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Investigation of Humidity and Electrostatic Charge on Anticholinergic Molecules in Dry Powder Inhalations

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Abstract

Background: Dry powder inhalers (DPIs) are commonly used for respiratory diseases such as asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD). DPIs have many advantages for patients, such as ease of use or rapid delivery to the patient's lungs. However, they can be very sensitive to environmental conditions such as ambient relative humidity (RH) and electrostatic charge, and therefore the manufacturing process and storage conditions of these pharmaceutical products must be carefully determined.

Method: In this study, two different active substances belonging to the anticholinergic family were studied and it was examined how the active substances of the same family might be affected by changing humidity conditions. The change in the amount of delivered active substance to the patient's lungs as the electric charge accumulated in the capsules was determined. Additionally, the effect of electrical charge of the inhaler device on fine particle dose (FPD) was studied in capsules manufactured with Active Substance-1.

Results and Conclusion: This study demonstrated that, with the increase in ambient humidity and aging of the capsule and powder, the FPD of Active Substance-1 and the total mass increased in parallelly. While Active Substance-2 was not affected by the aging of the capsules, it was observed that the FPD value increased with the increase in ambient RH during the manufacturing process.

Keywords: Dry Powder Inhaler; Next Generation Impactor; Relative Humidity; Electrostatic Charge; Fine Particle Dose

Abbreviations: AATD: Alpha-1 Antitrypsin Deficiency; CITDAS: Copley Inhaler Testing Data Analysis Software; COPD: Chronic Obstructive Pulmonary; DPI: Dry Powder Inhaler; EP: European Pharmacopeia; FPD: Fine Particle Dose; GSD: Geometric Standard Deviation; HPLC: High Performance Liquid Chromatography; MDI: Metered Dose Inhaler; MMAD: Mass Median Aerodynamic Diameter; NGI: Next Generation Impactor; RH: Relative Humidity

Introduction

Recently, chronic diseases that negatively affect the lungs and respiratory system such as asthma, chronic bronchitis, and chronic obstructive pulmonary (COPD) tend to increase due to environmental factors. Asthma and COPD cause excessive production of sticky material, which is described as mucus, wheezing, shortness of breath, and chest tightness [1]. While most of the causes of this disease are tobacco exposure, air pollution, chemical gases, or dust, a very rare part of it occurs due to a genetic disease called alpha-1 antitrypsin deficiency (AATD) [2]. According to the World Health Organization, it has been reported that COPD is the third leading cause of death worldwide and 3.2 million deaths were recorded in 2019 from COPD. According to the forecasts, it is predicted that COPD will rise to the 3rd place among the diseases that result in death by 2030 [3].

In the treatment of such diseases, many different inhalation products, such as dry powder inhalations (DPIs), nebule, and pressurized metered dose inhalers (MDIs), are used to provide local and systemic treatments to reduce inflammation in the respiratory system and increase airflow [4,5]. DPIs have become popular medical drugs due to their ease of use for patients, the absence of propellants, and the ability to quickly deliver small

amounts of API to the patient orally [6,7]. However, it is known that DPI products are sensitive to relative humidity (RH) and electrostatic charge, and the aerodynamic distribution in the lung is affected [8]. DPIs must be protected from the external environment to protect them from relative humidity [9]. For this reason, different humidity protection products are used by manufacturers, and desiccants can also be used in packaging [10].

In dry powder inhalation products, it is not important the amount of the active substance contained in the unit dose, it is important the amount of the active substance reaching the patient by inhalation. The effectiveness of DPIs is demonstrated by their ability to deliver reproducible fine particle doses (FPDs) of a given inhalable API to the site of action in the respiratory tract. Similarly, FPD can be defined as the dose of an aerosolized drug with a particle size < 5 μm [11].

Mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) parameters affect the deposition of inhaled particles. Particles with an aerodynamic diameter of 0.5 to 5 μm are more likely to accumulate in the lung, whereas smaller particles can penetrate deeper into the lungs [12]. The increase in the spread of the aerodynamic diameters of the particles depends on the high GSD value. The total dose is the amount of drug recovered from all parts (mouthpiece, induction port, pre-separator, NGI stages) used during analysis [13].

