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Research paper

Metered-dose inhaler formulations with beclomethasone-17,21-dipropionate using the ozone friendly propellant R 134a

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Abstract

Metered-dose inhalers (MDI) are the most widely prescribed devices in the treatment of lung diseases but the continued use of chlorofluorocarbons (CFC) as propellants has made them unpopular due to their influence on the stratospheric ozone layer. The purpose of this study was to show possibilities of formulating beclomethasone-17,21-dipropionate (BDP) with the alternative propellant R 134a as a solution or as a suspension-type metered-dose inhaler. Influencing factors such as surfactant concentration, cosolvent content and actuator tube design were investigated. Metered-dose inhaler formulations were manufactured using a pressure filling technique. The resulting formulations were characterized with regard to their emitted fine particle fraction using the two-stage impinger, BP 93. Fine particle fraction was found to be independent on the surfactant concentration but highly dependant on the cosolvent content and the actuator tube design. In vitro fine particle fractions of 50% were obtained with solution phase MDIs. Formulating BDP as a suspension resulted in unstable dispersions in most cases because of the partial solubility of the drug in the liquified propellant. Stable suspension formulations gave an in vitro fine particle fraction of about 30%. A comparison with established marketed BDP suspension formulations which were found to emit a fine particle fraction in the range 10–50% showed the equivalence of the new CFC-free formulations.

Keywords: Aerosol formulation; Beclomethasone dipropionate; CFC-free; Fine particle fraction; Metered-dose inhaler; Two-stage impinger

1. Introduction

The delivery of drugs to the lung is an excellent alternative to their peroral application, because the dose and the incidence of local and systemic side effects can be reduced [1]. Aerosol generation can be achieved using three different principles: the aerosolization of aqueous drug solutions or suspensions with ultrasonic or pneumatic nebulizers, the dispersion of a dry powder formulation or the atomization of micronized drug using a metered-dose inhaler (MDI) [2,3]. Most marketed MDIs are suspension-formulated MDIs containing the drug dispersed with help of a surfactant in the liquid propellant. Solution phase MDIs with CFC-free propellants usually were not performed due to the insolubility of drugs in the liquefied propellants. The commonly used propellants are chlorofluorocarbons (CFC) which are known to destroy the stratospheric ozone layer [4]. Different international and national agreements, such as the Montreal protocol, claimed to stop CFC production and to phase out their use, except for essential medical aerosols, such as those used in the treatment of asthma and other lung diseases [5,6]. The necessity of CFC replacement seems evident and two different types of propellants were discussed in the past: the flammable hydrocarbons such as dimethylether, propane and isobutane were rejected due to the lack of toxicological data [7,8], whereas the chlorine-free hydrofluorocarbons (HFC) R 134a, tetrafluoroethane, and R

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Table 1

Composition of the BDP metered-dose inhalers formulated as solutions (g)

Formulation	A	B	C	D	E	F	G
BDP	0.0163	0.0163	0.0163	0.0163	0.0163	0.0163	0.0163
Oleic acid	0.0082	0.0163	0.0326	0.0815	0.1630	0.0163	0.0163
Ethanol	0.50	0.50	0.50	0.50	0.50	0.20	1.00
R 134a	ad 10.0	ad 10.0	ad 10.0	ad 10.0	ad 10.0	ad 10.0	ad 10.0

227, heptafluoropropane, were found to have the same non-toxic properties as the CFCs (IPACT I or IPACT II) [9].

The challenge faced on going from CFC to CFC-free raises different problems because the commonly used surfactants such as lecithin, oleic acid and sorbitane trioleate only show poor solubility in the new propellants. The dissolved surfactant is the prerequisite for its migration into the interface of solid drug to liquid propellant [10] and with it for a suitable dispersion of the solid. As MDIs are easy to handle and well accepted by the patients, the request for metered-dose inhalers is still present [11]. Different studies have discussed the possible application of tetrafluoroethane, R 134a, in MDIs [12–15] so that the use of this propellant seems unobjectionable. Recently, three MDIs with R 134a were introduced into the market: the salbutamol containing Airomir™ from 3M Medica, Sultanol™ N with salbutamol and Flutide™ N with fluticasone propionate (Glaxo Wellcome). The latter two formulations were registered in Germany at first.

