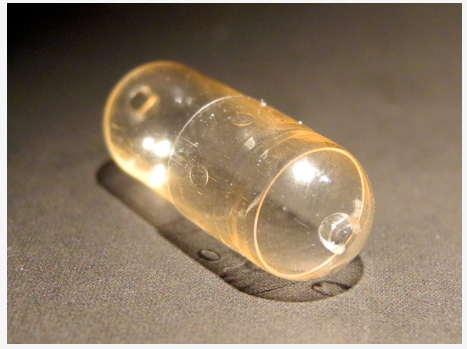
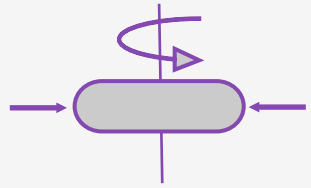
"Pierce and inhale" design in capsule based dry powder inhalers: Effect of capsule piercing and motion on aerodynamic performance of drugs

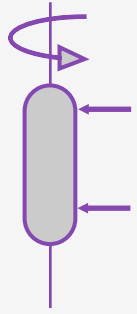
*Graphical Abstract (for review)

RS01

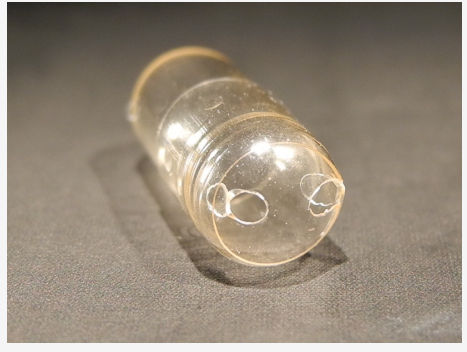


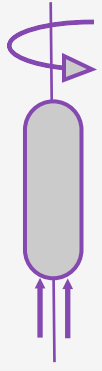


HandiHaler

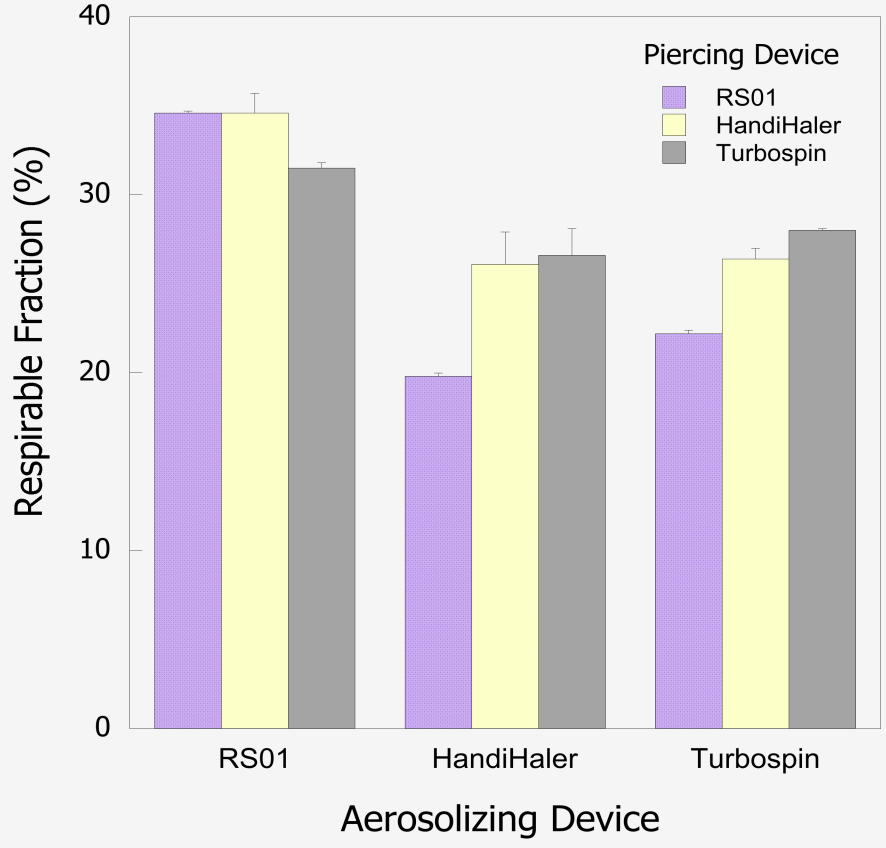


Turbospin





# «Pierce and Inhale» Design



# *"Pierce and Inhale" Design in Capsule Based Dry Powder Inhalers: Effect of capsule piercing and motion on aerodynamic performance of drugs*

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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 aerosolized in the same device or transferred and aerosolized 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; capsule motion.*

## 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 |

## 1. 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 (Adams et al., 2012; Buttini et al., 2008). 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 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 salmeterol xinafoatel/fluiticasone proprionate DPI entered in the inhaler market in 2013 (Grekas et al., 2014). 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 Spa) and Turbospin (Ph&T Spa) have been frequently used. Turbospin, in particular, has been used in high dose delivery of

antibiotics, such as in TOBI Podhaler® and Colobreathe® products (Geller et al., 2011; Schuster et al., 2013).

In the capsule pre-metered devices, the influence of the capsule piercing and motion during inhalation on the aerodynamic performance, 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 inside the device have been related to the powder emission and aerodynamic drug dispersion. The study was carried out using two technologically different dry powder formulations loaded in the capsule reservoir. An air jet micronized formoterol fumarate blended with coarse α-lactose monohydrate was used as model carrier formulation. In the specific case, the 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" cross-combination scheme, in which the capsules pierced with HandiHaler, RS01 and Turbospin were aerosolised 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 was used as reference.