In the study of Borgstrom et al., fluticasone propionate/salmeterol Accuhaler and budesonide/formoterol Turbuhaler were studied at different relative humidity conditions, and it was shown that their FPD was affected [14]. O'Callaghan et al. showed in their study that the electrostatic charge in inhaler devices made up of plastic materials causes the drug to be retained in the device [15,16].

Material and Methods

Next Generation Impactor (NGI)

The aerodynamic performance of the DPI formulation was studied by using an NGI (Copley Scientific, UK). The European Pharmacopeia was followed as conducting NGI experiments (EP 2.9.18). The NGI stages were coated by using 1% v/v silicone oil solution prepared in hexane. 15 ml of diluent was added to the pre-separator part of the NGI. The actuation was done by using vacuum pump (HCP5, Copley Scientific, UK) / critical flow controller (TPK-2000, Copley Scientific, UK) and the flow rate was adjusted to 80 L/min for Active Substance-1, and 100 L/min for active substance-2 by using flow meter (Copley Scientific, UK). The inhalation device was placed in an appropriate mouthpiece and connected to the NGI equipment for the inhalation process. In each NGI study, ten DPI capsules are used. At the end of the actuation, pre-separator, mouthpiece, induction port and all stages were washed with diluent into volumetric flasks. The FPD and total mass were calculated by using Copley Inhaler Testing Data Analysis Software (CITDAS) application (Copley Scientific, UK).

High Performance Liquid Chromatography (HPLC) Analysis

Active Substance-1

The active substance-1 was analyzed with a validated analytical method (Validation parameters; linearity R2=1.00 (working range between 0.3 μg /mL-12.9 μg /mL), repeatability RSD= 4.52%, recovery 101.5%) by using High Performance Liquid Chromatography (HPLC) coupled with a UV detector (Waters, Massachusetts, USA). The flow rate in the chromatography system was 1.2 mL / min with a gradient elution 60% Mobile Phase A-40% Mobile Phase B. Mobile Phase A consists of 0.05% Trifluoroacetic Acid in purified water and Mobile Phase B consists of 0.05% Trifluoroacetic Acid in Acetonitrile. Waters Symmetry C18 150 mm x 4.6 mm, 3.5 μm (Waters, Massachusetts, USA) column was used. Column temperature was set at 30 ^{o}C. The diluent for the samples was used as Methanol: Water (50: 50; v/v). The sample was injected into the system as 30 μL with a run time of 8 min and detected at 210 ± 2 nm.

Active Substance-2

The active substance-2 was analyzed with a validated analytical method (Validation parameters; linearity R2=1.00, (working range between 0.4 μg /ml-12.4 μg /ml), repeatability RSD= 2.45%, recovery 100.0%) by using High Performance Liquid Chromatography (HPLC) coupled with a UV detector (Waters, Massachusetts, USA). The flow rate in the chromatography system was 0.8 mL / min with an isocratic elution Mobile Phase consists of 65% buffer solution, 20% Acetonitrile and 15% Methanol. Zorbax Eclipse XDB C18, 150 x 3 mm, 5 μm column was used. Column temperature was set at 40 ºC and sample temperature was set at 4 ºC. The diluent for the samples was used as Methanol: Water (35:65; v/v). The sample was injected into the system as 50 μL with a run time of 10 min and detected at 222 ± 2 nm.

Results

Results of Active Substance-1

In order to evaluate the effect of aging of powder, capsules were filled with powder after 5 days of aging at room temperature. In addition, capsules were aged for 5 days at room temperature in a glass petri dish before NGI analysis. According to the results given in the (Figure 1A), there was a significant increase in FPD when both capsules and powder were aged for 5 days. The impact of inhalation device on FPD was determined by using conditioned (used before) device and unconditioned (unused, new) device. FPD of initial capsule filling was compared with 5 days aged powder filled capsules and 5 days aged capsules. As shown in the (Figure 1B), using a new device has a significant role in delivering active substances to the lungs. In order to assess the behavior of FPD under different humidity conditions, NGI analysis was conducted at both 30% RH and 50% RH humidity levels. As

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a result, illustrated in (Figure 1C), a remarkable increase in the FPD value was observed in a high relative humidity environment. In addition, when the stage distribution results of the aging of the capsules and powder, the use of new and old devices, and the ambient humidity during analysis were evaluated, especially the increase in ambient humidity during NGI analysis changed the distribution in stages (Figure 1D). The increase in ambient humidity and the aging of the capsules and powder caused the electric charge in the capsules to decrease and the FPD tended to increase. As a result, it was determined that the total mass value increased in parallel, but no significant change was detected in MMAD values. (Table 1).

