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Influence of the moisture on the performance of a new dry powder inhaler

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Abstract

An accelerated stability test was carried out on two prototypes of a new dry powder inhaler (DPI) to verify the influence of moisture uptake on the performance of the device. The prototypes were stored at 40°C and 75% relative humidity (RH) for different storage times and their performance was assessed in terms of emitted dose and respirable fraction (Twin Impinger). At the same time intervals, the water content of the powder contained in the drug reservoir was evaluated using Karl Fischer's method. The respirable fraction was strongly influenced by the moisture content of the powder, on the contrary, the dosing precision and reproducibility is independent of this variable. The results show that a suitable protection from the external environment is necessary to prevent moisture uptake in the powder and the consequent loss of efficiency of the delivery device.

Keywords: Dry powder inhaler; Deposition pattern; Respirable fraction; Twin Impinger; Stability test.

1. Introduction

Multidose dry powder inhalers (MDPIs) are believed to be the most suitable alternatives to metered dose inhalers (MDIs) for inhalation therapy (Timsina et al., 1994). MDPIs deliver the drug as a powder and do not require any propellant to disperse the drug (Bell et al., 1971); the energy required to disperse and deliver the drug is supplied by the patient's inhalatory effort (Bell et al., 1971; Hickey et al., 1994; de Boer et al., 1996).

Powder for inhalation can be pure micronized powder, mixtures or can be formulated as physical aggregates of the active and inert carrier (soft pellets). Micronized powders develop electrostatic charges, and as a consequence, they often present poor flow characteristics. However, this intrinsic property can be exploited to produce soft aggregates, which show improved flow characteristics, while the electrostatic charges are neutralized. This approach allows the filling process to be

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simplified and to improve dosage precision (Kirk, 1986; Morén, 1987; Wetterlim, 1988). On the other hand, soft pellets' deaggregation becomes a critical step to assure that the drug can reach the alveolar zone (Hickey et al., 1994): only particles with an aerodynamic diameter (d_{ae}) of less then 5–6 μm are believed to be able to penetrate the lower part of the lung (Byron, 1987; Hickey, 1992). Moreover, the hygroscopic nature of most pharmaceutical powder makes this deaggregation process particularly critical (Hickey et al., 1994) as the moisture content of the pellets may adversely affect aerosol generation and the particle size distributions in MDPIs (Braun et al., 1996), either by modifying adhesive or cohesive properties of the formulation or by inducing hygroscopic growth (Eaves and Jones, 1972; Visser, 1989; Jashnani and Byron, 1996). To protect the powder contained in MDPIs from external environment, two different approaches are used. The first is to use individually-sealed doses which had previously been measured out (Prime et al., 1997), while the other is to protect the powder reservoir or the entire inhaler from moisture, for example by means of a screwable cover or the inclusion of a desiccant stored in the operating unit (Wetterlim, 1988).

In this study we evaluated the influence of the storage conditions at 40°C and 75% relative humidity (RH) (Commission of the European Communities, 1993) on the performance of two prototypes of a new dry powder inhaler (DPI). After different storage time the water content of the powder was assessed to verify if the device is able to prevent moisture uptake in the powder contained in the dispensing reservoir. The performance of the device in terms of emitted dose and respirable fraction was evaluated also, to verify if a possible increase of the water content of the pellets could influence the delivery efficiency of the device.

2. Materials and methods

2.1. Materials

Three different batches of soft pellets were used: a placebo, which consists of lactose monohydrate alone; a first active product, coded A, which consists of disodium cromoglycate DSCG, 80.39% (w/w) in lactose monohydrate, and a second active product, coded B, which consists of DSCG, 71.15% (w/w) in lactose monohydrate (MIAT, Milan, Italy). The limits of the particle size distribution of the soft-pellets' batches are: 60–55% between 500 and 690 μm; 30–35% between 360 and 500 μm; and 10% below 360 μm. All the initial powders were micronized (99% lower than 8 μm; and 50% lower than 3 μm).