The aim of this study was to investigate the feasibility of MDI formulation with R 134a and to characterize MDIs with regard to their fine particle fraction. The influence of surfactant concentration, cosolvent content and actuator tube design on in vitro deposition was investigated. Chemical stability of both solution and suspension MDIs was neglected as this was the subject of several earlier studies [16–18].

2. Materials and methods

2.1. Sample preparation

Micronized BDP was directly weighed into pressure-resistant glass vials, bought from Glashüttenwerk, Kipfenberg, Germany and dissolved in absolute ethanol (>99.8% purity). Afterwards a 50 μl valve (Seaquist Perfect Dispensing, Dortmund, Division Valois Germany) was crimped onto the glass bottle. The liquified propellant R 134a (Solvay, Hannover, Germany) was then added under pressure through the valve. The last two steps were performed using a Pamasol P 2016 aerosol filling station (Pamasol, Pfäffikon, Switzerland). Table 1 gives information about the formulation parameters of solution-phase MDIs.

In the case of the suspension-type MDIs, the micronized BDP (0.0163 mg/vial) was dispersed in the liquid surfactant (1: 0.0163 mg/vial; 2: 0.0326 mg/vial) using a pestle and a mortar. The resulting suspension was weighed into glass vials, crimped, and liquid propellant added through the nozzle. If a cosolvent was additionally used, an amount of 0.5 g (5%) of *n*-hexane or *n*-pentane was mixed with the above mentioned suspension before crimping. Ultrasonication was performed for 60 s using a Sonorex RK 514 transistor (Bandelin Electronic KG, Berlin, Germany).

Different actuators were used (supplied by Seaquist Perfect Dispensing, Dortmund, Division Valois Germany) and are summarized in Table 2. Fig. 1 presents a schematic sketch of the actuators used: the very simple constructed actuator KN 1 only has an orifice of 3 mm length and releases the metered propellant volume directly into the environment. The actuators of the IN 3 and IN 4 series additionally include a 'swirl nozzle' (special jet). The delivered liquid propellant evaporates and aerosol droplets get a spin while penetrating through the nozzle. The actuators of the IN 4 series include a prolonged mouthpiece with a mouthpiece length of 8 cm.

2.2. Particle size analysis

A two-stage impinger (TSI) (Apparatus A, BP 93) was used for the determination of in vitro fine particle fraction (particles < 6.4 μm) at a continuous flow of 60 l/min [19]. For each determination, 7 ml of solvent (methanol 75%, v/v) 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 10 doses as proposed in the pharmacopoeia were

Table 2

List of actuators used

Actuator[a]	KN 1	IN 3/GP 3	IN 3/GP 4	IN 3/GP 5	IN 4/GP 4	IN 4/GPP 0.6
Special jet	No	Yes	Yes	Yes	Yes	Yes
Orifice ∅ (mm)	0.7	0.3	0.4	0.5	0.4	0.6
Mouthpiece	Normal	Normal	Normal	Normal	Prolonged	Prolonged

[a]Labelled by Seaquist Perfect Dispensing GmbH.

released into the impinger. Each part of the impinger was rinsed with solvent, the washing solutions were diluted to volume and analyzed by high-performance liquid chromatography (HPLC). For each formulation, three determinations were performed. The amount of drug recovered in the second stage of the impinger is equivalent to the fraction of particles under 6.4 μm and is termed 'fine particle fraction' or 'in vitro respirable fraction'.