Table 1: Results of FPD, total mass, and MMAD and distribution of Active Substance-1 on stages.

	Initial capsule (µg)	5 days aged powder (µg)	5 days aged capsule (µg)	Unconditioned device 5 days aged powder (µg)	Unconditioned device 5 days aged capsule (µg)	30% RH (µg)	50% RH (µg)
Induction Port	5.93 ± 0.22	5.89 ± 1.92	6.81 ± 0.07	6.57 ± 0.46	5.64 ± 0.17	5.716 ± 0.29	3.47 ± 0.17
Pre-Separator	11.90 ± 0.60	13.05 ± 0.08	14.58 ± 0.48	15.02 ± 0.13	13.89 ± 0.62	12.54 ± 1.20	11.30 ± 0.02
Stage-1	2.49 ± 0.12	2.14 ± 0.04	2.41 ± 0.02	2.05 ± 0.06	1.83 ± 0.08	2.66 ± 0.08	2.17 ± 0.26
Stage-2	5.39 ± 0.33	5.28 ± 0.31	5.77 ± 0.03	5.51 ± 0.52	4.94 ± 0.03	6.60 ± 0.21	6.61 ± 0.39
Stage-3	7.85 ± 0.21	8.57 ± 0.15	9.38 ± 0.14	7.77 ± 0.20	7.23 ± 0.33	9.16 ± 0.73	10.15 ± 0.63
Stage-4	9.52 ± 0.22	10.98 ± 0.01	11.43 ± 0.62	9.00 ± 0.31	8.76 ± 0.61	9.78 ± 0.58	13.87 ± 1.14
Stage-5	5.24 ± 0.15	5.73 ± 0.46	5.77 ± 0.46	4.12 ± 0.02	3.82 ± 0.13	4.27 ± 0.01	5.96 ± 0.90
Stage-6-7-8	1.91 ± 0.05	2.23 ± 0.27	2.14 ± 0.12	1.22 ± 0.08	1.17 ± 0.10	0.97 ± 0.11	1.83 ± 0.23
FPD	27.46 ± 0.71	30.43 ± 0.72	31.91 ± 1.36	25.18 ± 0.10	23.74 ± 1.14	27.40 ± 1.53	35.16 ± 2.62
Total Mass	50.24 ± 1.35	53.85 ± 2.55	58.28 ± 1.84	51.26 ± 0.64	52.63 ± 0.43	51.70 ± 2.63	55.35 ± 3.15
MMAD	2.39 ± 0.02	2.29 ± 0.05	2.36 ± 0.05	2.51 ± 0.03	2.46 ± 0.03	2.73 ± 0.00	2.41 ± 0.02
FPF (%)	54.65 ± 0.06	56.55 ± 1,34	54.74 ± 0.60	51.49 ± 0.14	50.20 ± 1.96	52.99 ± 0.26	63.43 ± 1.49
GSD	2.05 ± 0.01	1.97 ± 0.02	1.96 ± 0.00	1.93 ± 0.03	1.95 ± 0.00	1.95 ± 0.02	1.92 ± 0.02

