“Pierce and Inhale” Design in Capsule Based Dry Powder Inhalers: Effect of capsule piercing position and motion on aerodynamic performance of drug

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Abstract

In this work three capsule-based dry powder inhalers, available for generics product development, were compared. Two technologically different dry powder formulations were used in order to relate the capsule piercing position and motion in the device to their aerodynamic performance.

A “pierce and inhale” design, in which the capsules pierced with RS01, Handihaler or Turbospin devices were aerosolised in the same device or transferred and aerosolised with another device, was constructed and carried out.

The results obtained showed that the two dry powder formulations, i.e., a drug/lactose blend or a carrier-free powder, aerosolized using the capsule based inhalers, performed differently. The aerosolization of drug carrier mixture in terms of drug dispersion and emitted dose, was more sensible to the piercing and device combination than the carrier free powder. The motion of the capsule during the aerosolization boosted the powder emission, whereas the powder disaggregation was more influenced by the airflow pattern around the capsule and inside the inhaler turbulence chamber.

Keywords: RS01; HandiHaler; Turbospin; formoterol fumarate; spray-dried insulin; dry powder inhaler.
Abbreviation section

AR   Aerolizer
DD   Delivered Dose
DPI  Dry Powder Inhaler
FPD  Fine Particle Dose
FPF  Fine Particle Fraction
HH   HandiHaler
MMAD Mass Median Aerodynamic Diameter
NGI  Next Generation Impactor
RF   Respirable Fraction
TS   Turbospin
Introduction

Dry Powder Inhalers (DPI) are combination products in which formulation (therapeutic effect) and inhalation device (aerosol production) have to be developed together. The fluidization, disaggregation and aerodynamic size of drug particles are controlled by the powder physicochemical properties and by the design of the inhaler. Many DPIs contain the pre-metered labelled dose in blisters or capsules, which are pierced prior to delivery. Together with their own intrinsic resistance, the emission of powder from the device and the aerodynamic performance are related to capsule openings and motion (rotation, shake, vibration) (Islam and Cleary, 2012). In addition, others factors, such as the hole size and position in the pierced capsule, (Coates et al., 2005), the capsule chamber volume (Behara et al., 2011a, 2011b), the mouthpiece geometry (Coates et al., 2007) and grid structure (Coates et al., 2004) may influence the performance of the inhaler product.

The inhalation drug products already faced the appearance of generic versions, in particular metered dose inhalers. However, very few generic DPI have been registered, likely due to the difficulty to make copy of these demanding formulations. Rolenium®, a generic version of salmetero xinafoate/fluticasone propionate DPI entered in the inhaler market in 2013 ( ). In this case, the generic company developed its own device, Elpenhaler, for making the product similar to the marketed originator. Other generic companies do not will to develop their own new device and choose to use one among those available on the market. Therefore, the knowledge of the devices’ performance becomes an essential step in order to select the most appropriate to combine with the dry powder formulation. It is agreed that the simplest devices are the pre-metered ones using hard capsules as drug reservoirs. For example, among the marketed devices, RS01 (Plastiape) and Turbospin (PH&T) have been frequently used. Turbospin in particular, has been used in high dose delivery of antibiotics, such as in TOBI Podhaler and Colobreathe products ( ).
In the capsule pre-metered devices, the influence on the aerodynamic performance of the capsule piercing and motion under the during inhalation airflow, the type of formulation (with or without carrier) in dependence on the type of formulation (with or without carrier), the capsule piercing position and its motion during inhalation airflow has never been considered in dependence on the type of formulation (with or without carrier). In this work three approved capsule-based dry powder inhalers were compared for discovering their behaviour and adaptability to different formulations. The piercing position on the capsule and its motion and capsule motion inside the device were have been related to the powder emission and aerodynamic performance.

Formoterol fumarate blended with coarse α-lactose monohydrate was used as model carrier-formulation. In the specific case, the loaded size 3 capsules (size 3) of the commercial product Foradil® were used. The second formulation consisted of a novel insulin spray-dried powder without excipients having a MMAD value of 1.79 μm (Balducci et al., 2014)....

A “pierce and inhale” capsules and devices cross-game combination scheme, in which the capsules pierced with Handihaler, RS01, Handihaler, and Turbospin were aerosolised in with the same device or transferred and aerosolised with another device was designed (see Table 1). The nine possible combinations of the three DPIs were tested and their performance in terms of drug delivery discussed. Foradil Aerolizer performance was used as reference.
2. Materials and Methods

2.1. Materials

Formoterol fumarate lactose blend (Foradil® Aérolizer® ©, Novartis – inhalation powder in hard gelatine capsules combined with Aérolizer device ©, Batch U0093) was purchased from the local pharmacy. One capsule contains 12 µg of formoterol fumarate in 25 mg of lactose.

