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Development of SIMPATEC-USP: An abbreviated impactor for rapid testing of inhalation devices

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Abstract

Cascade impactors like the Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI) are complex and costly due to multiple stages. This study introduces SIMPATEC-USP (Simplified Impactor Developed at the University of São Paulo), a low-cost, single-stage alternative meeting US Pharmacopeia standards for testing dry powder inhalers (DPIs). SIMPATEC-USP simplifies particle retention into a single Petri dish stage, eliminating multi-stage complexity. Its design includes a straightforward closure system for easy assembly/disassembly. A collection chamber holds a glass Petri dish with filter paper for final filtration, ensuring efficient aerosol product collection. SIMPATEC-USP also offers potential use with culture media for applications like antibacterial screening. Operating at 30 L/min, SIMPATEC-USP consists of three parts: a single-stage chamber, an L-shaped tube mimicking the trachea, and a vacuum pump. Aerosol particles are deposited onto the Petri dish via a nozzle, and the collected sample is weighed to determine drug concentration.

Tested with inhalation-grade lactose, SIMPATEC-USP effectively collects and analyzes particles, allowing for rapid aerodynamic comparison of formulations, capsule retention assessment, and sample collection for drug release studies. The results demonstrate that it is possible to evaluate the performance of three inhalation devices regarding the mass migrating to the collection plate and that retained within the device itself. In conclusion, SIMPATEC-USP is highly suitable for exploratory studies and educational activities in pharmaceutical technology and pulmonary drug delivery systems.

Keywords: Dry Powder Inhalers; Cascade Impactor; SIMPATEC-USP; Aerodynamic Assessment; Pharmaceutical Technology; Inhalation Devices

1. Introduction

The pulmonary route offers distinct advantages for drug delivery: direct administration to the lungs exploits their high vascularity and large surface area, facilitating rapid pharmacological action. Inhaled doses are lower than those in solid forms, reducing adverse reactions, and promoting better systemic absorption compared to oral routes. This route plays a pivotal role in treating conditions like asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and pulmonary arterial hypertension [1].

Effective inhalation therapy requires devices delivering specified drug doses with particles sized for lower airway penetration [2]. Particle aerodynamic diameter influences deposition via impaction, sedimentation, and Brownian motion. Larger particles (>5 μm) impact in the oropharynx, while smaller ones (<5 μm) reach the bronchi and alveoli, enhancing sedimentation and diffusion with longer airway residence [3].

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Dry powder inhalers (DPIs) can be highlighted for being propellant-free, portable, and cost-effective with stable formulations [4]. Various DPI designs differ in resistance, mechanics, and powder storage strategies, impacting drug aerosolization efficiency [1]. Inhaler design, particularly mouthpiece geometry, affects airflow turbulence for effective drug release, while material and formulation properties influence electrostatic charge accumulation and aerosol behavior [5].

Regulatory standards mandate that DPIs deliver doses within 75-125% of label claims, ensuring efficacy and consistency [1, 6]. Particle size distribution analysis is crucial for DPI performance, and rely on cascading impactors like Andersen and Next Generation Impactors (ACI, NGI) [3, 7]. These instruments predict in vitro lung deposition, aiding formulation optimization, but the methodology is complex and time consuming [8].

Efforts to streamline DPI evaluation led to innovative single-stage impactors like Simplified Impactor Developed at the University of São Paulo (SIMPATEC-USP) here described, offering rapid in vitro assessments early in product development [1]. These tools gauge inhaler performance, dose uniformity, capsule retention, and aerodynamic behavior, crucial for quality control in pharmaceutical settings and academia.

2. Material and method

2.1. Impactor Design

The proposed impactor consists of a single-stage device with a final filter, incorporating an exclusive closing system that facilitates assembly and disassembly, eliminating the need for complicated springs or fastening mechanisms. The impactor design is based on the viable eight-stage Andersen device, with the difference that the collection chamber is larger to accommodate a Petri dish instead of a collection plate. The impactor uses a glass Petri dish as the collection medium, with final support of filter paper. This setup provides ease in collecting the viable product on the Petri dish after the inhaler device atomization. The blueprint for constructing this impactor is described in Figures 1, 2, and 3.

