. For each determination 7 ml of solvent (methanol 75%) were placed in stage 1 and 30 ml in stage 2. The metered-dose inhalers were attached to the glass inlet using a rubber gasket and ten doses were released into the impinger. Each part of the impinger was rinsed with solvent, the washing solutions were diluted to volume and analyzed by HPLC. The aerosol fraction collected in the second impinger stage is equivalent to the particle fraction which is smaller than 6.4 μm and is termed 'fine particle fraction'.

For each formulation three determinations were performed.

2.4. HPLC assay

The HPLC system consisted of a Gynkotek High Precision Pump Model 300 (Gynkotek, Munich, Germany), a Kontron HPLC Autosampler 360 (Kontron, Milano, Italy), a Shimadzu UV spectrophotometric detector, a Shimadzu Chro-

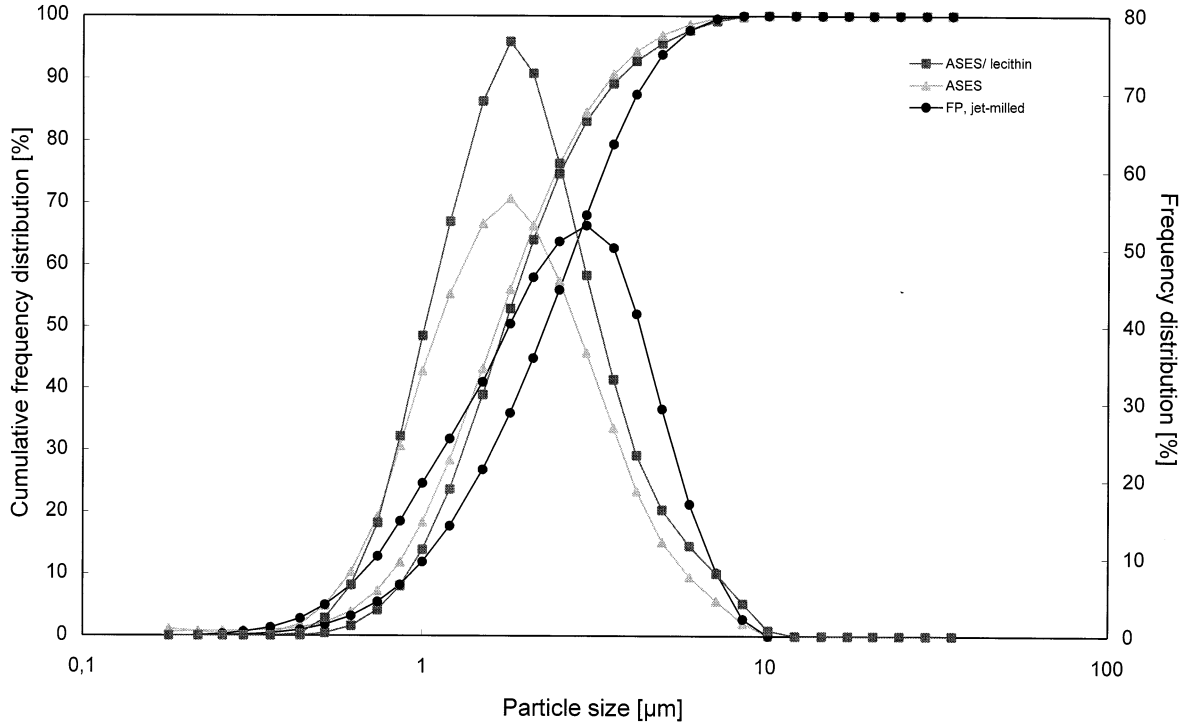

Fig. 3. Volume particle size distributions of jet milled and ASES processed FP.

matopak C-R 3A Integrator (Shimadzu, Kyoto, Japan) and a LiChrospher 100 RP-18 column (4.0 × 125 mm) obtained from Merck (Darmstadt, Germany). Samples of 100 μl were injected. The mobile phase was an acetonitrile/water mixture (60:40). Flow rate was 1.2 ml/min resulting in a pressure of about 7.5 MPa. FP was detected at a wavelength of 237 nm. The amount of drug was calculated using an external standard.

2.5. Reagents

FP was supplied from GlaxoWellcome, Bad Oldesloe, Germany (batch WE 0971971). Acetonitrile and methanol were HPLC grade and obtained from Merck, Darmstadt, Germany. Water was purified by double distillation. The excipients used for the suspension formulations were glycerintriacetate and glycerintrioctanoate (both from Hüls, Marl, Germany) and Pluronic L 92 (BASF, Ludwigshafen, Germany). Lecithin was supplied as Lipoid E 80-3 from Lipoid (Ludwigshafen, Germany).