Human recombinant insulin (Batch WEP1223) was purchased by Wako Chemicals (Japan).

The respirable insulin powder was obtained from an acidic drug solution spray dried according to the method previously described (Balducci et al., 2014). All chemicals used were of analytical grade and water was purified by Elix® Essential (Merck Millipore, USA). Size 3 hypromellose capsules (Vcaps® DPI), used for spray-dried insulin were provided by Capsugel (Colmar, France).

The devices used in the study were the following:

- Aérolizer® (Novartis, Switzerland), coded AR;
- RS01 (Plastiape Spa, Italy);
- HandiHaler® (Boehringer Ingelheim, Germany), coded HH;
- Turbospin® (PH&T, Italy), coded TS.

2.2 The “pierce and inhale” design

All the devices use a size 3 capsule as dose reservoir of powder formulation a size 3 capsule.

In general, the piercing mode of the selected inhalers consisted of two or more two-holes.
pierced in different capsule positions. Hole diameters were 1.15 mm for RS01® and Turbospin®, 1.45 mm for the HandiHaler®, and 0.60 mm for the Aerolizer®.

Two different formulations were used for the study, namely the lactose blend of formoterol fumarate contained in Foradil capsules and the insulin spray-dried powder without excipients loaded in capsule size 3. The experimental work “pierce and inhale” design was planned and organized as the following: first, each device was tested aerosolized the capsule pierced in itself and the capsules pierced with the other devices, as the using the label prescribed operational mode flow rate was set down determining the pressure drop of 4 kPa with the capsule in place. The scheme illustrating the nine aerosolizations performed is reported in Table 1 where are reported the operating flow rates. Afterwards, the “pierce and inhale” design was executed and the capsule was pierced and aerosolized in the same device or, pierced with one device, it was transferred for inserted and aerosolized with the other devices. The detail of these combinations and the list of tests performed are illustrated in the Table 1.

Two different formulations were tested, namely a lactose blend of formoterol fumarate and an insulin spray-dried powder without excipients previously described (Balducci et al., 2014).

When the capsule was pierced and transferred, the devices were held horizontally, with the capsule parallel to the working surface was carefully executed in order to prevent powder loss during the transfer to the other device. Also when the pierced capsule with RS01 was transferred into TS and HH, the devices were held horizontally and the head of the capsule was always placed up.

2.2. In vitro drug deposition
The aerodynamic assessment was performed using the Next Generation Impactor (NGI) (Copley Scientific, Nottingham, UK). The methodology followed the USP 36 guidelines for dry powder inhalers (Apparatus 5, United States Pharmacopoeia, Chapter 601). The collection stages were coated with Span 85 in cyclohexane solution (1% w/v) in order to prevent particles bouncing during the analysis. NGI was assembled as prescribed and the pre-separator was included in the system when the carrier-based formulation was tested. Powder formulations were aerosolised inside the NGI and the amounts deposited on the different parts of the impactor were collected using a water/methanol mixture (40:60) or hydrochloridric acid (0.01 M) for formoterol fumarate and insulin, respectively.

Foradil® capsules were stored under controlled conditions of temperature and humidity (25 ± 5 °C and 50 ± 5% R.H.). Five capsules were discharged in the impactor during each test. In the case of spray-dried insulin, one hypromellose capsule was loaded with 2 mg of powder (insulin content 95.8%) and aerosolized. A Micro-Orifice Collector (MOC) was placed below stage 7.

Table 2 shows the Cut-off aerodynamic diameter for stages of Next Generation Impactor at different flow rates. The measurement of drug deposition inside the impactor allows the calculation of different deposition parameters. The delivered dose (DD) was the amount of drug ex-device measured from induction port to MOC. The Fine Particle Dose (FPD) was the mass of drug particles with aerodynamic diameter lower than 5 µm; the Respirable Fraction (RF) was the ratio between FPD and the labelled/loaded dose of drug; the Fine Particle Fraction (FPF) was the ratio between the FPD and the total mass collected in the impactor. DD The Mass Median Aerodynamic Diameter (MMAD) was determined by plotting the cumulative percentage of
mass less than stated aerodynamic diameter on (probability scale) versus aerodynamic diameter on (logarithmic scale).