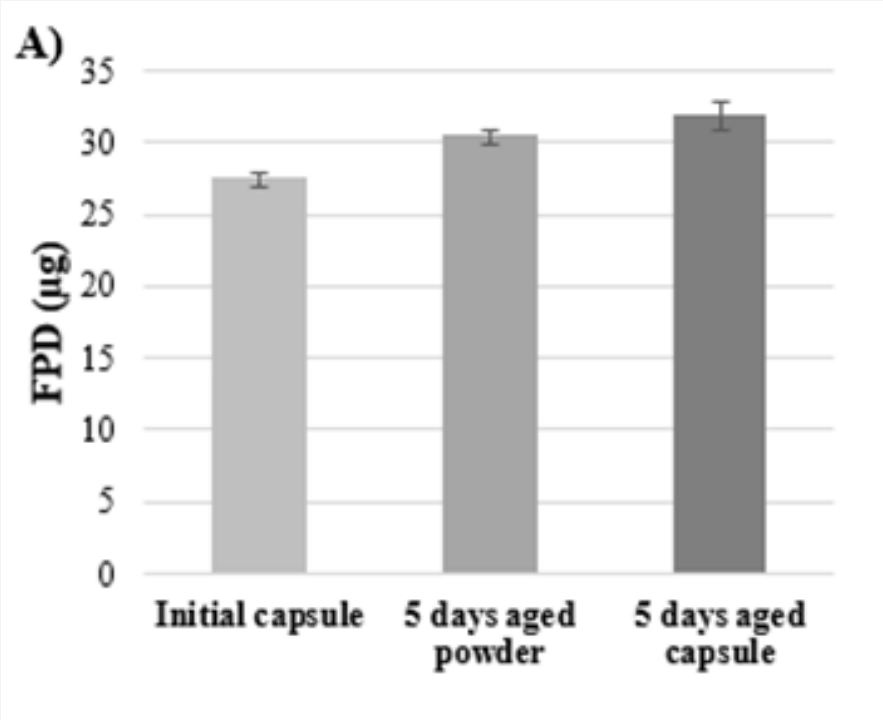

Figure 1A: FPD comparison of initial capsule filling with 5 days aged powder and 5 days aged filled capsule.

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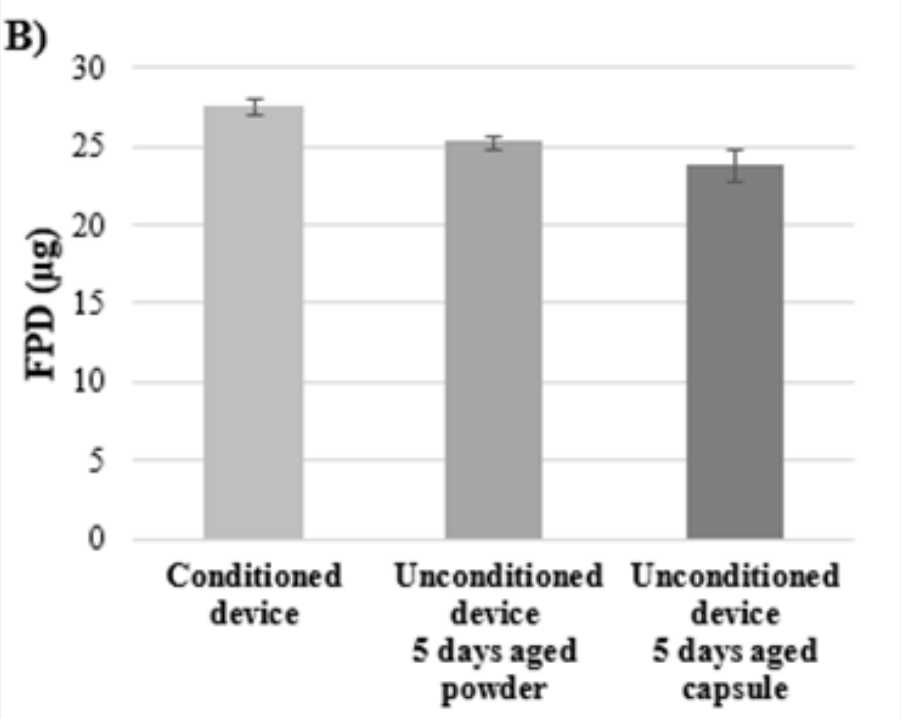

Figure 1B: FPD comparison of conditioned inhalation device use on initial capsule filling and unconditioned inhalation device use on 5 days aged powder and 5 days aged filled capsule.