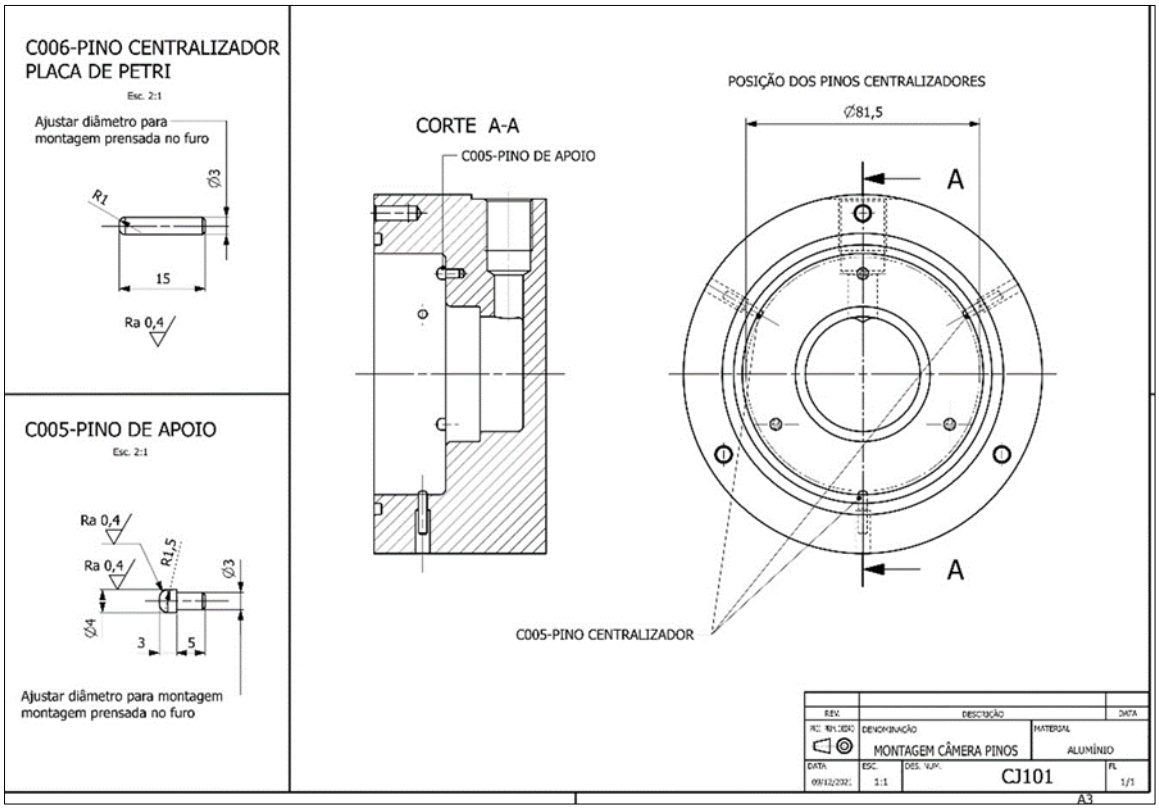

Figure 1 Technical drawing for the assembly of the pin camera

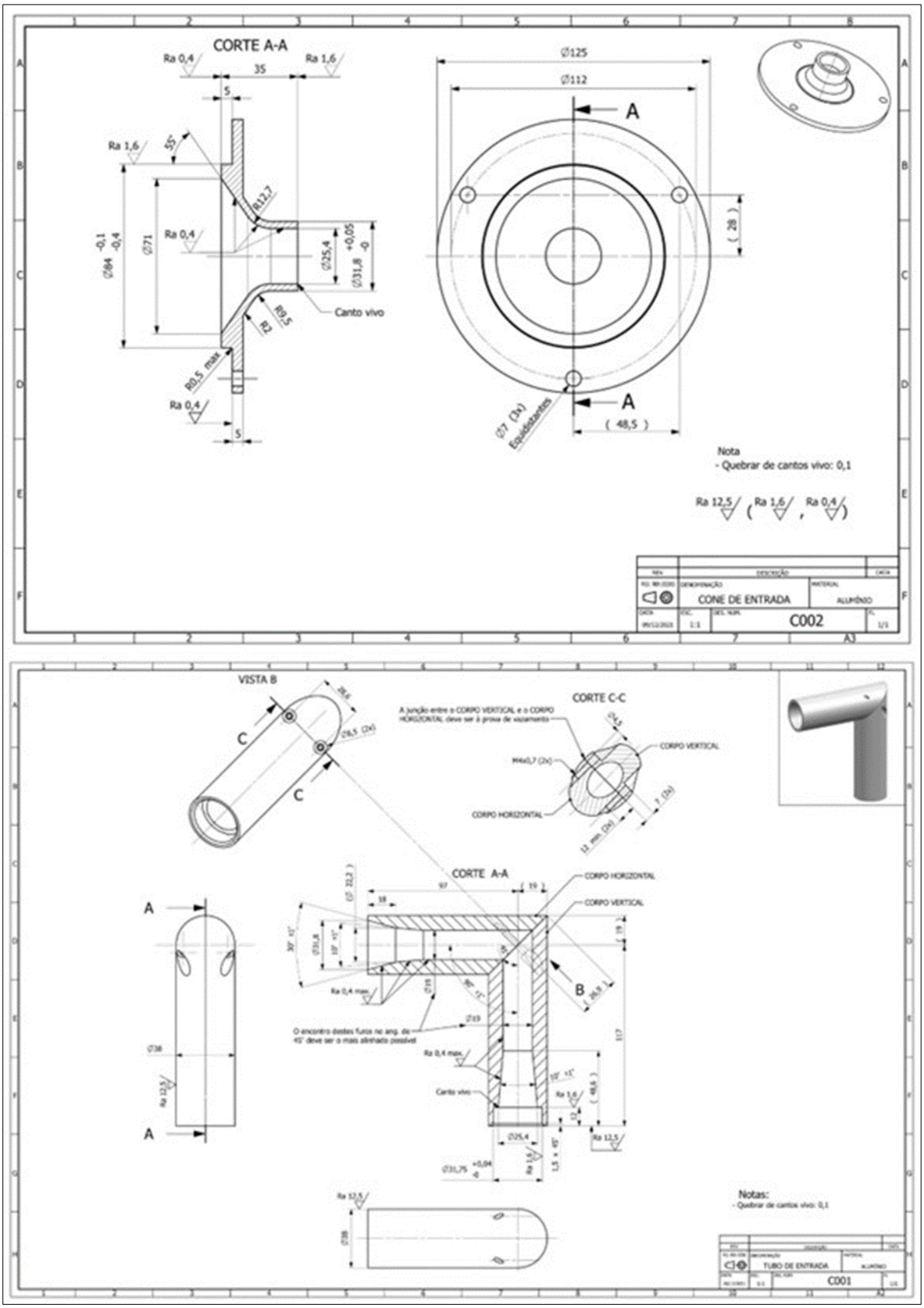

Figure 2 Technical drawing for the assembly of the inlet cone and inlet tube

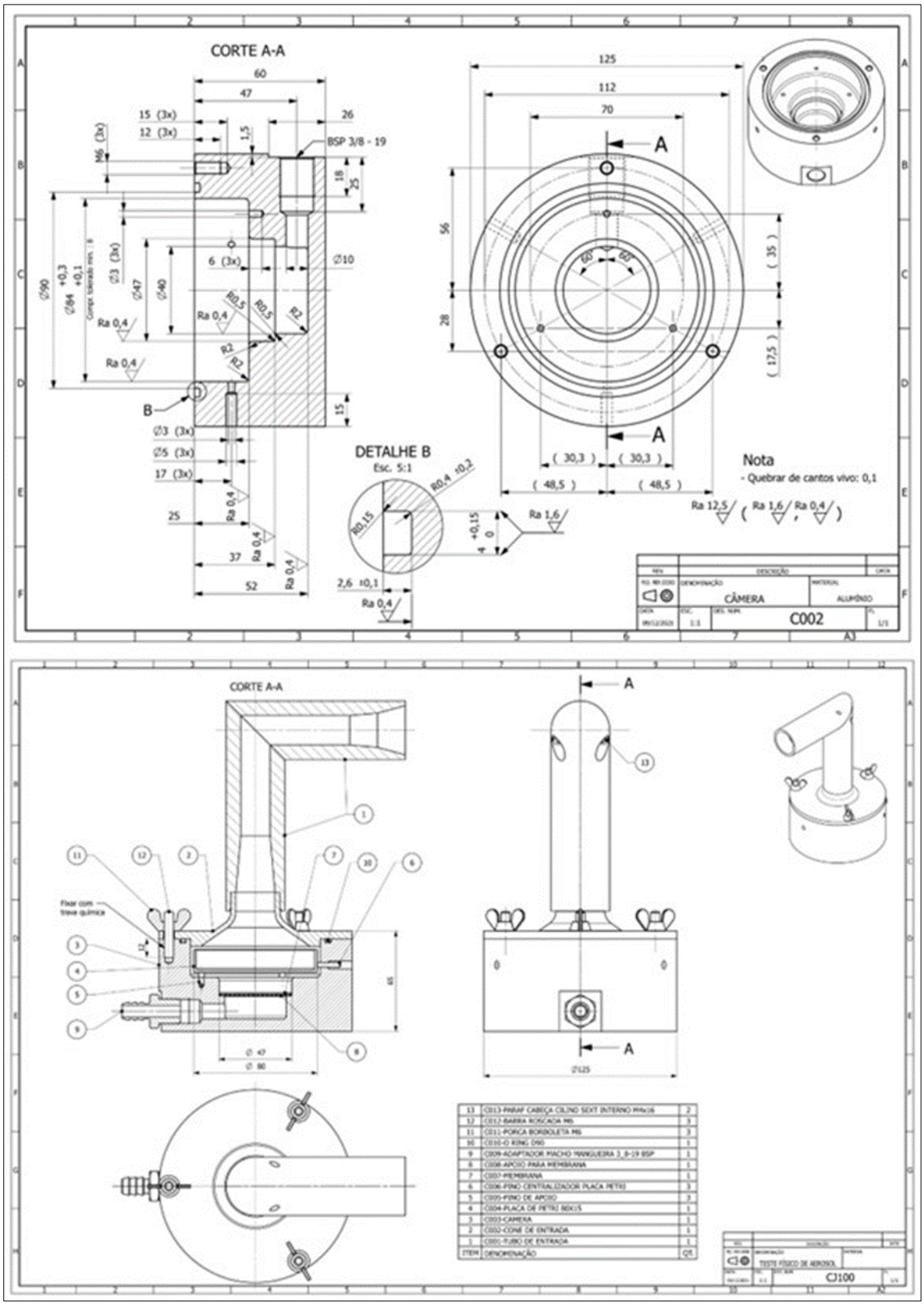

Figure 3 Technical drawing for the assembly of the chamber and physical aerosol testing area

2.2. Performance Testing

Performance tests were conducted to evaluate whether the developed SIMPATEC device is capable of assessing the performance of different inhaler devices using various types of lactose. This study included the evaluation of three DPI inhaler models (Aerocaps, Seebri Neohaler, and CDM Haler), 80 gsm filter paper, monohydrated lactose "InhaLac®", kindly donated by Meggle, of four different particle sizes grades (500, 400, 251 e 70), with particle size distribution as per Table 1, size 3 gelatin capsules, and uncoated Petri dishes under ambient conditions.