The tests were carried out on two different prototypes of the DPI, coded MH (Fig. 1) or MY (Fig. 2). The operating principle of the two prototypes is the same: the powder is dosed volumetrically and released in the suction chamber by pressing the plunger. The patient's inhalation removes the measured dose, which, going out of the delivery chamber, breaks its coarse lumps against the disaggregation unit fitted in the mouthpiece. However, the principles of moisture protection are different in the two prototypes and consist of an outer container with a desiccant, for MH prototype, and a screwable cover, for MY prototype. Moreover MY prototypes are more compact and lighter, compared to MH prototypes, and their design is more suitable to meet the patient's handling requirements.

2.2. Methods

Before starting the stability test the water content of the three batches of soft pellets was assessed according to Karl Fischer's method (Multidosimat E415, Metrohm Herisau, Switzerland) and the emitted dose deposition pattern was performed for both MH prototype, charged with pellets A, and MY prototype, charged with pellets B.

The deposition tests were carried out using the USP XXIII apparatus 2 (Twin Impinger (Erweka), equipped with a back flow pump (Edwards) with adjustable flow rate set at 60 l/min). The drug amount recovered in the different chambers of the Twin Impinger was assessed spectrophotometrically at 327 nm (Spectracomp

606, Advanced Products, Milan, Italy). The fraction deposited in the lower impingement chamber (second stage), corresponding to particles with $d_{ae} < 6.4$ μm, is considered the respirable fraction (Padfield et al., 1983; Hallworth and Westmoreland, 1987).

The test procedure for the first prototype, MH, starts with five blank shots fired to assure discharge uniformity, then the inhaler is fixed to the mouthpiece adapter of the Twin Impinger and ten doses were discharged in sequence in the apparatus with a 2-min interval between each consecutive shot. The test was repeated three times on each inhaler.

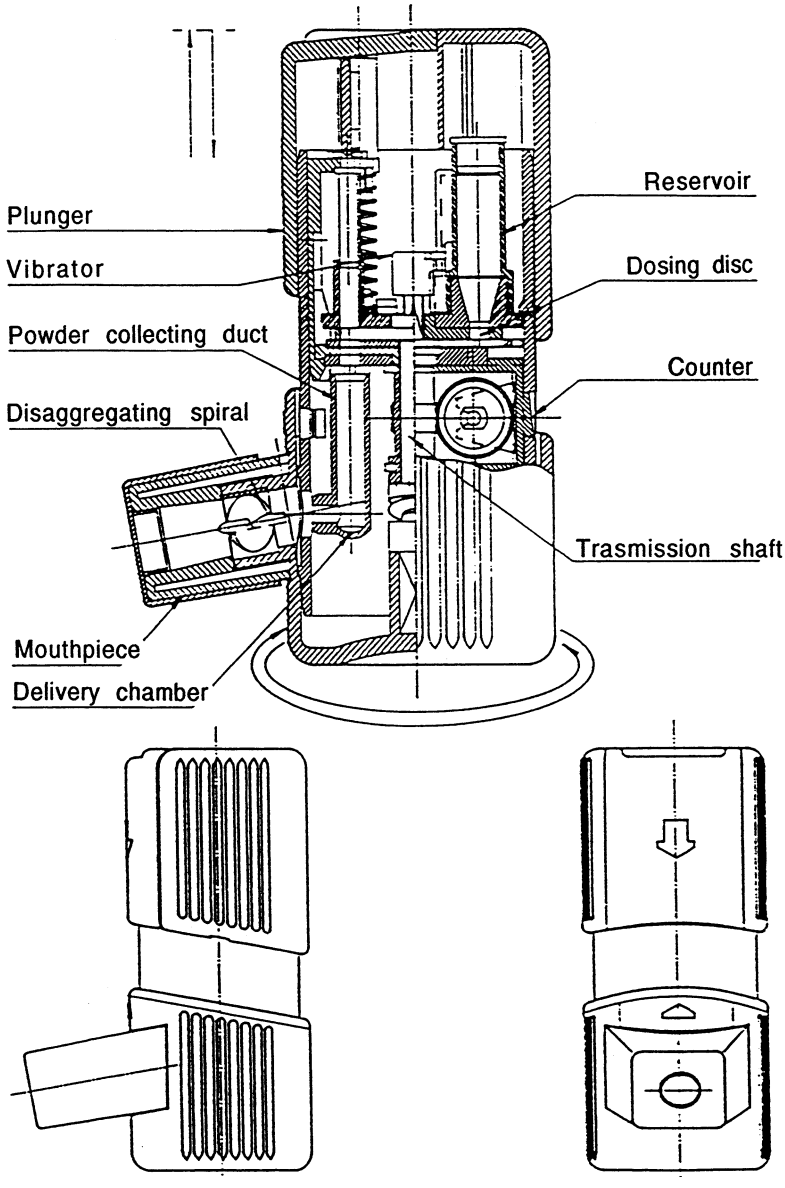

Fig. 1. Schematic drawing of the MH prototype.