2.3. Physical stability of suspension formulations

All suspension formulations produced were subject to an optical stability test. The test was performed visually to exclude those formulations which show drug agglomeration, adsorption of ingredients onto the container walls or crystal growth. With this simple test, most of the manifest incompatibilities were discovered directly after production of the MDIs.

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 Instruments, Milan, Italy), a Shimadzu UV spectrophotometric detector, a Shimadzu Chromatopak 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). The flow rate was 1.2 ml/min, resulting in a pressure of about 7.5 MPa. Beclomethasone dipropionate was detected at a wavelength of 237 nm. The amount of drug was calculated using an external standard of beclomethasone dipropionate (Sicor, Italy, batch no. 4888/M1).

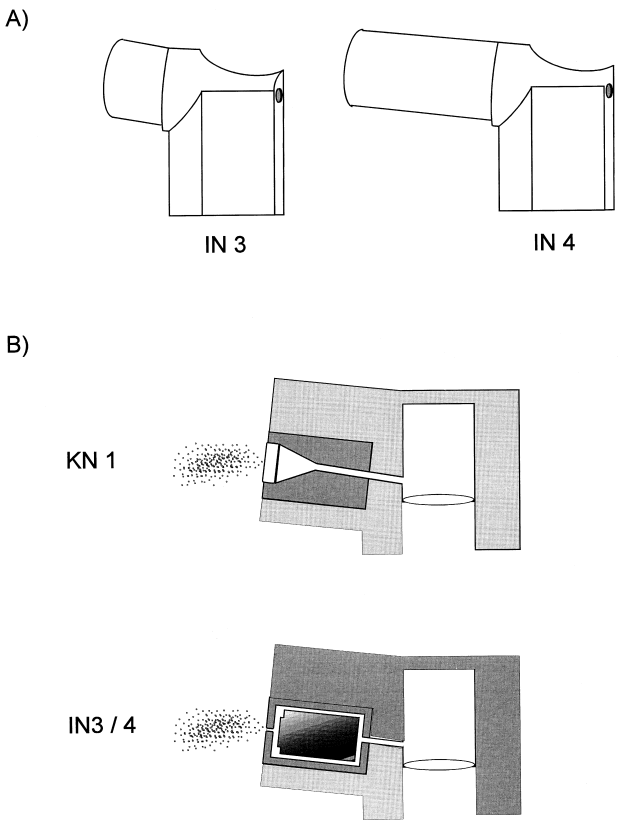

Fig. 1. (A) Front view of actuators IN 3 and IN 4; and (B) cross-sections of actuators KN 1 and IN 3/IN 4 which differ in jet construction.

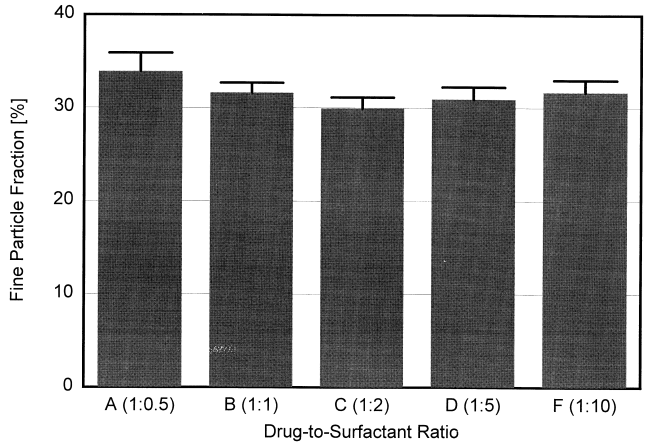

Fig. 2. Influence of drug-to-surfactant ratio on fine particle fraction.

2.5. Reagents

Acetonitrile, ethanol 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 glycerintriheptanoate, glycerintrioctanoate (both from Hüls, Marl, Germany) and Pluronic L 92 (BASF, Ludwigshafen, Germany). Cosolvents were *n*-pentane and *n*-hexane (Merck, Darmstadt, Germany). Oleic acid (Henkel, Düsseldorf, Germany) was used for the solution-type MDIs.