Table 1 Particle size distribution (laser diffraction) data available on the Meggle website or COA [9]

		Specified lactose type (µm)			
		InhaLac® 500	**InhaLac® 400**	**InhaLac® 251**	**InhaLac® 70**
Particle size distribution (Laser diffraction)	**X10**	-	0.8 - 1.6	7 - 22	110 - 160
	X50	NMT 5	4.0 - 11.0	40 - 70	180 - 250
	X90	NMT 10	15.0 - 35.0	80 - 120	270 - 340

Tests were performed in triplicate for each inhaler device, using four different types of lactose, the experiment was conducted as shown in Figure 4. Lactose from the same batch and a single operator were used to minimize measurement variations. For each collected sample, three atomizations were performed with distinct capsules containing the same lactose. All atomizations were conducted at a flow rate of 30 L/min, with a suction time of 5 seconds. The capsules were prepared with approximately 25 mg of lactose.

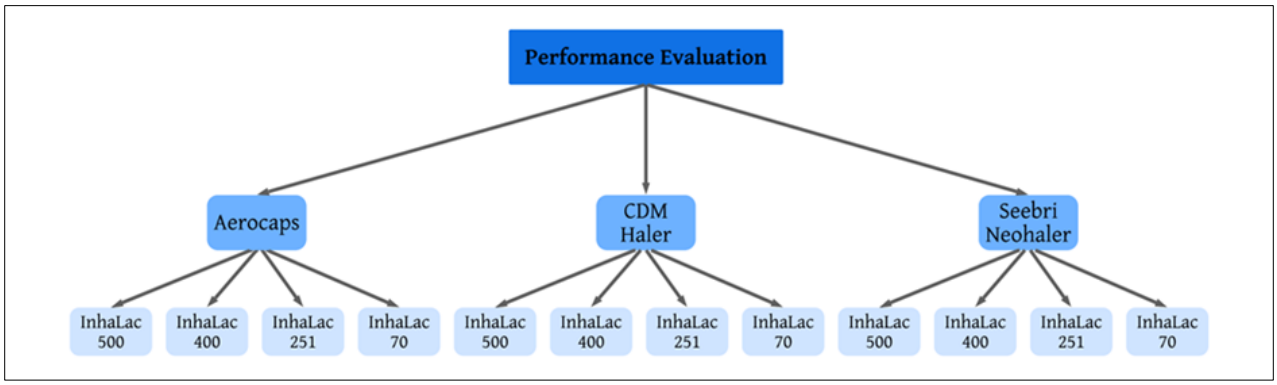

Figure 4 Performance analyses design: three inhalation devices (PMDIs) from different manufacturers were used: Aerocaps, CDM Haler, and Seebri Neohaler. Each device was tested in triplicate with four types of lactose, totaling 12 samples per device (36 in total)

3. Results

The device design was developed based on the specifications of complex impactors described in the United States Pharmacopeia [10]. The design includes the assembly of the induction port, inlet cone, and collection chamber in the impactor, as shown in Figures 5 and 6. The device was manufactured from materials such as aluminum, stainless steel, or other suitable materials, ensuring durability and corrosion resistance. The surface of the impactor was polished to achieve a roughness (Ra) of approximately 0,4 µm, which is essential for minimizing particle deposition on internal surfaces and ensuring result accuracy.

Figure 5 (1) - Capture chamber; (2) - Impactor design of a proposed stage; (3) - Overview of the 3D drawing of the IMPACTOR of a stage; (4) - Flow meter, capacity 50 l/min.; (5) - Vacuum pump, capacity of 60 l/min. and 6 – Nozzle