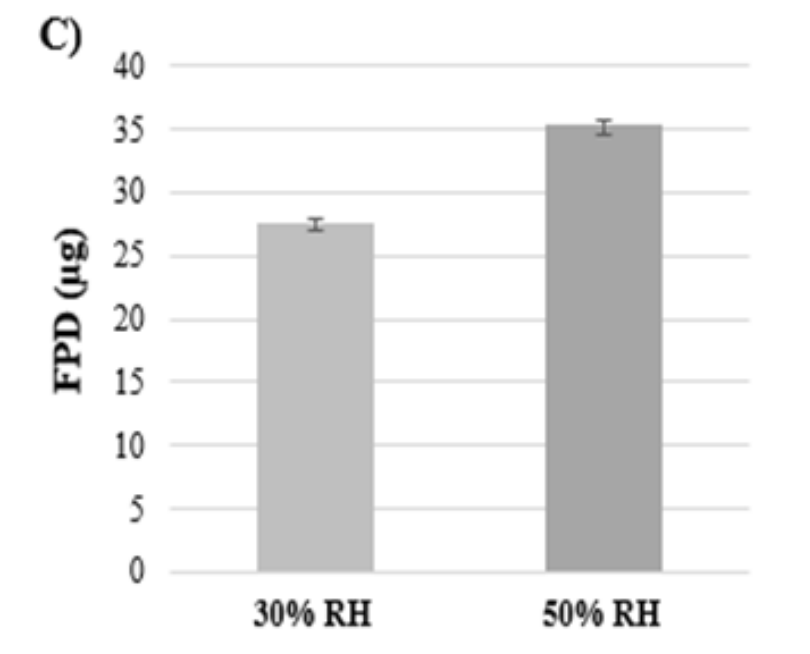

Figure 1C: FPD comparison of samples studied at different RH %.

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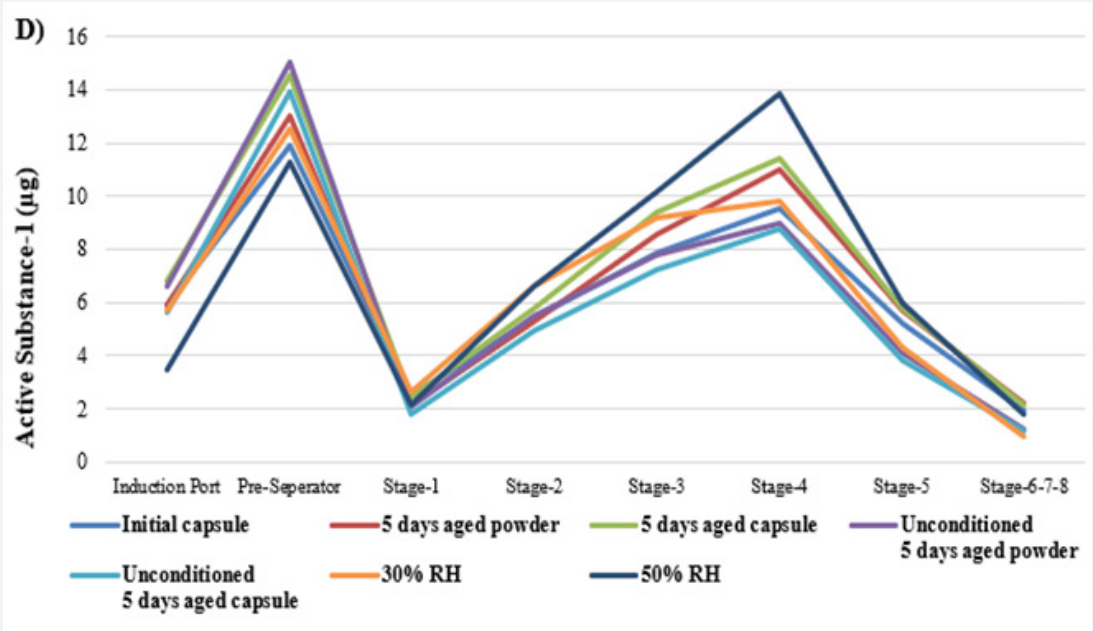

Figure 1D: Comparison of active substance delivered to NGI stages.