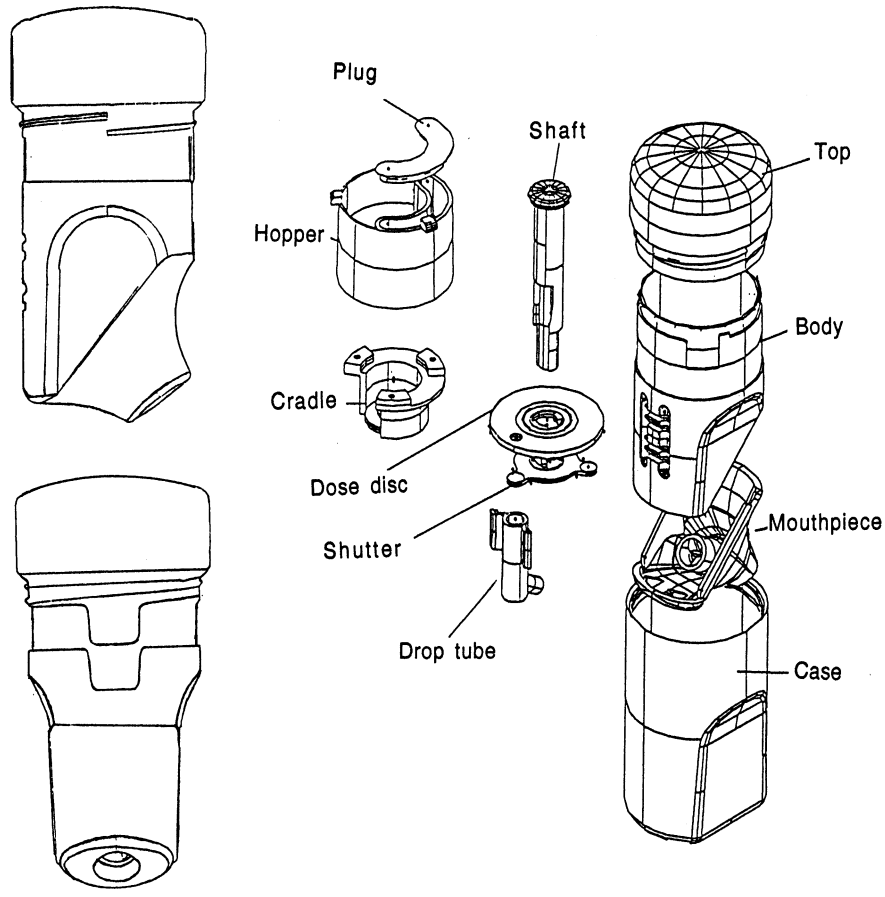

Fig. 2. Schematic drawing of the MY prototype.

For MY prototypes, an improved procedure was planned: the test was carried out on the first ten doses, blank shots from 11 to 51 were then fired and another deposition test was carried out on the doses from 52 to 61 (central doses); 41 blank shots (62–102) were fired again, and finally the test was carried out on the doses from 103 to 112 (final doses). The prototypes were weighed with precision (technical balance sensitivity 0.1 mg; Mettler Type AE260, Switzerland) before the beginning of the test and after the discharge of each group of ten doses, to verify the reproducibility of the amount of powder delivered throughout the entire life of the device. This procedure makes it possible to verify whether the amount of pellets contained in the reservoir could affect the delivery efficiency of the device.