2.6. Particle morphology

The particle morphology was performed by SEM. Photographs were taken by a Philips XL 20 (Philips, Eindhoven, Netherlands). The particles were fixed on a mutual conductive adhesive tape (Leittabs, Marburg, Germany) on an aluminium sample disk. These samples were sputtered with gold for 3 min choosing a current of 50 mA under argon atmosphere at 0.05 Pa using a Sputter Coater SCD 005 (Balzas, Balzas, Liechtenstein).

2.7. Volume particle size distribution

The volume particle size distribution of the micronized products was determined using a laser diffractometer (HELOS, Sympatec, Clausthal-Zellerfeld, Germany). The particles were suspended in an aqueous solution of polyoxyethylene sorbitane monooleate (0.01% per weight) and analyzed with a 20 mm lens in a suspension cell.

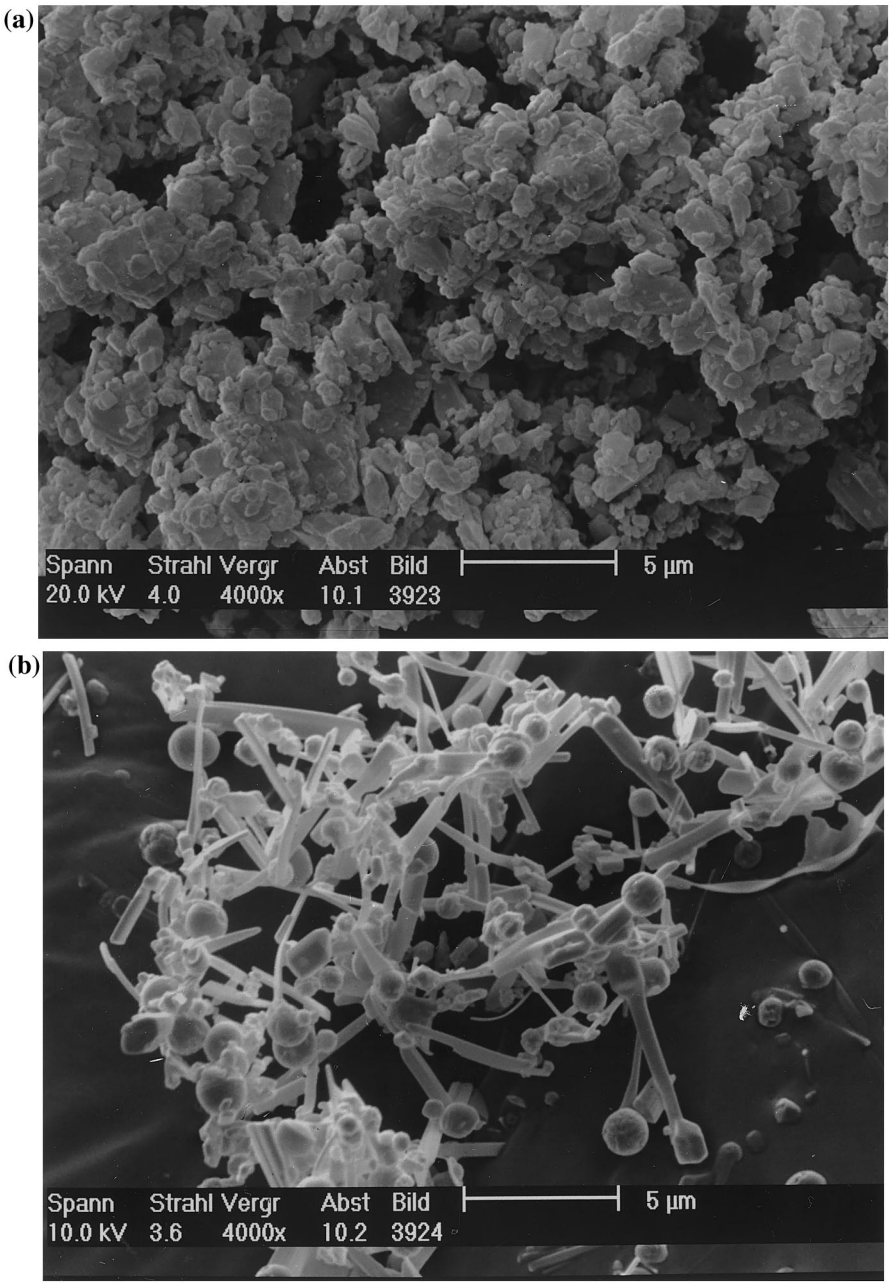

Fig. 4. SEM pictures of (a) jet milled, (b) ASES processed FP without and (c) ASES processed FP with addition of 5% lecithin.