Since the inhaler devices had different intrinsic resistance, they have been used at different air flows. The flow rate used during each test was adjusted with a Critical Flow Controller TPK (Copley Scientific, Nottingham, UK) in order to produce a pressure drop of 4 kPa over the inhaler. In particular, the flow rates correspondent to 4 kPa drop over the inhaler without capsule, controlled before each experiment, measured by Flow Meter DFM 2000 (Copley Scientific, Nottingham, UK) and obtained had the values reported in Table 1.

Finally, the test duration, so that a volume of 4 L of air was withdrawn through the inhalers, was set to 2.7, 3, 4 and 6 seconds for Aerolizer, TS, RS01 and HH, respectively.

2.3. Assays of formoterol fumarate and insulin

Formoterol fumarate assay was performed according to previous published method (Buttini et al., 2014) and insulin content was determined by HPLC according to (Balducci et al., 2014).

2.4. Statistical analysis

The significance of difference between the data was performed by using an unpaired t-test. When pairs had different variances, the Welch’s correction was used (significance level p < 0.05). Statistical analysis was performed using Prism 5 (GraphPad, Software Inc., USA).
3. Results and Discussions

3.1. Device description and powder delivery mechanism

The RS01—medium resistance RS01 device pierces the capsule, horizontally inserted in the housing chamber, using two opposing needles; the capsule is horizontally inserted in the housing chamber. Thus, two circular centred holes, one at the bottom of the capsule body and the other on the top of the head, are made. During the aerosolization, the air flow streams at 60 L/min enters via the two tangential inlets opposite in the capsule chamber. In this way, during the inhalation flux-air-flow, the capsule leaves the housing chamber and moves upside the housing chamber in a circular larger space where it can spins around the its minor axis. The result is the centrifugation out of the capsule content through the two opposite holes. This behaviour—capsule motion—is identical into Aerolizer® device, a low resistance inhaler, where in which the capsule is pierced on the top and bottom using four needles not centred and the mouthpiece is longer.

The HandiHaler® has two parallel needles which pierce the capsule, vertically inserted vertically in the device, on the same side close to the top and bottom. In this device, during the air flux-flow at 40 L/min, the capsule axially vibrates shaking out the its content (Shur et al., 2012).

Turbospin® device has a parallel couple of needles that make two nearby holes at the bottom of capsule body. The capsule vertically positioned shakes and twists when exposed to the inhalation air-flux of 80 L/min, allowing the content to be emitted and aerosolised (Aquino et al., 2012; Healy et al., 2014).

Fig. 1 shows the four inhalers employed in this “pierce and inhale” design, the holes’ position and the capsule motion direction inside the inhaler when flushed by the inhalation air-flow.
particular, the hole diameters were 1.05 ± 0.07 mm for TS, 1.72 ± 0.07 mm for HH and 1.26 ± 0.11 mm for RS01.

3.2. Aerodynamic performance of carrier-based formulation

Foradil capsules contained 12 µg of formoterol fumarate dispersed in 25 mg of lactose. The product uses gelatine capsules contain 12 µg of formoterol fumarate, coupled with the Aerolizer device. The device has two pairs of four needles (0.60 mm) with conical tips, which pierce the holes centrally on the bottom and on the top of the capsule. The four needles would prevent crack risks of gelatine shell; the capsule motion in the Aerolizer is the same as in RS01.

The Foradil formulation has been developed with the Aerolizer device; the type of lactose, its size distribution and the ratio in the mixture have been optimized for the combination with the Aerolizer this specific device. With the intent to constitute fix the establish a performance reference, the aerodynamic assessment of Foradil was firstly conducted (Table 23). The delivered dose was 9.754 µg, corresponding to 7981.5 ± 2 % of the formoterol fumarate labelled dose and the fine particle dose was 3.54 ± 71 µg.

Foradil formulation has been developed for the Aerolizer device; type of lactose, its size distribution and ratio in the mixture have been optimized for the combination with the Aerolizer. Keeping in mind this aspect, Then, the Foradil capsules were inserted in the other devices of the study, pierced and aerosolized. The measured aerodynamic parameters are reported in Table 23 and the particle size deposition distributions of formoterol fumarate determined within the Next Generation ImpactorNGI, are illustrated in Fig. 2.