In a preliminary test, three MH prototypes, without any outer container, were placed in the stability chamber (Branca Idealair, VA, Italy) at 40°C and 75% RH, and after 8 days the moisture content of the powder and the deposition pattern of the emitted dose were evaluated. Due to the negative results obtained from this preliminary test, the MH prototypes were then placed in the stability chamber closed in an outer provisional plastic container with a removable cap, containing also sachets of desiccant. After time intervals of 1, 3 and 6 months, three prototypes, charged with pellets A, were sampled. On these prototypes the emitted dose deposition and the water content of the powder were assessed. During the deposition tests the emitted dose was evaluated also, to verify if a possible increase in the moisture content of

Table 1
MH prototype: moisture content of pellets A at time zero and after different storage time at 40°C and 75% RH[a]

Time = 0	8 days[b]	30 days[c]	90 days[c]	180 days[c]	300 days[d]
8.87 (0.58)	17.95 (0.04)	7.87 (0.34)	10.12 (0.60)	13.74 (2.16)	9.94*

[a] Mean values (S.D.) $n = 3$.
[b] MH prototypes stored at 40°C and 75% RH without any container.
[c] MH prototypes in an outer plastic container with a desiccant agent, stored at 40°C and 75% RH.
[d] MH prototypes in a provisional plastic container with a desiccant agent, stored for 1 month at 40°C and 75% RH and for further 9 months at room temperature.
* Single value.

the powder affects the dosage precision of the device. In this case the emitted dose is considered the total amount of drug recovered in the Twin Impinger (calculated as the sum of the amounts recovered in the throat, in the first and second stages), which means the total amount of drug which leaves the device and deposited in the apparatus.

After time intervals of 1 and 6 months, three MH prototypes, charged with placebo pellets, were sampled. On these prototype only the water content of the soft pellets was assessed (in triplicate).

After this accelerated stability test, the prototypes which were stored for 1 month in controlled conditions were stored at room temperature for a further 9 months and after this period the performances of the DPIs were tested again.

Finally, new prototypes of the inhaler were designed with a screwable top to prevent water uptake inside the device. Three of these prototypes, coded MY and charged with pellets B, were placed in the stability chamber in the same conditions previously stated and after 2 months the water content of the pellets and the emitted dose deposition were assessed according to the improved procedure described before.

The significance of the difference in respirable fractions and emitted dose between the different tests was evaluated using the ANOVA test.

3. Results and discussion

The preliminary test, carried out on the MH inhaler without any packaging, showed that the prototype by itself cannot prevent the moisture uptake in the formulation. In fact, after only 8 days at 40°C and 75% RH, the water content of DSCG pellets rose from 10.7% to about 17.9% (Table 1). Together with this increase in water content, a strong reduction in the respirable fraction (second stage) was detected (Fig. 3). Therefore, a suitable protection is necessary to prevent the moisture adsorption in the powder.

In the following accelerated stability test, although the MH prototypes were closed in an experimental provisional packaging with a drying agent, an increase in water content while in the air-conditioning chamber is evidenced (Tables 1 and 2), particularly at the third and sixth month

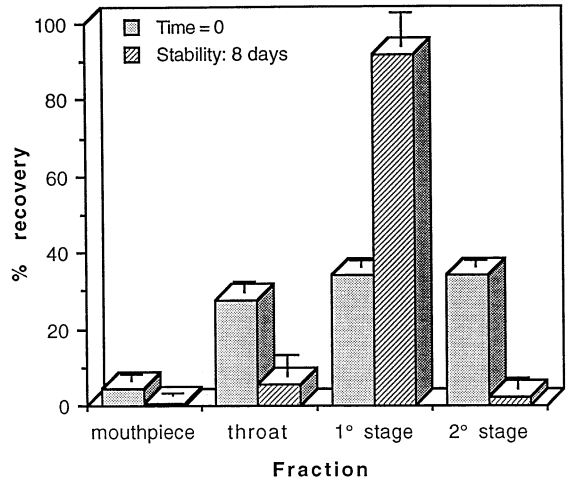

Fig. 3. Deposition pattern of powder emitted by MH prototypes at time 0 and after 8 days of storage at 40°C and 75% RH without any outer container (preliminary test; average value ± S.D., $n = 6$).

Table 2
MH prototype: moisture content of placebo pellets at time zero and after different storage time at 40°C and 75% RH with a provisional packaging[a]

Time = 0	30 days	180 days
5.72 (0.22)	6.09 (0.25)	6.42 (0.63)

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

of storage at 40°C and 75% RH. However, this increase is delayed and much slower if compared to the prototypes without container. Moreover, the moisture uptake is notable in the pellets containing the drug while the placebo pellets show less sensitivity to environmental humidity (Callahan et al., 1982), showing that the active drug is mainly responsible for water adsorption (Cox et al., 1971; Bell et al., 1973).