## 2. Materials and Methods

### 2.1. Materials

Formoterol fumarate lactose blend (Foradil® Aerolizer®, Novartis – inhalation powder in hard gelatine capsules, Batch U0093) was purchased from the local pharmacy. One capsule contains 12 μg of formoterol fumarate dispersed 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 Aerolizer® (Novartis, Switzerland), coded AR; RS01® (Plastiape Spa, Italy); HandiHaler® (Boehringer Ingelheim, Germany), coded HH and Turbospin® (PH&T, Italy) coded, TS.

## 2.2. The "pierce and inhale" design

All the devices use a size 3 capsule as dose reservoir. In general, the piercing mode of the selected inhalers consisted of two or more holes pierced in different capsule positions. Hole diameters were 1.15 mm for RS01 and Turbospin, 1.45 mm for HandiHaler and 0.60 mm for 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 "pierce and inhale" design was organized in such a way that each device aerosolized the capsule pierced in itself and the capsules pierced with the other devices. The scheme illustrating the nine aerosolization tests performed is reported in Table 1. Therefore, the capsule was pierced and aerosolized in the same device or, pierced and transferred for aerosolization with the other devices. The piercing and transferring of the capsule was carefully executed in order to prevent powder loss during the transfer.

## 2.3. *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).

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 hydrochloric 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.

The measurement of drug deposited in the impactor allows the calculation of different deposition parameters. The delivered dose (DD) was the amount of drug ex-device measured from induction port (IP) 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 FPD and DD. The Mass Median Aerodynamic Diameter (MMAD) was determined by plotting the cumulative percentage of mass less than stated aerodynamic diameter (probability scale) versus aerodynamic diameter (log scale).

Since the inhaler devices had different intrinsic resistance, they have been used at different airflows. The flow rate used during each test was adjusted with a Critical Flow Controller

155 TPK (Copley Scientific, Nottingham, UK). In particular, the flow rates correspondent to 4
156 kPa drop over the inhaler without capsule, controlled before each experiment by Flow Meter
157 DFM 2000 (Copley Scientific, Nottingham, UK) and obtained by the vacuum pump VP1000,
158 Erweka GmbH, Heusenstamm, Germany, are reported in Table 1.
159

160 ## 2.3. Assays of formoterol fumarate and insulin

161 Formoterol fumarate assay was performed according to previous published method (Buttini et
162 al., 2014) and insulin content was determined by HPLC according to (Balducci et al., 2014).
163

164 ## 2.4. Statistical analysis

165 The significance of difference between the data was performed using an unpaired t-test. When
166 pairs had different variances, the Welch's correction was used (significance level $p < 0.05$).
167 Statistical analysis was performed using Prism 5 (GraphPad, Software Inc., USA).
168

## Results and Discussions

### 3.1. Device description and powder delivery mechanism

The medium resistance RS01 device pierces the capsule, horizontally inserted in the housing chamber, using two opposite needles. 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, airflow streams enter via the two tangential inlets in the capsule chamber. In this way, under the inhalation airflow, the capsule moves upside the housing chamber in a circular larger space where it can spin around its minor axis. The result is the centrifugation out of the capsule content through the two opposite holes. This capsule motion is identical to Aerolizer device, a low resistance inhaler, in which the capsule is pierced on the top and bottom using four needles and the mouthpiece is longer.

HandiHaler® has two parallel needles which pierce the capsule, vertically inserted in the device, on the same side close to the top and bottom. In this device, during the airflow, the capsule axially vibrates shaking out 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, 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.

### 3.2. Aerodynamic performance of carrier-based formulation

Foradil® gelatine capsules contain 12 μg of formoterol fumarate, coupled with the Aerolizer device. The device has two pairs of four needles with conical tips, which pierce the holes on the bottom and on the top of the capsule. The Foradil formulation has been developed with

194 the Aerolizer device: the type of lactose, its size distribution and the ratio in the mixture have
195 been optimized for the combination with this specific device. With the intent to establish a
196 performance reference, the aerodynamic assessment of Foradil was firstly conducted (Table
197 2). The delivered dose was 9.74 μg, corresponding to 81.2% of the formoterol fumarate
198 labelled dose, and the fine particle dose was 3.71 μg.
199 Then, Foradil capsules were inserted in the other devices of the study, pierced and
200 aerosolized. The measured aerodynamic parameters are reported in Table 2 and the deposition
201 distributions of formoterol fumarate within the NGI, are illustrated in Fig. 2.
202 More than 81% of the formoterol fumarate labelled dose was delivered from AR, RS01 and
203 HH. Turbospin showed a lower dose emission since the capsule and mouthpiece withhold
204 more than 25% of drug (see Fig. 2). Although the TS device exhibited the lowest delivered
205 dose, its FPD was not the lowest, due to the smaller amount of drug deposited in the throat
206 and pre-separator. This substantiated an efficient dispersion of powder emitted in the air
207 stream by TS.
208 Among the three devices, HH exhibited the lowest fine particle dose (3.13 μg) justified by the
209 high MMAD value (3.59 μm), despite the large size of capsule holes (1.72 mm) favoured the
210 dose emission. However, the hole size of capsule inversely affects the inhaler performance,
211 having shown that, increasing the hole size, the drug disaggregation decreased (Son et al.,
212 2013). The less efficient disaggregation capacity of HH determined the Foradil formulation
213 did not effectively combine with this device, since the mouthpiece and capsule retained a high
214 fraction of the drug formulation. As a consequence, the deposition on respirable size stages
215 was low.
216 The RS01 resulted in the most efficient device for aerosolizing Foradil capsule content as the
217 values of delivered dose, fine particle dose and fraction indicated. The centrifuge spinning of
218 the capsule in RS01 supported high powder emission and disaggregation (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.

Aerolizer showed a FPD value significantly lower compared to the similar RS01 device (3.71 µg versus 4.15 µg). The difference could be assigned to the lower emitted dose as result of the low resistance of Aerolizer, together with the different size and position of holes. In regard to 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, presented the holes at the extremities.