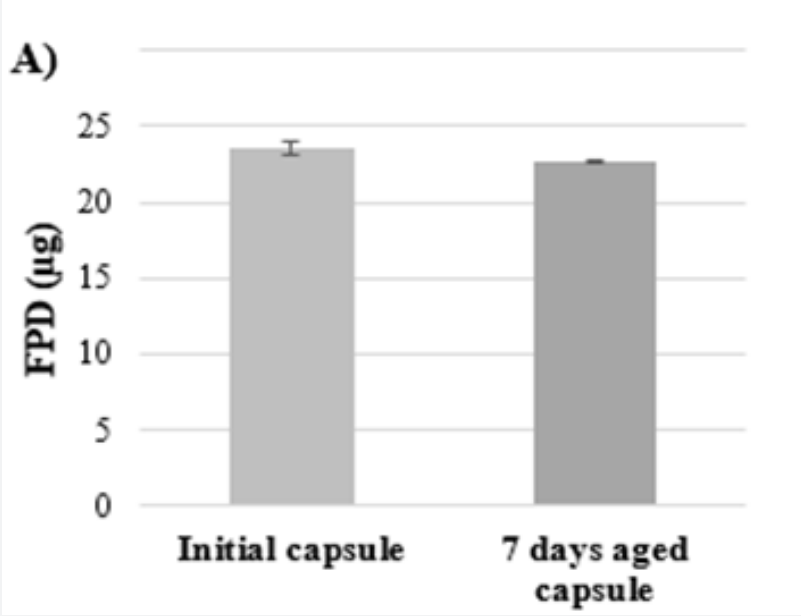

Figure 2A: FPD comparison of initial capsule filling with 7 days aged capsule.

Results of Active Substance-2

In order to evaluate the effect of aging of capsules, capsules were aged at room temperature < 55% RH for 7 days. The capsules were aged in a glass petri dish before NGI analysis. As shown in the (Figure 2A), no significant change in the FPD results was observed as capsules were aged. In order to examine the effect of relative humidity on the manufacturing process, manufacturing was also carried out in a high humidity condition. For this, high humidity condition more than 55% RH at a constant room temperature was set during the production process. When the results given in (Figure 2B) are analyzed, it is shown that the FPD value of capsules produced at high humidity is increased compared to capsules produced at low humidity (< 55% RH). In addition, while

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the aging of the capsules did not have a significant effect on the stage distribution, the increase in ambient humidity during the manufacturing process changed the distribution in stages (Figure 2C). Aging the capsules for 7 days and increasing the ambient humidity during production created an increase in the total mass value but did not cause a significant effect on the MMAD values. When the results of the initial capsule produced at low humidity and the capsule produced at high humidity were compared, it was observed that although the total mass value delivered to the patient remained constant, the amount of FPD delivered to the lungs increased (Table 2).

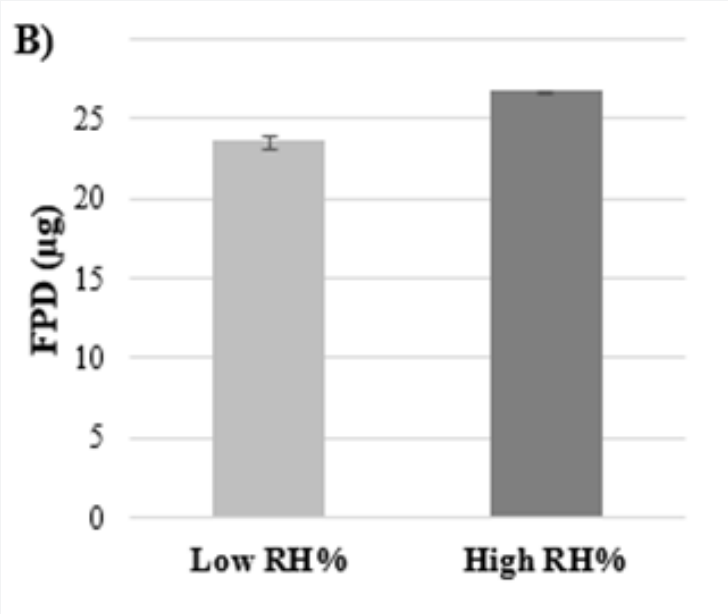

Figure 2B: FPD comparison of capsules produced at high humidity (> 55% RH) and produced at low humidity (< 55% RH).