The deposition patterns of the powder aerosol produced by the MH prototype as a function of storage time at 40°C and 75% RH are shown in Fig. 4. A progressive decrease in the amount of powder recovered in the second stage of the Twin Impinger, as a function of storage time, can be evidenced. Statistical tests (one-way ANOVA, $p \leq 0.0001$) have shown a significant difference between respirable fraction at time 0 and after

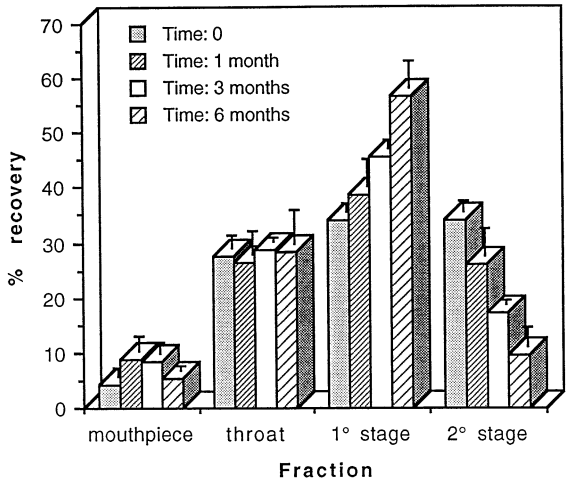

Fig. 4. Deposition patterns of powder emitted by MH prototypes closed in a provisional plastic container with a desiccant agent, charged with pellets A, after different storage time at 40°C and 75% RH (average value ± S.D., $n = 9$).

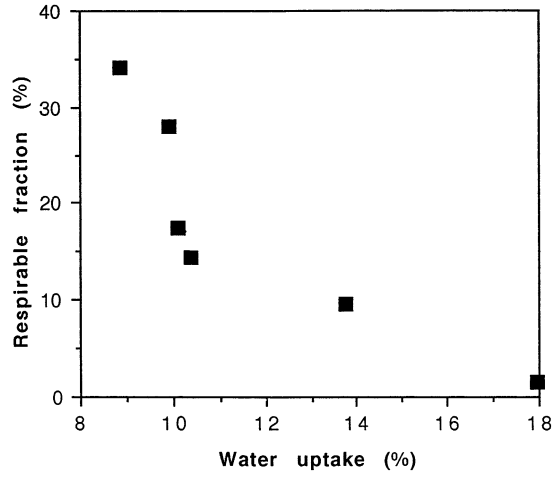

Fig. 5. Relationship between moisture content of pellets A and the respirable fraction emitted by MH prototypes.

different storage times. A significant difference in the respirable fractions is evidenced also between 3 and 6 months of accelerated stability. This trend shows that the fraction of drug able to reach the alveolar zone of the lung could be strongly affected by the moisture content of the pellets; in fact a close correlation can be evidenced by plotting the respirable fraction against the water content of the DSCG pellets (Fig. 5). This means that the presence of water in the powder may not allow for the deaggregation of the particles in the

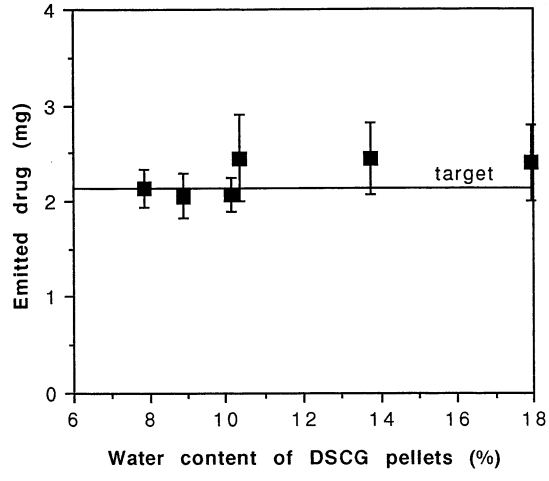

Fig. 6. MH prototypes: emitted dose (average value ± S.D.) as a function of the water content of the soft pellets A.