### 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 aerosolize the formulation are reported in Table 2. The Aerolizer was not included in the "pierce and inhale" design because it has similar piercing position and motion of RS01.

The aerosolization with RS01 reached a high efficacy also when the Foradil capsule was pierced with 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 DD and FPD values significantly lower compared to the previous 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 extremities of the capsule body and cap. It vaults to underline that the fine particle fraction values of these three hole/device experiments were similar but, in reality, different doses have been deposited in the respirable-size stages.

Aerosolizing with HandiHaler 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 (10.62 µg), but the poorest FPD (2.38 µg). The air flow of HH device efficiently extracts the powder even with the RS01 holes, but the disaggregation was strongly affected by the hole position. The 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, 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 emission from the capsule was not different in terms of DD and FPD compared to HandiHaler. 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 are also situated in the low pressure region of HandiHaler turbulence chamber.

However, since the emission from RS01 pierced capsule was high, 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 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 high 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 2) consisted of Foradil capsules pierced with the other devices and aerosolized with Turbospin. Differences in delivered dose were observed and TS exhibited the lowest emission value (9.49 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 (10.19 μg). The drug delivered amount of capsule pierced with HH could be favoured by bigger hole size and the non centred bottom 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 disaggregation efficiency, also due to the fastest airflow rate for aerosolization among the three devices. In fact, the FPD reached the highest value in this set of experiments (3.35 μg). The FPDs from capsules pierced with RS01 and HH were significantly lower compared to TS data. This result was confirmed by their 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 is ranked in Table 3 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

294 rotates around its minor axis, Foradil formulation achieved the maximum emission and
295 disaggregation when the holes were oppositely pierced on the capsule. In fact, RS01 was less
296 performing when the holes are confined on one side of the capsule, such as in TS.
297 Turbospin inhaler evidenced a clear dichotomy between emission and disaggregation of
298 drug/carrier mixture. The air turbulence in this device provided high disaggregation together
299 with low emission. This inhaler constantly retained in the device/capsule important amount of
300 powder, reasonably due to the holes at the bottom of the capsule in the turbulence chamber of
301 the device.
302 The HH device, that aerosolizes through a depression in correspondence of the lateral surface
303 of the capsule bottom, worked well also with the two holes provided by Turbospin, but badly
304 when the bottom hole was centred on the capsule body, such as with the capsules pierced with
305 RS01.
306 The aerosolization with Turbospin or HandiHaler, where the capsule vibrates and shakes for
307 powder emission, was negatively affected in case of the two opposite holes pierced by RS01.
308

309 ## 3.4. Aerodynamic performance of a carrier-free insulin formulation

310 For aerosolizing the insulin inhalation powder, the carrier-free formulation only requires the
311 disaggregation of the powder. 2 mg of a recombinant human insulin spray-dried powder were
312 loaded in HPMC size 3 capsules and aerosolized with the three devices. By piercing and
313 aerosolizing the capsule within the same device (Table 4), the RS01 device showed the best
314 results in terms of delivered dose and FPD. In comparison, Turbospin and HandiHaler devices
315 showed FPD values significantly lower. MMAD values confirm the better disaggregation
316 performance of RS01.
317 The distribution of the powder inside the impactor is illustrated in Fig. 5. RS01, HH, TS
318 devices had a different average device/capsule powder retention. As found for Foradil, among

319 the devices, Turbospin showed a low insulin spray dried emitted dose. Thus, the result
320 observed in the case of formoterol blend was confirmed: the capsule spinning during
321 aerosolization (RS01 device) boosted the delivered dose and the powder respirability.
322 After that, the capsules pierced with a device were used with other devices, in all possible
323 combinations. Aerosolizing with the RS01 device, an emitted dose of insulin always above
324 80% of loaded dose was measured. Moreover, the different piercing position of the capsule
325 did not affect significantly the delivered dose. The FPD of capsule pierced and aerosolized
326 with RS01 was not significantly modified when the capsules were pierced with the other
327 devices, indicating that this highly respirable spray dried insulin reduced the effect of the hole
328 position when the capsule is spinning.
329 The HandiHaler device, as aerosol producer, gave similar emission performance with all the
330 piercing combinations and the fine particle dose did not change with the piercing positions.
331 The MMAD values resulted increased compared to the RS01 inhaler, indicating a lower
332 disaggregation efficiency.

333 Finally, when the capsule was pierced and aerosolized with the Turbospin, the two holes
334 made on the bottom end of the capsule led to a high retention of the powder in the inhaler also
335 with this formulation. Powder aerodynamic distribution (Figure 6) shows that, using TS to
336 aerosolize the capsules pierced by the other two inhalers, in particular HH, the amount of
337 powder non-emitted and remaining in the capsule and device was significantly reduced.
338 In the case of this carrier free insulin powder, the disaggregation was less demanding than the
339 emission from the capsule. In fact, insulin spray dried powder was very flowable and the
340 particles do not have the tendency to aggregate (Buttini et al., 2012).
341 Comparing the Respirable Fraction of the various combinations (Table 5), the differences in
342 the values measured resulted less pronounced than in the case of the drug/carrier mixture.

343 Again, the performance of the RS01 as dry powder inhaler was at the top of the ranking of
344 respirable fractions and the values were more reproducible.
345

346 ## 3. Conclusions

347 The two aerodynamic delivery variables of dry powder inhaler i.e., powder emission and drug
348 disaggregation (DD and FPD), are differently maximized by the capsule behaviour in the
349 inhaler in relation to capsule holes' position. The different combination between piercing site
350 and aerosolizing device revealed that the capsule motion under inhalation airflow essentially
351 governs the powder emission, whereas the airflow pattern around the capsule in the
352 turbulence inhaler chamber reinforced the disaggregation and dispersion of the powder.
353 The dose emission and drug dispersion of the two dry powder formulations, aerosolized with,
354 differently pierced capsules, helps to optimize the combinations of device and generic
355 formulations. The spinning motion of capsule is the most powerful mechanism for improving
356 the overall aerodynamic performance.
357 In case of formoterol fumarate/lactose blend, the capsule motion during the aerosolization
358 was the critical factor for emission. The drug aerodynamic performance, i.e., the powder
359 disaggregation, was significantly modified by the different combinations between hole
360 position and inhaler type.
361 In case of insulin spray-dried powder without carrier, the capsule motion was the most
362 relevant element for the drug aerodynamic behaviour. Using the high respirable pure insulin
363 powder, the capsule piercing position was less influent on the device performance as
364 measured by respirable fraction.