3. Results and discussion

The drug-to-surfactant ratio was varied from 1:0.5 to 1:10 (formulations A–E); formulations B, F and G represent MDIs with varying ethanol content.

Previous studies with CFC propellant mixtures showed that the fine particle fraction of the released aerosol cloud increased with decreasing surfactant concentration [20]. Fig. 2 shows that varying the surfactant concentration from half the concentration up to a 10-fold concentration of drug had only a slight influence on the in vitro fine particle fraction of solution-phase MDIs with R 134a. Only the switch from the lowest surfactant concentration (formulation A) to the ratio 1:2 (formulation C) showed significant differences ($P = 0.01$). Obviously, the vapour pressure of R 134a is high enough (about 0.6 MPa) to disperse the metered

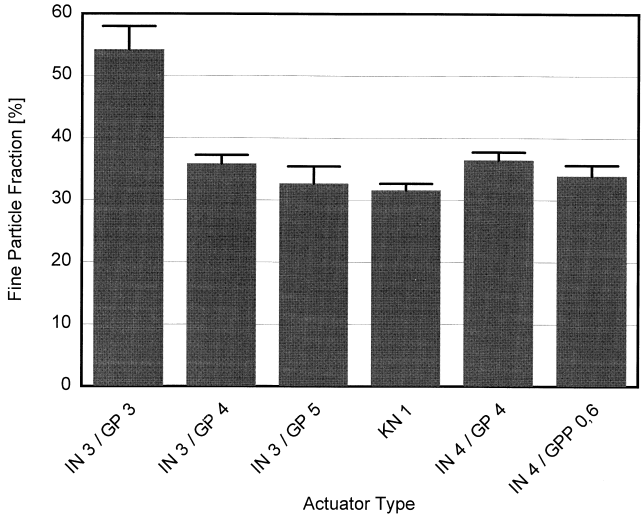

Fig. 3. Influence of actuator tube design and orifice diameter on fine particle fraction.

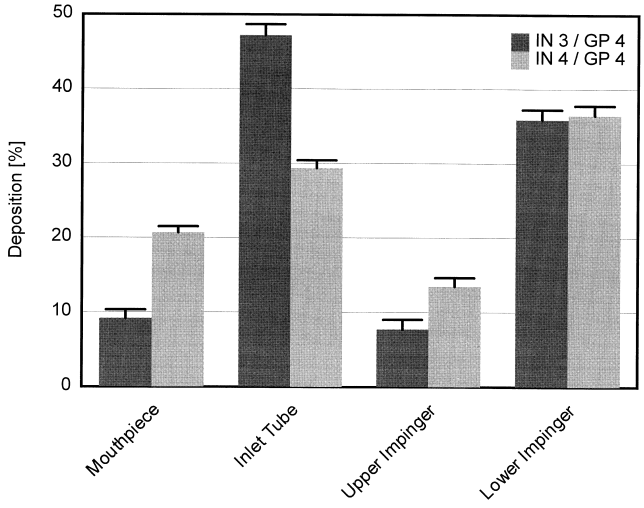

Fig. 4. Influence of actuator design on in vitro deposition.

volume even if the amount of involatile oleic acid is increased.