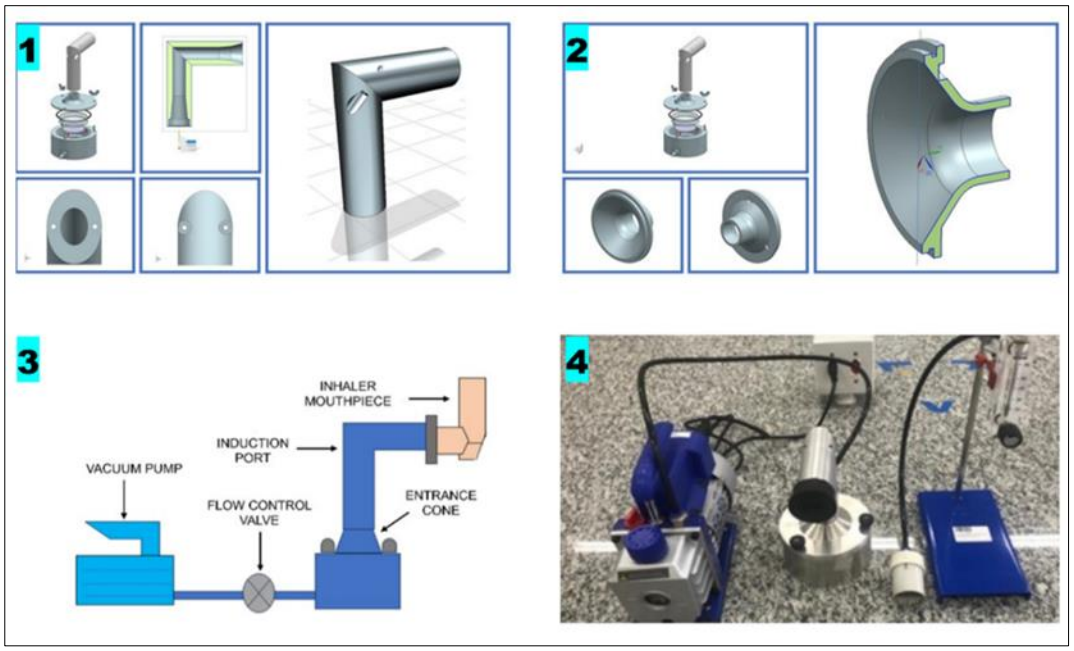

Figure 6 (1) - 3D drawing of the L-tube (trachea), schematic based on USP Pharmacopeia; (2) - 3D drawing of the entry cone (trachea), schematic based on USP Pharmacopeia; (3) - General control equipment; 4 - SIMPATEC-USP equipment

The performance of the SIMPATEC-USP impactor was assessed by measuring the percentage recovery of four types of inhalation-grade lactose (InhaLac® 500, InhaLac® 400, InhaLac® 251, and InhaLac® 70) across three different inhalation devices (Aerocaps, CDM Haler, and Seebri Neohaler). Recovery and losses of lactose through the recovery plate, walls, and filter were analyzed. We quantified the mass recovered on the plate to evaluate the behavior and repeatability of the impactor. Losses on the walls and filter were included in the calculation, along with the material recovered on the collection plate, to determine the mass differential and the delivery efficiency of the devices. The total

recovery of the mass emitted by the DPI actuator was calculated by summing the particles collected from the mouthpiece adapter, USP throat, impactor collection plates, and filter. The mean recovery percentages and their corresponding dispersions (DPR) for each combination of device and lactose type are summarized in Table 2.

Table 2 Result of the average lactose recovery in the tests. The experiments followed the order of the lactose particle fractions, from smallest to largest (InhaLac® 500, 400, 251, and 70). Equipment from 3 manufacturers was tested

Lactose Recovery					
Manufacturer	**Statistic**	**InhaLac® 500**	**InhaLac® 400**	**InhaLac® 251**	**InhaLac® 70**
Aerocaps	Mean	19%	27%	77%	93%
	DPR	0.27	0.18	0.04	0.06
CDM Haler	Mean	22%	27%	70%	94%
	D PR	0.03	0.15	0.1	0.03
Seebri Neohaler	Mean	15%	11%	77%	96%
	DPR	0.18	0.27	0.05	0.03

For the Aerocaps device, the highest recovery was observed with InhaLac® 70 (93%) and the lowest with InhaLac® 500 (19%). The device showed moderate DPR values, indicating relatively stable performance across different samples. The CDM Haler exhibited the highest recovery with InhaLac® 70 (94%) and the lowest with InhaLac® 500 (22%). The DPR for InhaLac® 500 was very low (0.03), suggesting high consistency in the recovery performance for this lactose type. The Seebri Neohaler displayed the highest recovery with InhaLac® 70 (96%) and the lowest with InhaLac® 400 (11%), with the high DPR for InhaLac® 400 (0.27) indicating greater variability and potential inconsistencies in performance or formulation-device interactions.