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367 RS01 inhaler.

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# Figure captions

Fig 1. Dry powder inhalers, corresponding pierced capsules and their motion direction; top to bottom: Aerolizer, RS01, HandiHaler, Turbospin.

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

Fig 3. Next Generation Impactor deposition of formoterol fumarate dry powder aerosolized with HandiHaler, (n=3; mean ± sd); (D+C: Device and capsule, IP: induction port). Legend refers to the piercing device.

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

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

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

# Tables

Table 1. List of the experiments: device used to aerosolize, to pierce the size 3 capsule and the flow rate adopted for aerodynamic assessment.

| Exp # | Aerosolising Device | Piercing Device | Operating flow rate (L/min) |
|---|---|---|---|
| **1** | Aerolizer® | Aerolizer® | 90* |
| **2** | RS01® | RS01® | 60 |
| **3** | RS01® | HandiHaler® | 60 |
| **4** | RS01® | Turbospin® | 60 |
| **5** | HandiHaler® | HandiHaler® | 40 |
| **6** | HandiHaler® | RS01® | 40 |
| **7** | HandiHaler® | Turbospin® | 40 |
| **8** | Turbospin® | Turbospin® | 80 |
| **9** | Turbospin® | RS01® | 80 |
| **10** | Turbospin® | HandiHaler® | 80 |

* The flow rate was limited to 90L/min due to the capability of the Erweka® pump.

Table 2. Aerodynamic parameters of formoterol fumarate delivered by different devices: Delivered Dose (DD), Mass Median Aerodynamic Diameter (MMAD), Fine Particle Dose (FPD) and Fine Particle Fraction (FPF); (n=3; mean ± sd). Labelled dose: 12 µg.

| **Aerosolizing device** | **Piercing device** | **DD (µg)** | **MMAD (µm)** | **FPD (µg)** | **FPF < 5 µm (%)** |
|---|---|---|---|---|---|
| Aerolizer (AR) | Aerolizer | 9.74 ± 0.12 | 2.52 ± 0.04 | 3.71 ± 0.09 | 38.1 ± 0.4 |
| RS01 | RS01 | 11.18 ± 0.15 | 3.14 ± 0.01 | 4.15 ± 0.02 | 37.1 ± 0.5 |
| | HandiHaler | 11.13 ± 0.19 | 3.10 ± 0.11 | 4.15 ± 0.13 | 37.3 ± 0.4 |
| | Turbospin | 10.13 ± 0.13* | 2.95 ± 0.01 | 3.78 ± 0.03 * | 37.3 ± 0.6 |
| HandiHaler (HH) | HandiHaler | 10.54 ± 0.07 | 3.59 ± 0.01 | 3.13 ± 0.21 | 29.7 ± 1.3 |
| | RS01 | 10.62 ± 0.23 | 4.03 ± 0.18 | 2.38 ± 0.03 * | 22.4 ± 0.5 * |
| | Turbospin | 10.19 ± 0.73 | 3.46 ± 0.17 | 3.19 ± 0.18 | 31.3 ± 0.4 |
| Turbospin (TS) | Turbospin | 9.49 ± 0.24 | 3.12 ± 0.01 | 3.35 ± 0.01 | 35.3 ± 0.5 |
| | RS01 | 9.67 ± 1.04 | 3.37 ± 0.06 | 2.66 ± 0.03 * | 27.5 ± 2.3 * |
| | HandiHaler | 10.19 ± 0.17 * | 2.98 ± 0.03 | 3.17 ± 0.07 * | 31.1 ± 0.2 * |

* significantly different from the reference of each set; $p < 0.05$

Table 3. Ranking of the different combinations between the inhalers on the base of the Respirable Fraction (RF), i.e., the ratio between the Fine Particle Dose (FPD<5 μm) and the labelled dose.

| **Aerosolizing Device** | **Piercing Device** | **RF (%)** |
|---|---|---|
| RS01 | RS01 | 34.6 ± 0.1 |
| RS01 | HandiHaler | 34.6 ± 1.1 |
| RS01 | Turbospin | 31.5 ± 0.3 |
| Aerolizer | Aerolizer | 30.9 ± 0.4 |
| Turbospin | Turbospin | 28.0 ± 0.1 |
| HandiHaler | Turbospin | 26.6 ± 1.5 |
| Turbospin | HandiHaler | 26.4 ± 0.6 |
| HandiHaler | HandiHaler | 26.1 ± 1.8 |
| Turbospin | RS01 | 22.2 ± 0.2 |
| HandiHaler | RS01 | 19.8 ± 0.2 |

Table 4. Aerodynamic parameters of spray-dried insulin delivered by different devices: Loaded dose (LD), Delivered Dose (DD), Mass Median Aerodynamic Diameter (MMAD), Fine Particle Dose (FPD) and Fine Particle Fraction (FPF); (n=3; mean ± sd).