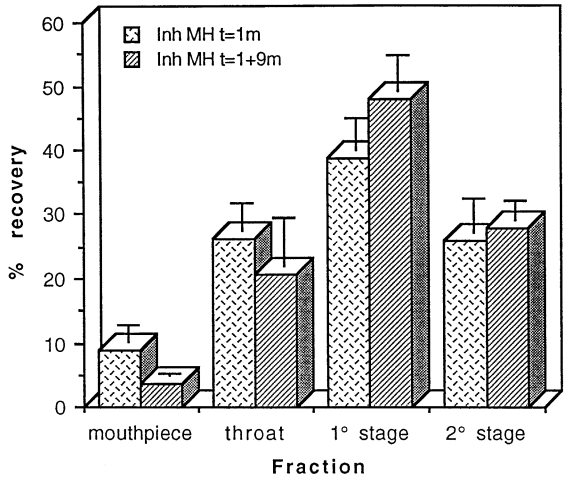

Fig. 7. MH prototypes closed in a provisional plastic container: comparison between deposition pattern after 1 month at 40°C and 75% RH and after further 9 months of storage at room temperature (1 + 9 test; average value ± S.D., $n = 6$).

pellets to their original dimensions (micrometric) and as a consequence may reduce the fraction of the drug able to reach the alveolar zone.

On the other hand, the dose emitted by the device in drug terms is independent of the water content of the powder (Fig. 6). The amount of the drug which leaves the device and is deposited in the Twin Impinger (emitted dose ex-mouthpiece) is reproducible (no significant differences among

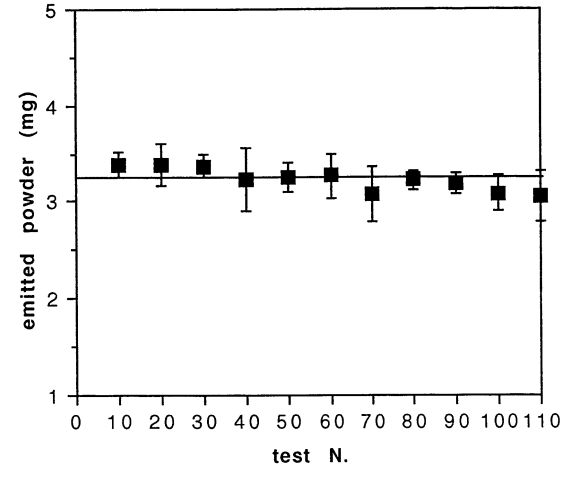

Fig. 8. Amount of soft pellets delivered by MY prototypes in the progressive shots (average value ± S.D., $n = 6$).

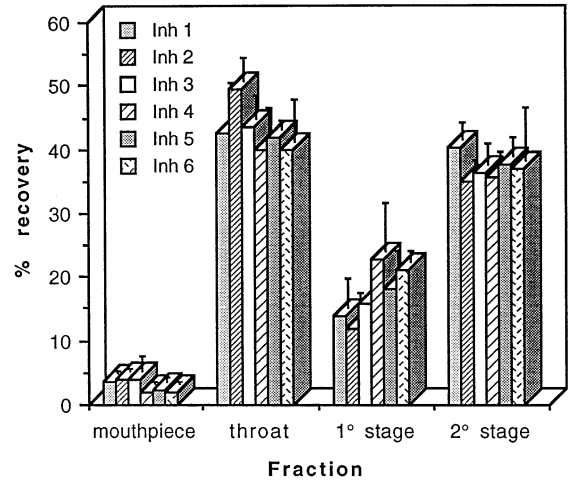

Fig. 9. MY prototypes: comparison among the deposition patterns of different inhaler at time 0. For each prototype the mean value of the initial, central and last doses is reported.

the doses emitted at different storage time; one-way ANOVA, $0.1 < p \leq 0.25$). Therefore, as expected, the moisture content of the pellets affects only the deaggregation efficiency of the device but does not affect the dosage precision and reproducibility.

The further storage of the prototypes at room temperature does not produce any significant increase in the moisture content of the soft pellets.