The results obtained from the measurements with different actuator tubes which varied in orifice diameter (OD), mouthpiece length and construction are given in Fig. 3. The measurements were undertaken with a cosolvent content of 5% and a drug-to-surfactant ratio of 1:1 (formulation B). The very simplest actuator, KN 1, with the largest orifice diameter showed, as expected [20,21], the lowest fine particle fraction. Decreasing the orifice diameter led to an increasing fine particle fraction. The in vitro respirable fraction was found to be 54% for an orifice diameter of 0.3 mm. The complete deposition data is presented in Table 3. Using an OD of 0.4 mm resulted in a fine particle fraction of 36% and then decreased only slightly with an OD of 0.5 and 0.6 mm. This is in good agreement with a study of Warren and Farr [21], who observed similar effects using a CFC propellant mixture. The actuators IN 4/GP4 and IN4/GPP 0.6 are principally of the same construction as those from the IN 3 series but they additionally have a elongated mouthpiece. As to the in vitro deposition, this led to a spacer effect, allowing the aerosol particles to slow down and to evaporate their propellant covering. Hence, the deposition of drug decreased in the glass inlet tube (‘throat’) and increased in the actuator itself. Fine particle fraction remained constant at 35% of total drug deposited in the impinger (Fig. 4).

Table 4 gives information on the dependence of fine particle fraction on the ethanol content. The lower the ethanol content, the higher the in vitro respirable fraction. This must be due to the diminution of vapour pressure with the addition of increasing fractions of ethanol [22,23]. Other influencing factors that change with increasing ethanol content may be the variations in specific heat, latent heat of vaporization or viscosity of the physical mixture of propellant and alcohol. Additionally, the remaining percentage of drug in the mouthpiece and deposition in the glass throat increased with increasing amount of alcohol.

In a second test series, the same aerosol formulations were measured with an actuator having a smaller orifice diameter and an elongated mouthpiece. The in vitro respirable fraction using the actuator IN 4/GP 4 with 5 and 10% ethanol is significantly higher ($P = 0.05$) as compared to the results from the KN 1 actuator (Fig. 5). This observation is due to the smaller orifice diameter of the actuator IN 4/GP 4. The formulation with the lowest cosolvent content showed, contrary to the expectation, a lower fine particle fraction compared to the results with the actuator KN 1. A possible explanation for this phenomenon is that the higher boiling point of the 2% mixture led to a higher mouthpiece retention

Table 3

Influence of orifice diameter and actuator design on in vitro deposition (% of total amount recovered[a])

Actuator	IN 3/GP	IN 3/GP 4	IN 3/GP 5	KN 1	IN 4/GP 4	IN 4/GPP 0.6
Orifice ∅ (mm)	0.3	0.4	0.5	0.7	0.4	0.6
Mouthpiece	9.24 (0.92)	9.19 (1.14)	8.58 (0.52)	17.00 (0.61)	20.68 (0.80)	20.65 (2.22)
Inlet tube	27.38 (1.05)	47.20 (1.48)	48.90 (2.32)	43.57 (1.29)	29.38 (1.05)	33.72 (2.13)
Upper impingement	9.15 (2.11)	7.73 (1.30)	9.84 (1.23)	7.84 (0.66)	13.46 (1.17)	11.70 (1.31)
Lower impingement	54.23 (3.75)	35.88 (1.36)	32.68 (2.74)	31.60 (1.06)	36.48 (1.29)	33.93 (1.69)
Total emitted dose (μg)	86.0 (1.4)	83.7 (1.5)	88.1 (2.5)	88.9 (3.1)	90.1 (1.1)	93.3 (7.0)
Label claim (μg)	100	100	100	100	100	100

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

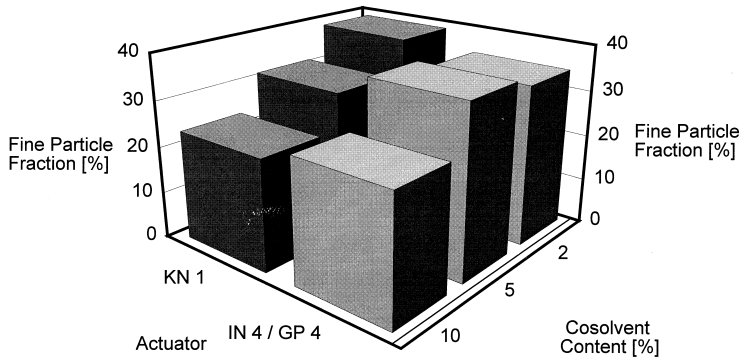

Fig. 5. Influence of cosolvent content and actuator design on fine particle fraction.

by inertial impaction. As a consequence, less drug particles were released into the impinger, leading to a decreased percentage of fine particle fraction.