More than 81% of the Formoterol fumarate labelled dose was delivered dose fromby AR, RS01 and HH was higher than 81% of the labelled dose. Turbospin had a problem showed a
lower in dose emission (73%) since the capsule and mouthpiece withhold 22% of drug (see Fig. 2). Although the TS device showed the lowest delivered dose, the FPD was close to Aerolizer due to the low amount of drug deposited in the throat and pre-separator. This substantiated an efficient dispersion of delivered powder emitted in the air stream, leading to a FPD comparable to Aerolizer.

Among the three devices, HH exhibited the lowest fine particle dose (3.13 µg) justified by the high MMAD value (3.59 µm), despite the large size of capsule holes (1.72 mm) could favour the dose emission. However, it is known that the aperture hole size of the capsule has significant inversely effects on the inhaler performance having shown that increasing the capsule hole size, the drug deaggregation decreased (Son et al., 2013). The less efficient deaggregation capacity of HH determined the Foradil formulation did not effectively combine with this device, since the mouthpiece and capsule retained a high drug amountfraction of the drug formulation. As a consequence, the deposition on respirable size stages was low.

The RS01 resulted in the most efficient device for aerosolizing the Foradil® capsule content as the values of delivered dose, fine particle dose and fraction indicated. The centrifuge spinning of the capsule in RS01 (and Aerolizer too) supported high powder emission and deaggregation (Chew et al., 2002). Mechanistically, the reported higher number of particle collisions in RS01 respect to Handihaler (Donovan et al., 2012) is at the base of the drug detachment from the carrier.

Finally, Aerolizer showed a FPD value significantly lower compared to the similar RS01 device (3.53 versus 4.15 µg). The difference could be assigned to the lower emitted dose as result of the lower resistance of Aerolizer together with the different size and number position of holes and mouthpiece length. In regard to the mouthpiece different length, it has been demonstrated that the Aerolizer mouthpiece geometry had no effect...
on device retention, but strongly affected the amount of throat deposition (Coates et al., 2007).

In summary, the capsule motion behaviour (rotation for Aerolizer and RS01, shaking and vibration for HandiHaler and shaking and twisting for Turbospin) evidently favoured the respirability of the formulation when the capsule, rotating along the minor axis, with presented the holes at the end-extremities of capsule.

3.3. Foradil capsules pierced with one device and aerosolized with another one.

The in vitro respirability parameters of all the combinations between the device used to pierce the capsule and the device employed to aerosolise the formulation are reported in Table 23. The Aerolizer was not included in the "pierce and inhale" game-design because it has the same/similar piercing position and motion characteristics of RS01.

The aerosolization with RS01 reached a top-high efficacy also when the Foradil capsule was pierced with the other devices. In particular, the aerodynamic parameters obtained when the capsule was pierced with HH were not significantly different from the values obtained by piercing with RS01. On the contrary, the capsule pierced using Turbospin and aerosolized with RS01 exhibited a DD and a FPD values significantly lower compared to the previous other combinations. This has to be attributed to the hole positions: RS01 and HH devices made two opposite holes located on the furthermost part of capsule cap and body, whereas TS made two close holes only on the body end. Thus, the capsule spinning in the RS01 maximized the emission under centrifugal force when two opposite holes were present at the end-extremities of the capsule body and cap. It vault to underline that the fine particle fraction values of the three hole/device experiments were similar but, in reality, different doses have been deposited in the peripheral lung region.
Aerosolizing with the HandiHaler inhaler the Foradil capsules pierced with the other two devices, it was found that the capsule pierced by RS01 device gave the highest delivered dose value (10.07 µg), but the poorest FPD, equal to (2.38 µg). The air flow of HH device efficiently extracts the powder even with the RS01 holes, but the deaggregation process was strongly affected by the hole position. This different behaviour could be justified considering the described path of air flow around the capsule in the HH inhaler (Shur et al., 2012). It has been reported that during the axial vibration of the capsule, the pressure distribution around the capsule in HH, calculated by Computational Fluid Dynamic, showed that the lower hole was situated within a low-pressure region. Hence, the air was drawn into the capsule through the upper pierced hole and out from the lower pierced hole, causing the powder dose to leave the capsule through the bottom (Shur et al., 2012). When the capsule was pierced by TS, the powder emission from the capsule was not differently in terms of DD and FPD compared to the HandiHaler-HH. In HH, the published flow field shows a high air velocity profile at the bottom of the capsule. Considered that Turbospin makes two holes on the capsule bottom side, it could be assumed that the holes made with TS were involved in the air velocity region of the HandiHaler turbulence chamber.