Among the different lactose types, InhaLac® 500 showed recovery rates ranging from 15% with the Seebri Neohaler to 22% with the CDM Haler, with higher variability (DPR 0.18) observed for the Seebri Neohaler. InhaLac® 400 had uniformly low recovery rates across all devices, with the Seebri Neohaler performing the worst (11%) and displaying the highest DPR (0.27). InhaLac® 251 demonstrated high recovery rates for both Aerocaps and Seebri Neohaler (77%), while CDM Haler had a slightly lower recovery (70%), all with low DPR values indicating consistent performance. InhaLac® 70 had the highest and most consistent recovery rates across all devices, particularly with the Seebri Neohaler (96%), and low DPR values indicating stable performance.

4. Discussion

The SIMPATEC-USP impactor demonstrated effective performance in evaluating the mass of particles collected from various inhalers, revealing differences in recovery rates based on lactose type and inhaler model. The simplified design allowed for easy assembly and disassembly, and the use of a Petri dish for particle collection proved efficient.

The performance results reveal significant variations in recovery rates among the different devices and types of lactose. For the Aerocaps device, higher recovery rates for larger particle sizes (InhaLac® 70) indicate efficient particle collection by the SIMPATEC-USP impactor. Moderate DPR values suggest consistent performance across different samples. The CDM Haler also showed high recovery for InhaLac® 70 and consistent performance, as indicated by low DPR values. The device performed consistently well with InhaLac® 500, suggesting good compatibility with this type of lactose. The Seebri Neohaler exhibited the highest variability, especially with InhaLac® 400, where the recovery rate was the lowest and DPR was the highest. This suggests potential issues with device-formulation compatibility or aerodynamic behavior. However, the device performed well with InhaLac® 70, showing the highest recovery rate among all devices tested. The overall trend across all devices indicates that larger particle sizes (InhaLac® 70) are collected more efficiently by the SIMPATEC-USP impactor.

The lower recovery rates observed for InhaLac® 400 and 500 in this study can be attributed to their fine particle size and high cohesiveness, which, while beneficial for improving the fine particle fraction (FPF) and facilitating the release of active pharmaceutical ingredients (APIs) by covering high-energy binding sites on carrier particles, also result in increased particle aggregation and adherence to device surfaces. This cohesiveness, suitable for enhancing API delivery and forming stable agglomerates, affects fluidization behavior, leading to inefficient dispersion during inhalation and

ultimately lower recovery rates. In contrast, larger particles like those in InhaLac® 70 exhibit better flow properties and are less prone to adherence, resulting in higher recovery rates. To balance the properties of flow and API release, the use of lactose blends and additives such as magnesium stearate can be effective alternatives. These blends can optimize the overall performance by enhancing flow properties while maintaining efficient drug delivery

In summary, the results demonstrate the SIMPATEC-USP impactor's capability to effectively differentiate performance among various inhalation devices and types of lactose. These observed differences underscore the well-known importance of considering both the inhalation device and lactose type in the formulation and evaluation process, as these factors significantly influence the overall performance and efficiency of dry powder inhalers.

5. Conclusion

The results presented demonstrate that the SIMPATEC-USP impactor effectively evaluated the performance of three inhalation devices regarding the mass migrating to the collection plate and retained within the device itself. The development of the impactor facilitated the application of practical knowledge, providing an effective means to compare the total mass recovered across different devices. SIMPATEC-USP proved highly suitable for teaching and exploratory research activities. Its straightforward design and ease of use make it an excellent educational tool, enabling students and researchers to conduct basic aerodynamic assessments without requiring complex and expensive equipment. To further enhance its utility, future improvements incorporating additional stages are necessary to establish important correlations, such as the experimental determination of the Fine Particle Fraction (FPF) for active pharmaceutical ingredients. The availability of the construction blueprint ensures that this innovation can be widely adopted, thereby supporting educational and investigational endeavors in pharmaceutical technology and pulmonary drug delivery systems.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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