2.8. X-ray powder diffraction

To determine the crystallinity patterns of the micronized steroid batches an X-ray powder diffraction system (Stoe and Cie, Darmstadt, Germany) with a rotating anode was used. The measuring unit consists of a rotating anode in transmission technique and with the following specifications: Cu $K\alpha_1$ radiation, graphite monochromator, voltage: 40 kV, current: 200 mA,

(c)

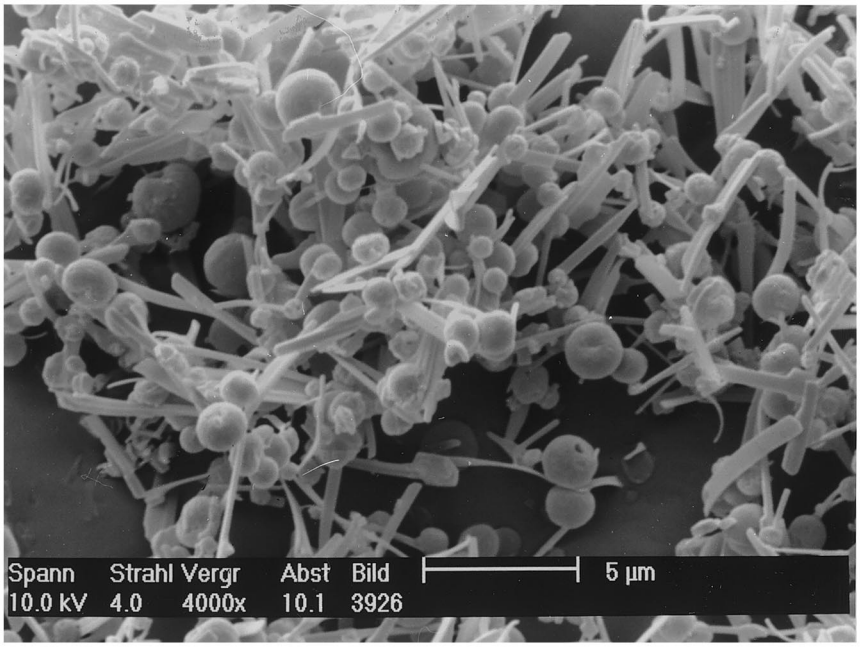

Fig. 4. (*Continued*)

position scanning detector (PSC), scanning rate of 10 s/2θ over a range of 5–50° 2θ.

Table 3
In vitro deposition in dependence on actuator orifice diameter (% of total emitted dose[a])

Actuator tradename	IN 3/GP 3	IN 3/GP 5	KN 1
Orifice diameter (mm)	0.3	0.5	0.7
Mouthpiece	8.61 (0.53)	7.63 (2.10)	5.72 (1.59)
Glass inlet	10.94 (1.17)	19.99 (1.37)	24.93 (2.57)
Upper impingement	3.59 (0.88)	6.35 (0.89)	8.01 (0.27)
Lower impingement	76.86 (0.82)	66.1 (2.56)	61.4 (4.43)
Total emitted dose (μg)	113.5 (1.9)	113.7 (7.2)	114.4 (5.5)
Approx. label claim (μg)	125	125	125

[a] Mean value (S.D.), $n = 3$.

3. Results and discussion

HPLC studies directly after the processing with supercritical carbon dioxide showed no chemical decomposition of FP (Steckel et al., 1997).

The X-ray analysis of FP delivers different patterns before and after the ASES process: new peaks occurred in the diffractogram of ASES-FP while peaks from the micronized drug disappeared. Furthermore the peak intensity of ASES products was distinctly lower (Fig. 2). The authors suppose of having produced a pseudo-polymorphic modification of FP with inclusion of dichloromethane but the described effects may also originate from the different micronization techniques or the different particle size distributions (Beyer and Maasz, 1987).

The laser diffraction measurement of FP showed a smaller median particle size for both ASES processed (X50 = 1.7 μm) than for the jet milled product which had a median diameter of 2.28 μm (Fig. 3).