However, since the emission from RS01 pierced capsule was the highest, there must have been a different pathway of the air inside capsule, since the RS01 hole was centred on the capsule bottom. This caused a lower deaggregation or detachment of drug from lactose carrier. In fact, analysing the deposition of powder in the NGI, a significant higher deposition in the pre-separator for RS01 pierced capsule was measured in this experimental set, meaning that higher amount of drug remained attached to the carrier after aerosolization (see Fig. 3). Also the value of MMAD was the highest in comparison with the other devices and combinations.
The third set of experiments (see Table 23) consisted of Foradil capsules pierced with the other devices and aerosolized with Turbospin. Differences in delivered dose were observed and TS had exhibited the lowest emission value (8.76 µg), not significantly different from RS01 pierced capsule. Significantly, the DD value obtained aerosolizing with TS increased when the capsule was pierced with HH device (10.27 µg). The drug delivered amount of capsule pierced with HH could be favoured by bigger hole size and the position of the hole. It was observed that when the holes were centred on the bottom of the capsule, a higher amount of powder was recovered in the capsule housing of TS device (Fig. 4). However, despite the lowest amount of formoterol fumarate emitted, Turbospin showed high deaggregation efficiency, also due to the fastest airflow rate for aerosolization among the three piercing devices. In fact, the FPD reached the highest value in this set of experiments (3.35 µg) and the MMADs were always low.

The FPDs from capsules pierced with RS01 and HH were significantly lower compared to TS reference data. This result was in agreement confirmed with the high pre-separator deposition (around 40%, see Fig. 4).

In summary, in this combination study between different aerosolization devices and capsule piercing, the aerodynamic performance of the different inhalers loaded with the drug/carrier formulation in the combination study between aerosolization and capsule piercing, is ranked in the Table 34 as Respirable Fraction (RF), a parameter taking into account both the emission and the disaggregation performances.

The powder emission from the capsule was definitely boosted by the centrifugation due to the capsule spinning as realized in RS01 or Aerolizer inhalers. In fact, in discharging the Foradil powder, the RF values depicting the highest efficient drug deposition were exhibited by RS01 device, independently of the capsule piercing position. However, since in RS01 the capsule
rotates around its minor axis, Foradil formulation achieved the top emission and
deaggregation/disaggregation when the holes are oppositely pierced on the capsule. In fact, RS01 was less performing when the holes are confined on one side of the capsule, such as in TS.

Turbospin inhaler evidenced a clear dichotomy between emission and deaggregation/disaggregation of drug/carrier mixture. The air turbulence of in Turbospin-this device provided high deaggregation/disaggregation in front-of together with low emission. This inhaler constantly retained in the device/capsule important amount of powder, reasonably due to the holes at the bottom of the capsule in the turbulence chamber of the device.

The HH devices, that aerosolizes through a depression in correspondence of the lateral surface of the capsule bottom, worked well also with the two holes provided by Turbospin, but badly when the bottom hole was centred on the capsule body, such as with the capsules pierced with RS01.

The aerosolization with Turbospin or HandiHaler, where the capsule swirl and shakes for powder emission, was negatively affected in case of the two opposite holes pierced by RS01.

3.4. Aerodynamic performance of a carrier-free insulin formulation

AFor aerosolizing The same study design applied to the Foradil® was performed with the insulin inhalation powder. This, the carrier-free formulation did not require the carrier detachment of drug, but only requires the particle deaggregation/disaggregation of the soft aggregated powder. 2 mg of a recombinant human insulin spray-dried powder were loaded in HPMC size 3 capsules and aerosolized with the three devices. By piercing and aerosolizing the capsule within the same device (Table 45), the RS01 device showed the best results in
In comparison, Turbospin and HandiHaler devices showed FPD values significantly lower compared to RS01. MMAD also depicts a better deaggregation performance by RS01. The distribution of the powder inside the impactor is illustrated in Fig. 5. RS01, HH, TS devices had a different average device/capsule powder retention. As found for Foradil, among the devices, Turbospin showed the lowest insulin spray dried emitted dose, but the high variability of the data did not allow to claim a strong significance. Thus, spray-dried insulin confirmed the result observed in the case of formoterol blend was confirmed: the capsule spinning during aerosolization (RS01 device) boosted the delivered dose and the powder respirability.

To investigate the effect of the combination between hole position and device, capsules pierced with a device were used with other devices, in all possible combinations. Aerosolizing with the RS01 device, an emitted dose of insulin always above 85% of loaded dose was measured. Moreover, the different piercing position of the capsule did not affect significantly the delivered dose. The FPD of capsule pierced and aerosolized with RS01 was not significantly modified when the capsules were pierced with the other devices, indicating that this highly respirable spray dried insulin the capsule spinning reduced the effect of the hole position with this highly respirable spray dried insulin when the capsule is spinning.