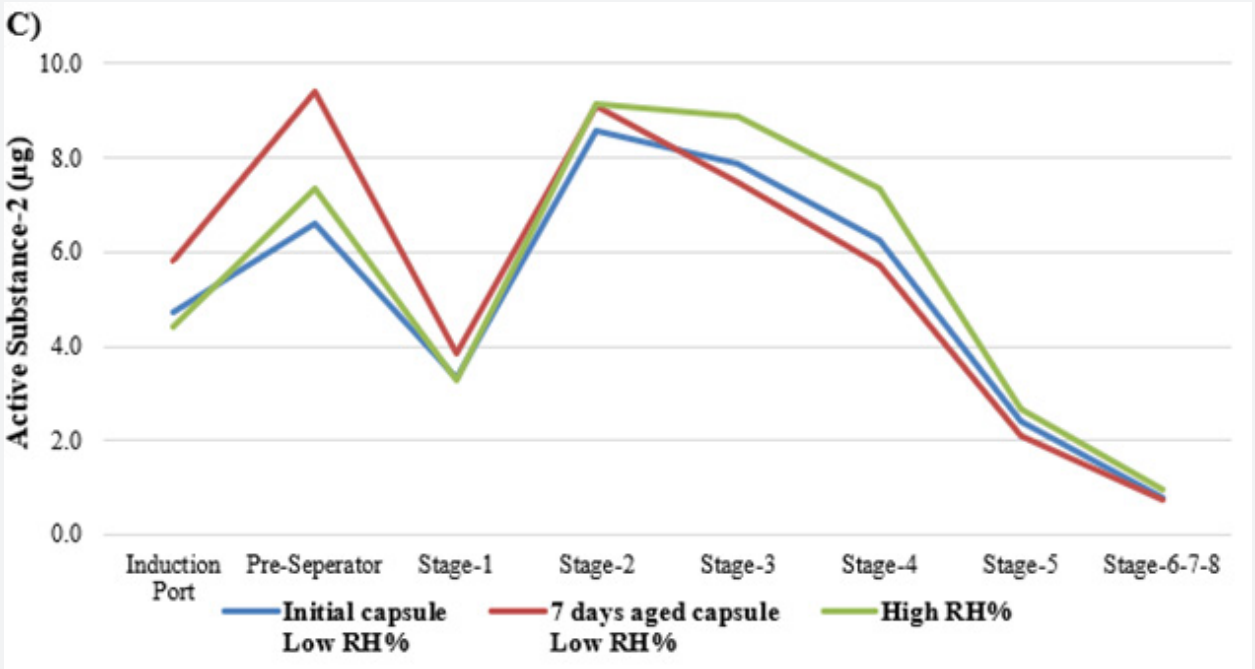

Figure 2C: Comparison of active substance delivered to NGI stages.

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Table 2: Results of FPD, total mass, and MMAD and distribution of Active Substance-2 on stages.

	Initial capsule Low RH% (μg)	7 days aged capsule (μg)	High RH% (μg)
Induction Port	4.72 ± 0.24	5.84 ± 0.44	4.40 ± 0.53
Pre-Separator	6.62 ± 0.93	9.40 ± 0.37	7.34 ± 0.41
Stage-1	3.33 ± 0.03	3.85 ± 0.01	3.27 ± 0.08
Stage-2	8.58 ± 0.20	9.10 ± 0.19	9.17 ± 0.11
Stage-3	7.87 ± 0.31	7.46 ± 0.00	8.89 ± 0.07
Stage-4	6.25 ± 0.22	5.73 ± 0.18	7.35 ± 0.38
Stage-5	2.40 ± 0.02	2.10 ± 0.11	2.67 ± 0.03
Stage-6-7-8	0.79 ± 0.01	0.76 ± 0.03	0.97 ± 0.07
FPD	23.52 ± 0.67	22.65 ± 0.11	26.66 ± 0.20
Total Mass	40.56 ± 0.01	44.24 ± 0.74	44.06 ± 0.19
MMAD	2.96 ± 0.01	3.13 ± 0.04	2.839 ± 0.04
FPF (%)	57.99 ± 1.67	51.20 ± 1.11	59.43 ± 0.20
GSD	1.84 ± 0.01	1.83 ± 0.02	1.83 ± 0.01

Discussion and Conclusion

The results of this study have shown that the relative humidity, the electrostatic charge, and the inhalation device play a significant role in delivering active substance in DPIs to the lungs. The samples that were exposed to higher RH during the inhalation process tend to have higher FPD levels compared to samples exposed to low levels of RH. If the results are evaluated, changing RH conditions affects the distribution of the active substance in the patient's lungs. However, RH do not affect the total dose of active substance delivered to the patient.