| **Device** | **Capsule Pierced with** | **Loaded Dose (mg)** | **DD (mg)** | **DD (%)** | **MMAD ($\mu$m)** | **FPD (mg)** | **FPF (%)** |
|---|---|---|---|---|---|---|---|
| RS01 | RS01 | 1.94 ± 0.02 | 1.56 ± 0.08 | 80.4 | 1.52 ± 0.13 | 1.33 ± 0.07 | 85.5 ± 0.19 |
| | HH | 1.93 ± 0.03 | 1.68 ± 0.06 | 87.0 | 1.61 ± 0.16 | 1.33 ± 0.02 | 79.3 ± 1.41 |
| | TS | 1.88 ± 0.02 | 1.51 ± 0.02 | 80.3 | 1.46 ± 0.17 | 1.23 ± 0.13 | 81.7 ± 7.93 |
| HandiHaler | HH | 1.96 ± 0.02 | 1.51 ± 0.07 | 77.0 | 1.87 ± 0.37 | 1.10 ± 0.02 | 72.8 ± 3.32 |
| | RS01 | 1.94 ± 0.05 | 1.63 ± 0.02 | 84.0 | 2.48 ± 0.38 | 1.12 ± 0.02 | 68.7 ± 0.21 |
| | TS | 1.95 ± 0.01 | 1.52 ± 0.03 | 78.0 | 2.12 ± 0.04 | 1.11 ± 0.02 | 72.9 ± 0.23 |
| Turbospin | TS | 1.90 ± 0.01 | 1.41 ± 0.17 | 74.2 | 2.03 ± 0.53 | 1.09 ± 0.13 | 77.5 ± 4.45 |
| | RS01 | 1.91 ± 0.09 | 1.60 ± 0.12 | 83.8 | 1.55 ± 0.23 | 1.27 ± 0.19 | 79.5 ± 5.7 |
| | HH | 1.91 ± 0.01 | 1.63 ± 0.08 | 85.3 | 1.94 ± 0.26 | 1.28 ± 0.04 | 78.3 ± 1.4 |

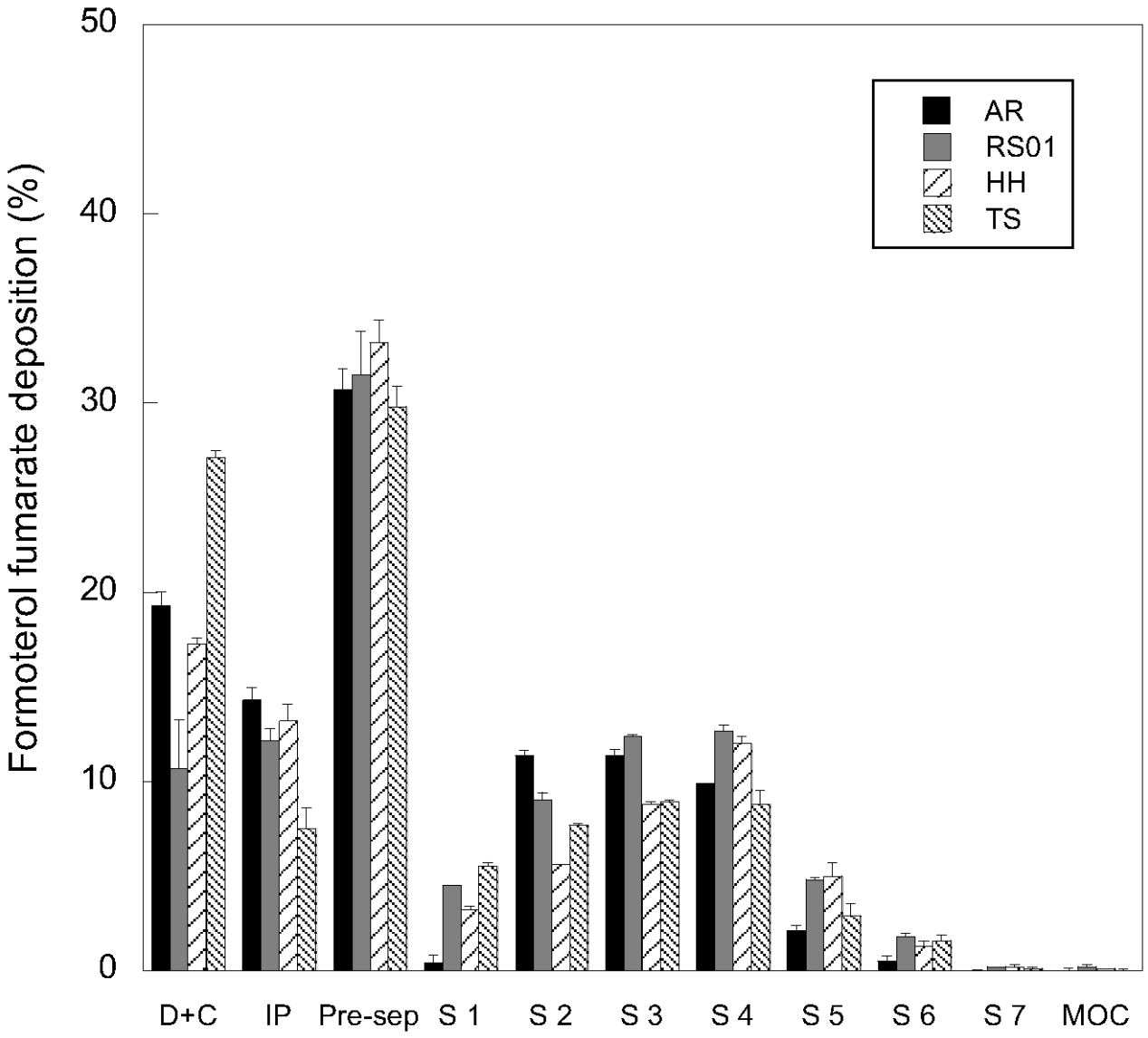
* significantly different with each reference at the top; $p < 0.05$.