The HandiHaler device, as aerosol producer, gave the same delivered dose of (1.6 mg) with all the piercing combinations and the fine particle dose did not change with the different piercing positions. The MMAD values resulted increased compared to the RS01 as inhaler, indicating a lower deaggregation efficiency.

Finally, when the capsule was pierced and aerosolized with the Turbospin, the emitted dose and fine particle dose were the lowest compared to the other devices. Two holes made on the
bottom end of the capsule in TS device led to a **high** retention of the powder in the inhaler and also with this formulation. Powder aerodynamic distribution (Figure 6) shows that, using TS to aerosolize the capsules pierced by the other two inhalers, in particular HH, the amount of powder **non-emitted and remaining** in the capsule and device was significantly reduced.

-In the case of this carrier free insulin powder, the **deaggregation-disaggregation** was less demanding than the emission from the capsule. In fact, insulin spray dried powder was very flowable indicating that the particles do not have the tendency to aggregate.

Comparing the Respirable Fraction of the various combinations (Table 56), the differences in the values measured resulted less pronounced than in the case of the drug/carrier mixture. Again, the performance of the RS01 as dry powder inhaler was at the top of the ranking and of the respirable fractions and the values were more reproducible.

4. Conclusions

The results obtained allow to conclude that the two aerodynamic delivery variables of dry powder inhaler i.e., powder emission and **drug deaggregation-disaggregation** (MMAD and FPD), were differently maximized by the **capsule motion in the inhaler** and in relation to holes position on the pierced capsule hole position. The different combination between piercing site and aerosolizing revealed that the capsule motion under the inhalation air-flow The powder emission was essentially boosted by the motion of the capsule during air-flow, whereas the air-flow pattern around the capsule in the turbulence chamber of inhaler reinforced the **powder deaggregation-disaggregation and dispersion** resulted more dependent on the air-flow pattern around the capsule and inside the turbulence chamber of the inhaler, of the powder.
The dose emission and drug dispersion of the two different dry powder formulations, i.e., carrier blend or pure drug, aerosolized using capsule based inhalers performed differently-the three devices-in terms of emission and drug dispersion in the devices, as evidenced when in which the pierced capsules were pierced were aerosolized with another device, could drive to optimize the optimization of other combinations of device with generic formulations. When in case of formoterol fumarate/lactose blended with lactose was used, the capsule motion during the aerosolization was the critical factor for the emission. The drug aerodynamic performance due to the powder disaggregation powder was significantly affected by the different combinations between hole position and inhaler type. When in case of insulin spray-dried powder without carrier was employed, results stressed the importance of capsule motion was the most relevant characteristic for the drug aerodynamic performance. Using the high respirable pure insulin powder, the capsule piercing position was less influent on the device performance measured as respirable fraction.

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Fig 1. Dry powder inhalers, the relative pierced capsules and the motion of the capsule, top to bottom: Aerolizer, RS01, HandiHaler, Turbospin.

Fig 2. Deposition of formoterol fumarate dry powder aerosolized with different devices inside the Next Generation Impactor; (n=3; mean ± sd); (D+C: Device and capsule, IP: induction port). The cut-off of each stage (S) has not been represented since the devices operated at different flow rate.

Fig 3. Deposition of formoterol fumarate dry powder aerosolized with HandiHaler inside the Next Generation Impactor. Operating flow rate 40 L/min (n=3; mean ± sd); (D+C: Device and capsule, IP: induction port). Legend refers to the piercing device.

Fig 4. Deposition of formoterol fumarate dry powder aerosolized with Turbospin inside the Next Generation Impactor. Operating flow rate 80 L/min (n=3; mean ± sd); (D+C: Device and capsule, IP: induction port). Legend refers to the piercing device.

Fig 5. Deposition of insulin spray-dried powder aerosolized with different devices inside the Next Generation Impactor; (n=3; mean ± sd); (D+C: Device and capsule, IP: induction port). The cut-off of each stage (S) has not been represented since the devices operated at different flow rate.

Fig 6. Deposition of insulin spray-dried powder aerosolized with Turbospin inside the Next Generation Impactor. Operating flow rate 80 L/min (n=3; mean ± sd); (D+C: Device and capsule, IP: induction port). Legend refers to the piercing device.