According to the previous study of Jetzer et al. in 2019, it has been shown that the inhalation device material is also important in the inhalation performance of DPIs since the plastic material may be affected from electrostatic charge 16. Moreover, previous studies have also evaluated that most of the common excipients such as lactose, magnesium stearate, and the type of capsules may be the cause of accumulation of electrostatic charge 4. In this study, using a new device reduced the delivered amount of Active Substance-1 to the patient's lungs due to its high electrostatic charge.

Considering all the results, it has been observed that anticholinergic molecules behave differently depending on environmental conditions. For example, while Active Substance-1 is affected by the conditions of the analysis environment, Active Substance-2 is not affected by the conditions in the analysis environment but is affected by the humidity during the manufacturing process. In conclusion, relative humidity levels with a certain temperature during the manufacturing process and also the storage environment can be optimized for reducing the negative effects of humidity and electrostatic charge on DPIs.

References

1. Rau JL (2006) Practical problems with aerosol therapy in COPD. Respiratory care 51(2): 158-172.
2. National Heart, Lung and Blood Institute (NIH) (2023).
3. Chronic obstructive pulmonary disease (COPD) (2023).
4. Chow KT, Zhu K, Tan RB (2008) Investigation of electrostatic behavior of a lactose carrier for dry powder inhalers. Pharmaceutical research 25(12): 2822-2834.
5. Young PM, Sung A, Traini D (2007) Influence of humidity on the electrostatic charge and aerosol performance of dry powder inhaler carrier-based systems. Pharmaceutical research 24(5): 963-970.
6. Bailey AG (1997) The inhalation and deposition of charged particles within the human lung. J Electrostat 42(1-2): 25-32.
7. Edwards D (2010) Applications of capsule dosing techniques for use in dry powder inhalers. Therapeutic Delivery 1(1): 195-201.
8. Chew N, Chan HK (2002) The role of particle properties in pharmaceutical powder inhalation formulations. Journal of aerosol medicine 15(3): 325-330.

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9. Berard V, Lesniewska E, Andres C (2002) Dry powder inhaler: influence of humidity on topology and adhesion studied by AFM. International journal of pharmaceutics 232(1-2): 213-224.

10. Price R, Youn PM, Edge S (2002) The influence of relative humidity on particulate interactions in carrier-based dry powder inhaler formulations. International Journal of Pharmaceutics 246(1-2): 47-59.

11. Janson C, Lööf T, Telg G (2016) Difference in resistance to humidity between commonly used dry powder inhalers: an *in vitro* study. NPJ Primary Care Respiratory Medicine 26(1): 1-5.

12. Sheth P, Stein SW, Myrdal PB (2015) Factors influencing aerodynamic particle size distribution of suspension pressurized metered dose inhalers. AAPS PharmSciTech 16(1): 192-201.

13. Heyder JJGCFW, Gebhart J, Rudolf G (1986) Deposition of particles in the human respiratory tract in the size range 0.005–15 μm. Journal of aerosol science 17(5): 811-825.

14. Borgström L, Askin L, Lipniunas P (2005) An *in vivo* and *in vitro* comparison of two powder inhalers following storage at hot/humid conditions. Journal of aerosol medicine 18(3): 304-310.

15. O'Callaghan C, Lynch J, Cant M (1993) Improvement in sodium cromoglycate delivery from a spacer device by use of an antistatic lining, immediate inhalation, and avoiding multiple actuations of drug. Thorax 48(6): 603-606.

16. Jetzer W, Morrical BD (2019) Investigation of electrostatic behavior of dry powder-inhaled model formulations. Journal of pharmaceutical sciences 108(9): 2949-2963.

DOI: 10.19080/GJPPS.2025.12.555831

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