The formulated suspension MDIs with R 134a showed lower fine particle fractions than the solution-phase metered-dose inhalers. Fig. 6 shows the in vitro respirable fractions of a selection of suspension formulations aerosolized with the actuator KN 1 which led to stable dispersions after formulation. Data from the formulations H, I and K suggest that a higher surfactant concentration leads to lower fine particle fractions. Nevertheless, all formulations were found to emit a fine particle dose between 20 and 30% of total dose.

The addition of a cosolvent, *n*-pentane or *n*-hexane, led to higher in vitro fine particle fractions. This should be due to the better surfactant solvency in the liquid phase. Experiment N was performed without the addition of surfactants and cosolvents. The in vitro fine particle fraction was 33% for this formulation. It was concluded that the addition of surfactant led to a higher cohesiveness of the micronized BDP and drug agglomerates were not separated when the propellant evaporated.

Table 4

Influence of ethanol content on in vitro deposition (% of total amount recovered[a])

% Ethanol (formulation)	2 (F)	5 (B)	10 (G)
Mouthpiece	12.66 (0.63)	17.00 (0.61)	18.56 (1.98)
Inlet tube	41.29 (0.86)	43.57 (1.29)	50.25 (2.15)
Upper impingement	7.16 (0.57)	7.84 (0.16)	7.45 (1.03)
Lower impingement	38.45 (1.28)	31.60 (1.06)	23.74 (3.04)
Total emitted dose (μg)	91.2 (2.7)	88.9 (3.1)	85.8 (4.1)
Label claim (μg)	100	100	100

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

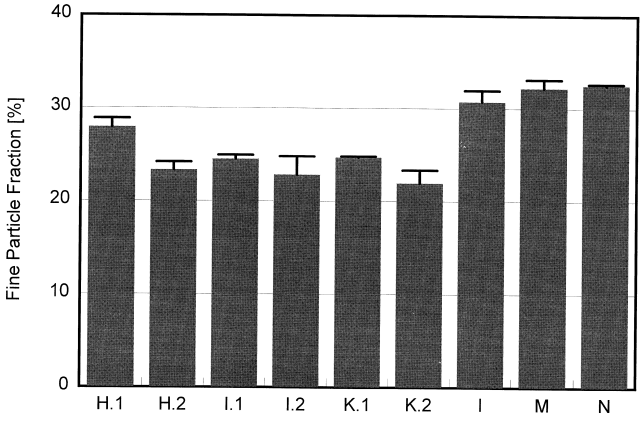

Fig. 6. Fine particle fractions of BDP suspensions aerosols, H Glycerintriheptanoate, I Glycerintrioctanoate, K Isopropylepalmitate (drug-to-surfactant ratio: (1) 1:1, (2) 1:2), L Pluronic L 92 with *n*-pentane, M Pluronic L 92 with *n*-hexane, N without any additives.

Table 5

Qualitative composition of commercial BDP metered-dose inhalers formulated as suspensions using mixtures of CFC propellants

Formulation	Propellant type	BDP/dose (μg)	Surfactant
O	R11 + R12	50	Oleic acid
P	R11 + R12	50	Oleic acid
Q	R11 + R12	50	Sorbitantrioleate
R[a]	R11 + R12	250	Oleic acid
S	R11 + R12	250	Sorbitantrioleate
T	R11 + R12	250	Sorbitantrioleate

[a]Contains additionally ethylacetate.