It is the more astonishing that the ASES product with a smaller median diameter resulted

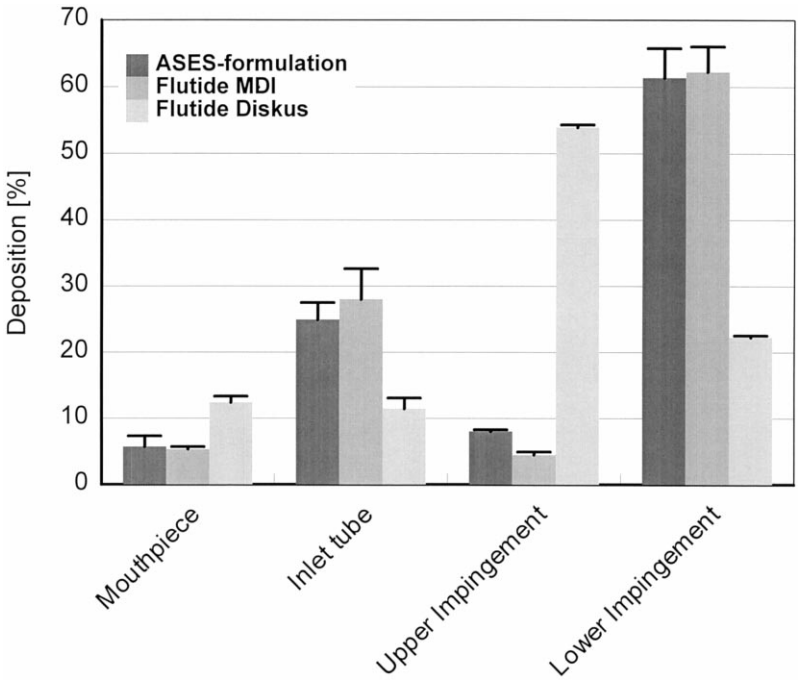

Fig. 5. In vitro deposition of Flutide™ MDI vs Flutide™ Diskus™ vs non-CFC formulation with lecithin coated FP.

in lower fine particle fractions (Table 2). The deposition data showed that nearly the same amount of drug remained in the mouthpiece (about 5%). Very good in vitro fine particle fractions were observed for the formulations A and C which both consisted of the jet milled FP and Pluronic L 92 respectively glycerintriacetate. The HFA formulations with the ASES products resulted in distinctly lower fine particle fractions in vitro. Formulations with the additive glycerintrioctanoate showed nearly the same in vitro deposition behaviour for the ASES and the jet milled product (Table 2). A possible explanation may be the completely different particle morphology of the ASES product as shown in the SEM photographs (Fig. 4a–c). The pure ASES product appeared in a non-homogenous habit and exhibits spherical particles beside small 'ribbons' whereas the jet milled drug showed angular particles of very variable size. By adding a surfactant to the ASES product to perform the raw dispersion in the mortar it is quite possible that the 'ribbons' stick together with their longer side leading to agglomerates which cannot be redispersed by the evaporating propellant.

If an ASES product which is coated with 5% lecithin is dispersed in the liquid propellant (without the addition of any further additive) the fine particle fraction increases up to 61% with the standard actuator (Table 3 and Fig. 5). A comparison of the in vitro deposition data of the latter HFA formulation with the marketed CFC product demonstrated their equivalence. The dry powder formulation (FP blended with lactose and aerosolized via the Diskus™) only gave a fine particle fraction of about 25% using the standard flow rate of 60 l/min. The very high deposition of Diskus™ FP in the upper stage of the impinger is to be interpreted as follows: dry powder particles showed a lower tendency to impact on the glass surface of the inlet throat (as opposed to the MDI which released more sticky particles). These dry particles were then collected on the liquid surface of the first impinger stage.

In a last study different actuators were used with formulation G (surfactant coated FP) in order to improve the fine particle fraction. Table 3 shows that decreasing the orifice diameter of the actuator

tube led to an increase in fine particle fraction. This is a confirmation that the aerosol cloud and droplet size of suspension formulated MDIs is highly dependent on the jet orifice diameter, too, and that it is not only an effect which can be observed with solution formulations (Warren and Farr, 1995). On the other hand the amount of drug remaining within the mouthpiece slightly increases (Table 3) due to the smaller actuator outlet.

In summary, a very high fine particle fraction was achieved with the propellant HFA-227. Similar high amounts of fine particles were observed with solution formulated MDIs as reported from Woodcock (1997). Possibly the metered drug dose has to be adjusted with reformulated HFA-MDIs having a fine particle fraction of more than 50%.

4. Conclusions

The study proved the feasibility to formulate FP with the alternative propellant HFA-227. Obviously some HFA-227 propellant formulations had advantages with regard to the emitted aerosol cloud and in vitro fine particle fraction. Reformulation with other anti-asthmatic drugs which are established in the therapy of lung diseases seems possible within the next three years. The ASES process proved to be a useful micronization technique leading to particles with a regular shape. A surfactant coating within the same process was possible.

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