Table 5. Insulin powder aerosolization of the different combinations between the inhalers ranked as Respirable Fraction (RF), i.e., ratio between Fine Particle Dose (FPD) and Loaded Dose (LD).

| **Aerosolizing Device** | **Piercing Device** | **RF (%)** |
|---|---|---|
| RS01 | HandiHaler | 68.9 ± 0.1 |
| RS01 | RS01 | 68.6 ± 3.2 |
| Turbospin | HandiHaler | 67.1 ± 1.9 |
| Turbospin | RS01 | 66.4 ± 6.7 |
| RS01 | Turbospin | 65.4 ± 7.8 |
| HandiHaler | RS01 | 57.7 ± 2.5 |
| Turbospin | Turbospin | 57.4 ± 6.5 |
| HandiHaler | Turbospin | 56.9 ± 0.9 |
| HandiHaler | HandiHaler | 56.2 ± 4.2 |

Figure(s)


Fig. 1


Formoterol fumarate deposition (%)
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40
30
20
10
0
AR
RS01
HH
TS
D+C
IP
Pre-sep
S 1
S 2
S 3
S 4
S 5
S 6
S 7
MOC

Fig. 2

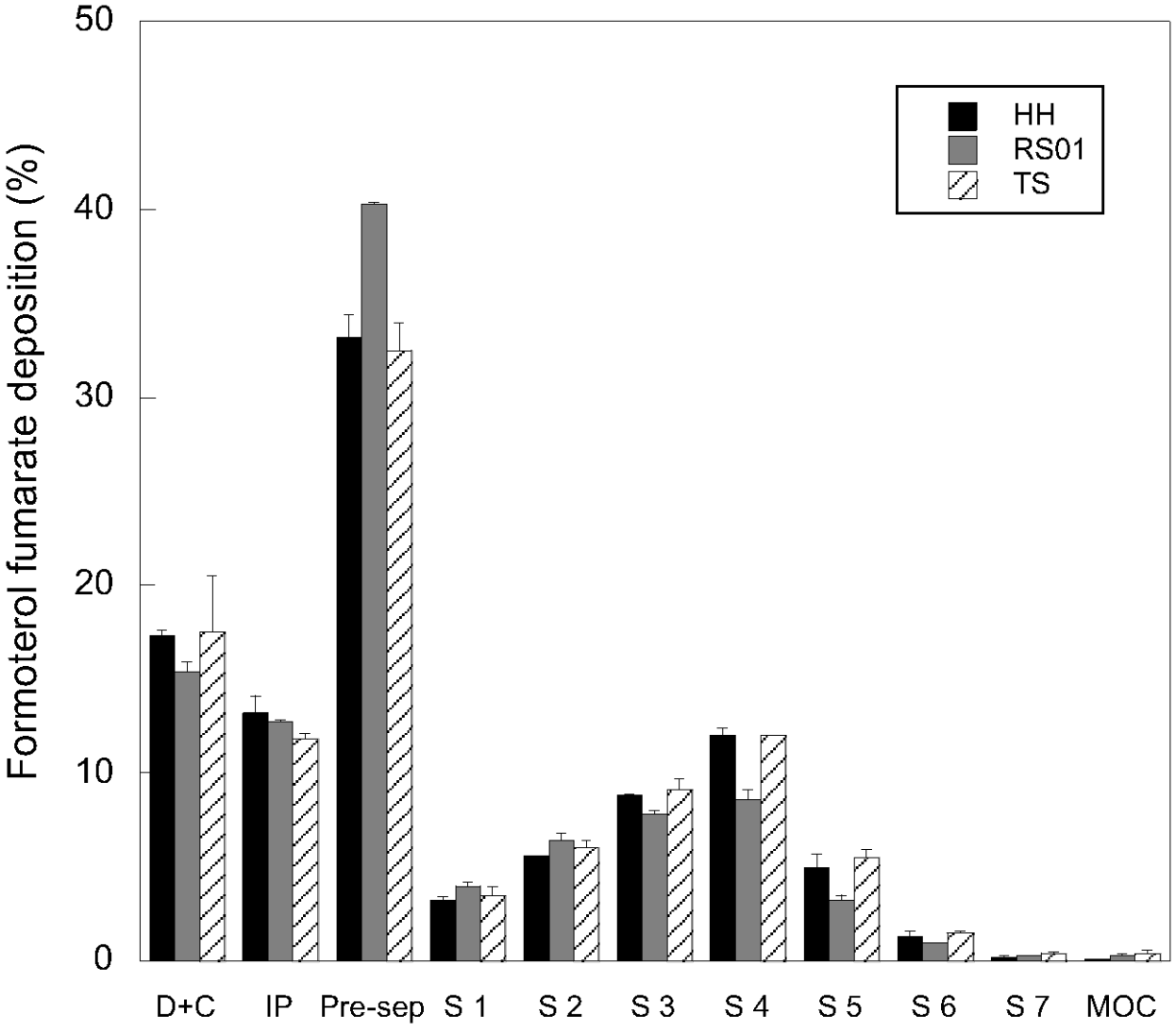
Formoterol fumarate deposition (%)
50
40
30
20
10
0
HH
RS01
TS
D+C
IP
Pre-sep
S 1
S 2
S 3
S 4
S 5
S 6
S 7
MOC