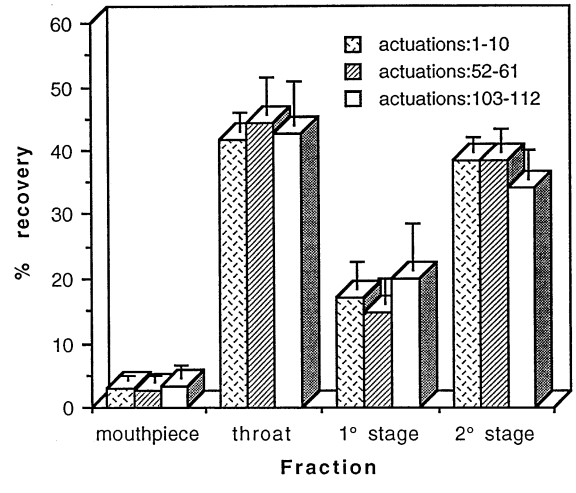

Fig. 10. MY prototypes: comparison between the deposition patterns of the initial, central and final actuations (average value ± S.D., $n = 6$).

Table 3
MY prototype: moisture content of pellets B, at time 0 and after 60 days of storage at 40°C and 75% RH[a]

Time = 0	60 days
8.73 (0.53)	15.83 (0.14)

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

(Table 1). The deposition pattern of the aerosol emitted from MH prototypes stored for 1 month at 40°C and 75% RH is comparable to the test carried out on the device stored for the following 9 months at room temperature ($1 + 9$ test; Fig. 7). No significant difference between the respirable fractions obtained in the two different conditions (one-way ANOVA, $0.1 < p \leq 0.25$) can be evidenced.

To solve the problems related to moisture adsorption, a new prototype of the inhaler was designed and produced. The new prototypes, coded MY, are equipped with a screwable top to protect the powder reservoir from the outer environment.

At zero time, the amount of powder delivered from the new MY prototypes is precise and reproducible from the initial to the very last doses

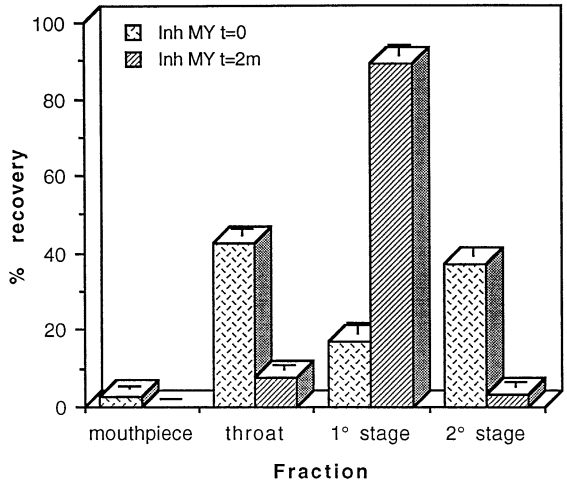

Fig. 11. MY prototypes: comparison between the deposition patterns at time 0 and after 2 months at 40°C and 75% RH. For each prototype the mean value of the initial, central and last doses is reported.

(Fig. 8). The devices tested are able to deliver about 37% of the dose as respirable particles (no significant inter-device difference, two-way ANOVA, $p = 0.70$; Fig. 9) and the respirable fraction is reproducible throughout the life of the device (Fig. 10; two-way ANOVA, $p = 0.12$).

Unfortunately, after 2 months at 40°C and 75% RH the water content of the powder rises to 15.8% (Table 3), despite the presence of the protective top, and at the same time the respirable fraction falls to about 3% (Fig. 11). These results confirm again how critical the moisture present in the soft pellets is on the overall performance of the inhaler.

4. Conclusion

The results of the tests performed on MH prototypes show that the deaggregation performance of the device is strongly related to the moisture content of the pellets, whereas the emitted dose is independent of this variable. The preliminary test showed that the device by itself cannot prevent the moisture uptake in the powder. By closing the prototypes in a plastic container with a desiccant, the rate of water adsorption in the pellets is slower but this is only a provisional solution. Results obtained from the stability test prove that in the presence of a suitable protection, the storage at room temperature causes only a slight increase in the water content of the formulation and no changes in the deposition patterns of the emitted powder.

The tests carried out on MY prototypes confirm the critical importance of the moisture content of the pellets for the delivery of an effective dose to the lung. The value of water content in the formulation after 2 months at 40°C and 75% RH shows that also the new prototype's design, with a screwable top, is not able to prevent the moisture uptake in the powder and the consequent reduction of the dose delivered to the alveolar zone. However it must be underlined that the drug tested in this study is particularly sensitive to moisture adsorbtion.

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