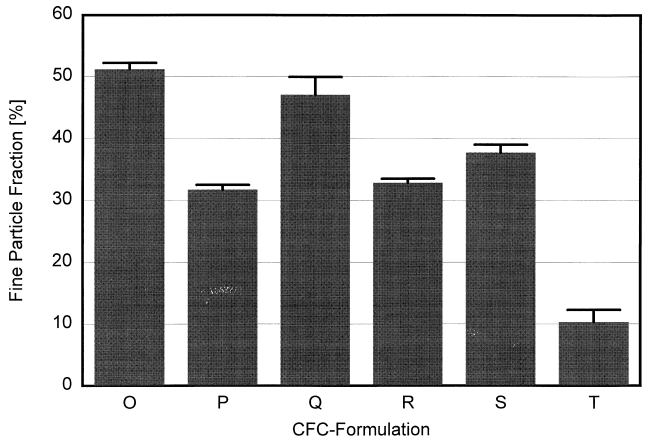

Fig. 7. Fine particle fractions of CFC-driven metered-dose inhalers formulated as suspension.

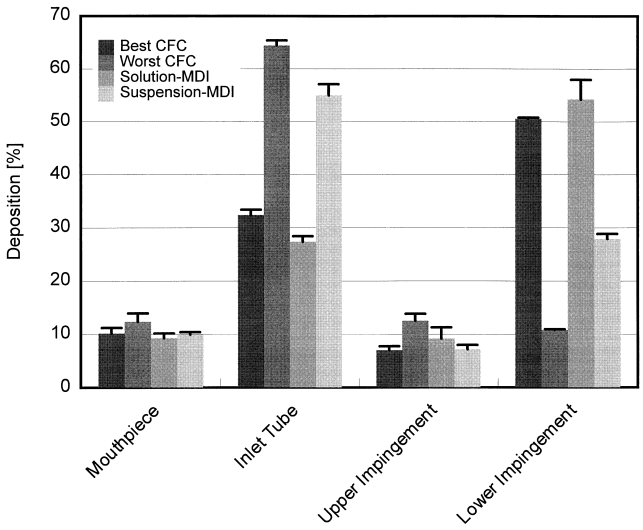

Fig. 8. Comparison of in vitro deposition of selected MDIs.

As to the physical suspension stability, those suspension systems containing a cosolvent (L, M) or neither cosolvent nor surfactant (N) showed crystal growth occurring after a storage period of 8 weeks; Ostwald ripening was observed (dissolving of smaller particles recrystallizing on the surface of the larger ones, leading to an increased particle size [16]). Those formulations without cosolvent but with additive (H, I and K) seemed to be protected from dissolution in the liquid propellant and remained resuspendable.

For a comparison of the new formulations with established CFC suspension formulations, six brands from the German market were chosen as standard. They differed in the surfactant type and the metered drug content (Table 5). A comparison of the in vitro respirable fraction of these products showed no correlation between drug concentration or surfactant type and fine particle fraction (Fig. 7). Obviously, manufacturing parameters such as particle size distribution of the active drug, milling technique, etc., predetermine the quantity of fine particles in the aerosol cloud. Generally, a lower amount of drug seemed to be advantageous (formulations O, P, Q versus R, S, T).

Fig. 8 summarizes the benefit from this study: a solution-phased MDI with an actuator with a small orifice diameter showed the highest in vitro fine particle fraction of 54% and is equivalent to the best CFC suspension MDI (50 μg BDP/dose), with a fine particle fraction of 50%. Even the BDP suspension formulation with glyceroltriheptanoate (H.1 in Fig. 6) showed an in vitro fine particle fraction of 28%.

4. General conclusions

The present study showed the feasibility of reformulation of the anti-asthmatic drug beclomethasone dipropionate. In addition to the marketed CFC-free formulations of salbutamol and fluticasone, a CFC-free BDP solution MDI is expected to be available on the market at the end of 1997. The use of ethanol as a solvent for the incorporated drug may be transferable to other anti-asthmatic drugs so that the phasing out of CFCs may be completed by the turn of the century.

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