Fig. 3

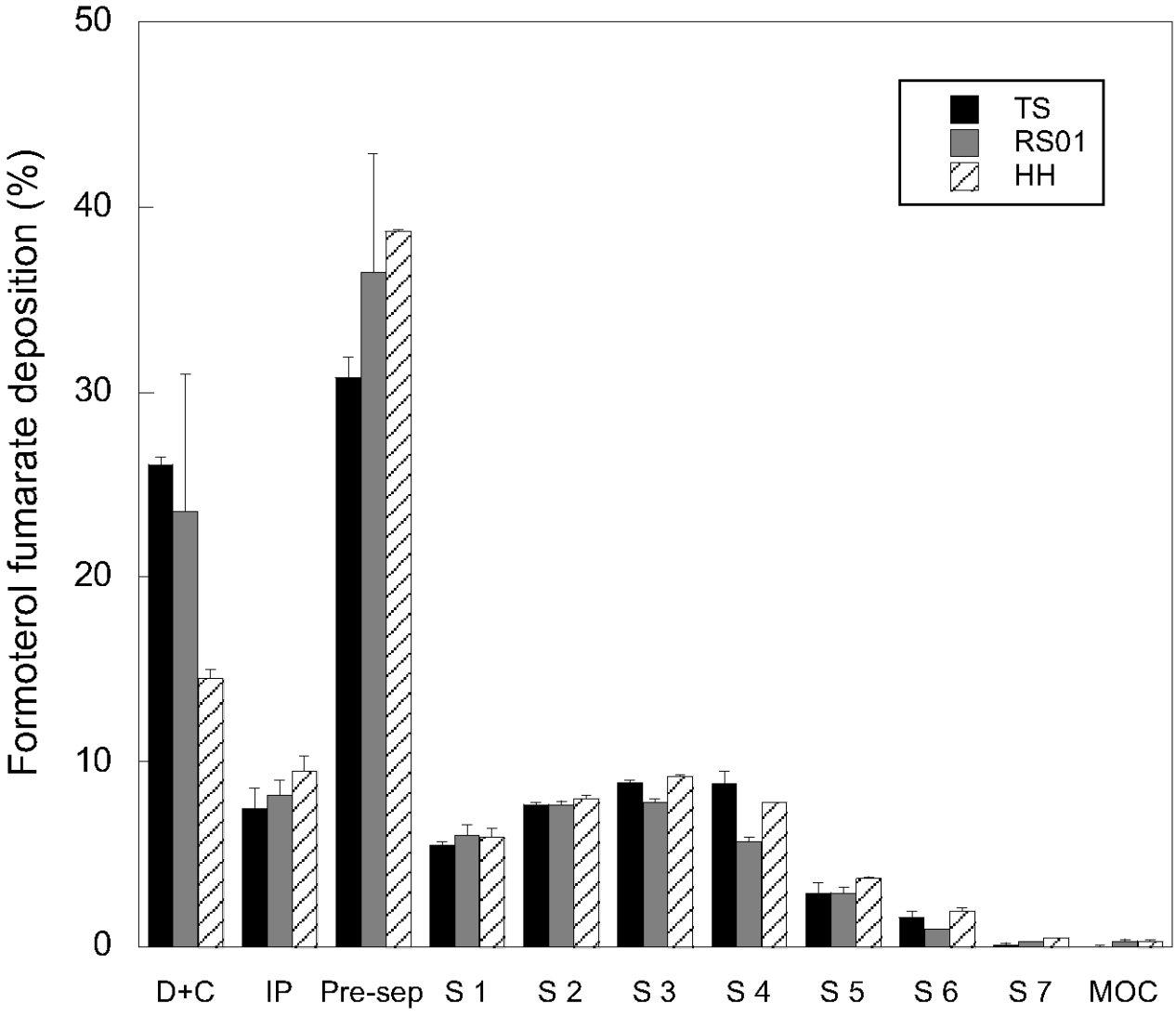
Formoterol fumarate deposition (%)
50
40
30
20
10
0
TS
RS01
HH
D+C
IP
Pre-sep
S 1
S 2
S 3
S 4
S 5
S 6
S 7
MOC

Fig. 4

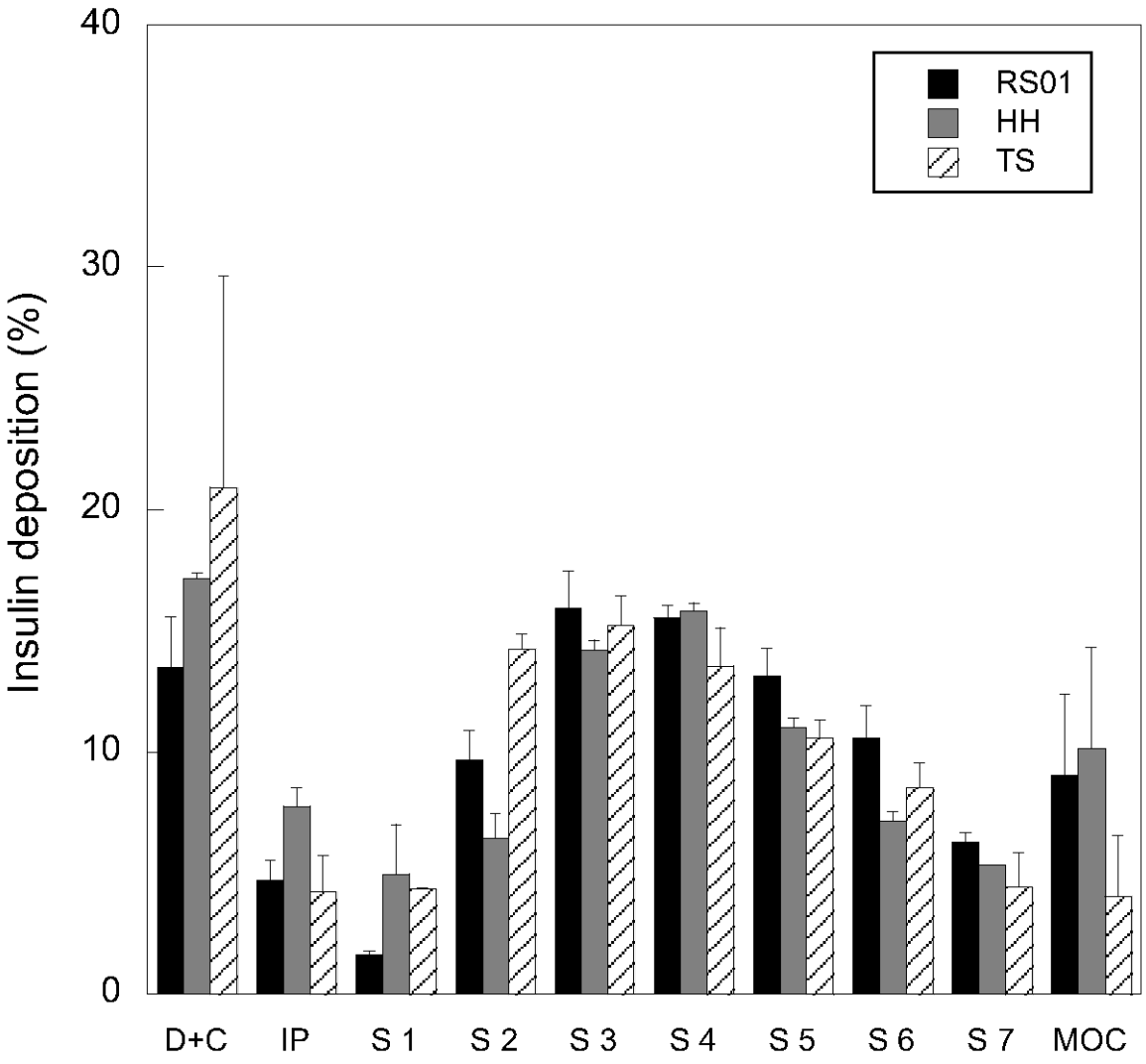
40
30
20
10
0
Insulin deposition (%)
RS01
HH
TS
D+C
IP
S 1
S 2
S 3
S 4
S 5
S 6
S 7
MOC

Fig. 5

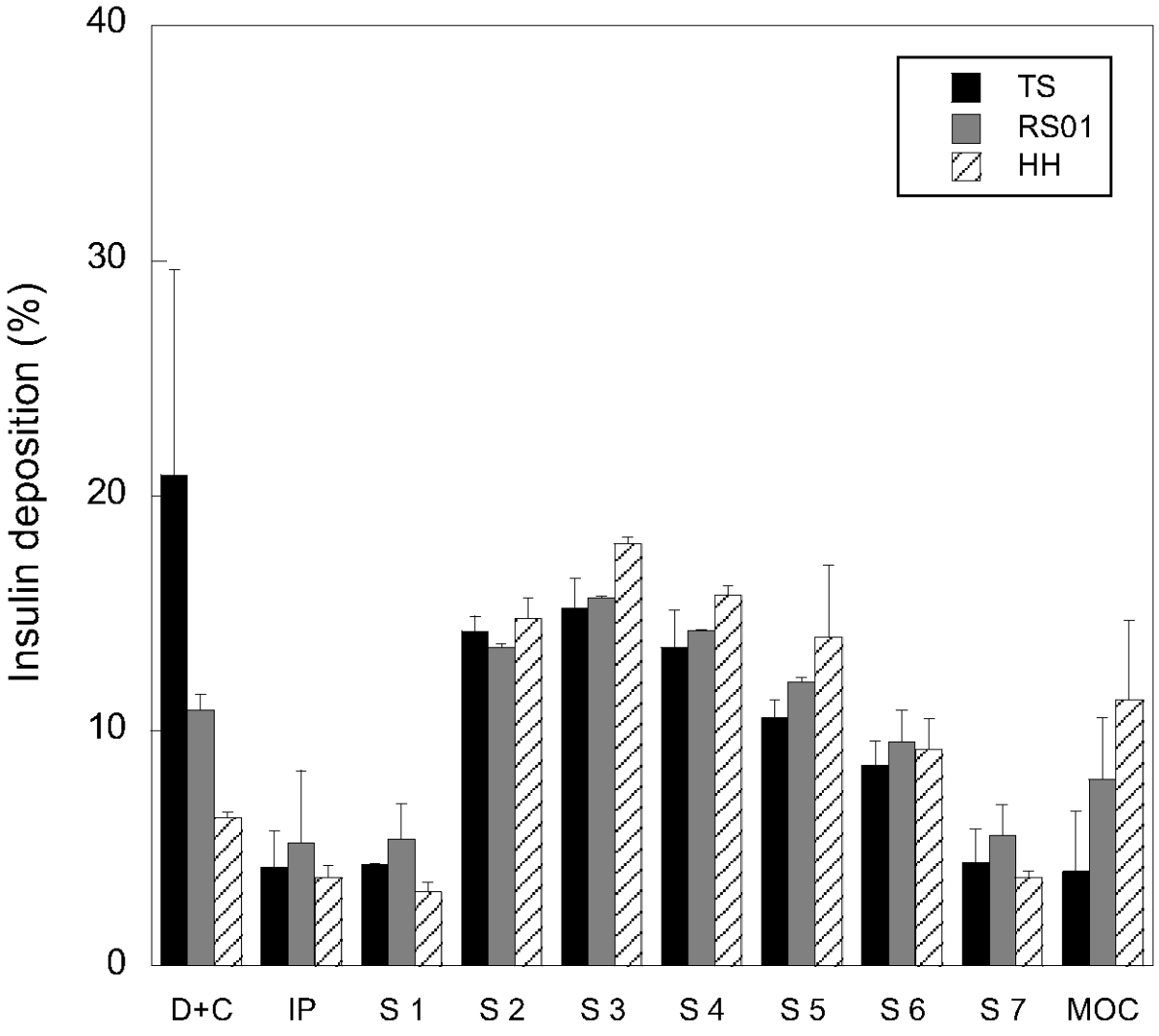
40
30
20
10
0
Insulin deposition (%)
TS
RS01
HH
D+C
IP
S 1
S 2
S 3
S 4
S 5
S 6
S 7
MOC

Fig. 6