

Methods in Determining the Bioequivalence of Inhaled Products

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Abstract: Aerosol delivery to the lungs can be achieved with several devices that differ in their operating mechanisms and efficacies of aerosol delivery. There are several methods to measure aerosol delivery and deposition in a subject's lung, in order to assess the efficacy of aerosol generators and the impact of certain drugs. Instruments such as cascade impactors, imaging techniques, and laser diffraction are available for measuring the particle size of aerosols, which is the main factor in the deposition and distribution of the produced aerosol. From impactors to laser diffractors, they have different operating mechanisms, analysis times, and characteristics, in which each has its own advantages and limitations. Several models are available to investigate aerosol delivery and deposition, such as in vitro, in vivo, and ex vivo models.

Keywords: In vitro; In vivo; Ex vivo; Clinical study

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1. Pharmacokinetic methods

Gamma scintigraphy and pharmacodynamic approaches are commonly used in (in vivo) research studies, in order to determine the deposition in lungs. As doses supplied are modest and distribution volume is enormous, it is not easy to apply standard pharmacokinetic approaches to these investigations. In view of low systemic drug concentrations, the use of sensitive measurement methods is called for.

The drug's plasma and urine concentrations have been employed in pharmacokinetic approaches to assess relative drug bioavailability in the lungs. Collecting blood specimens during the lag time of oral medications has been reported as a plasma pharmacokinetic technique for salbutamol. As a result, the medication deposited in the lungs following inhalation can be determined by the concentration of these samples. Plasma samples should be taken at 5, 10, and 20 minutes following inhalation. However, in view of the low concentration, multiple dosages are required, rather than the usual inhaled amount. The initial pharmacokinetic approach employed to assess the outcome of inhaled medication utilized urinary excretion in conjunction with oral charcoal administration to block the absorption of consumed oral medication in the stomach. Borgstrom and Nilsson first described the charcoal-block and urinary approach, which demonstrated its use in determining the amount of medication transported into the lungs. Healthy participants were given terbutaline sulphate through MDI along with charcoal via oral route in this study

(5 grams prior to inhalation, 5 grams following inhalation, and 10 grams after 1 hour, 2 hours, and 3 hours). Urine samples were collected at intervals of 0-12 hours, 12-24 hours, 24-36 hours, and 36-48 hours following dose inhalation. The amount of drug excreted in the urine was determined. Since charcoal absorbs 97% of the orally consumed dose, the oral bioavailability to total body bioavailability following inhalation can be neglected.

A study used the urine pharmacokinetic approach to evaluate the lung and total body bioavailability of inhaled salbutamol based on the lag period of oral absorption. The study found that after taking salbutamol orally, the quantity of salbutamol excreted in the urine was minimal during the initial half an hour from drug administration, but significantly higher levels ($p < 0.001$) were excreted after half an hour from inhalation. They discovered that the amount of salbutamol excreted in the urine after half an hour from inhalation is an indicator to pulmonary bioavailability, whereas the amount excreted within 24 hours following the treatment is an indicator of systemic bioavailability.

2. Approaches used in measuring the bioequivalence of different inhaled medications

When two medications have identical pharmacokinetic and lung deposition patterns, they are considered bioequivalent^[1].

In medication research and production, determining respiratory drug absorption and deposition has become more critical. Drug absorption and deposition in the lungs can be studied using a multitude of approaches. Pharmacokinetic studies, gamma scintigraphy approach, pharmacodynamics studies, and ex vivo research, are among the approaches used^[2].

2.1. Pharmacokinetic studies using urine and plasma samples

The inhaled medication will be precipitated in the lungs and ingested in the digestive system; then, it will travel throughout the body via the blood circulation, where it will be exposed to metabolism and excretion, as shown in **Figure 1**^[3]. The ingested part will be exposed to the first pass effect in the liver and then absorbed after a delay in time or a lag time. To assess an inhaled medication, pharmacokinetic approaches are used. These approaches include measuring medication elimination via the urine and medication concentration in the blood.

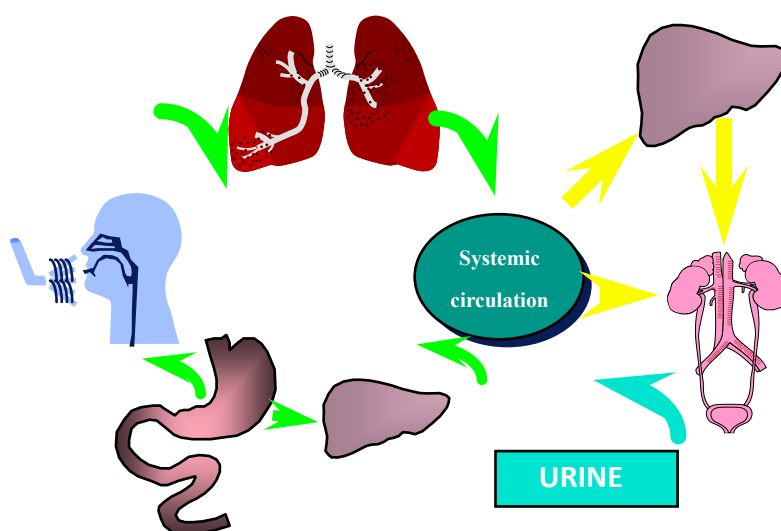


Figure 1. Inhaled medication pharmacokinetics

In order to determine the amount of medication deposited in the lungs (effective dose) and the overall medication quantity transported throughout the body, pharmacokinetic approaches are used. The absorption of the inhaled medication from the lungs and gastrointestinal system is determined by the drug's plasma or urine concentrations. For a drug having excessive first pass effect, such as fluticasone, using pharmacokinetic techniques to measure the relative deposition in the lungs will be simple because oral absorption is minimal. As a result, measuring relative deposition in the lungs using urine or plasma sampling after drug inhalation would be very precise. Ingestion of a measured quantity of charcoal was shown to prevent gastrointestinal absorption of a portion of medication ingested orally [4]. **Figure 2** [4] shows the importance of charcoal blocking in determining the amount of medication transported to the lungs based on the original investigation conducted by Borgstrom and Nilsson in 1990. However, because this procedure involves the administration of charcoal through oral route, it would be illegal to apply it to patients participating in research [5].

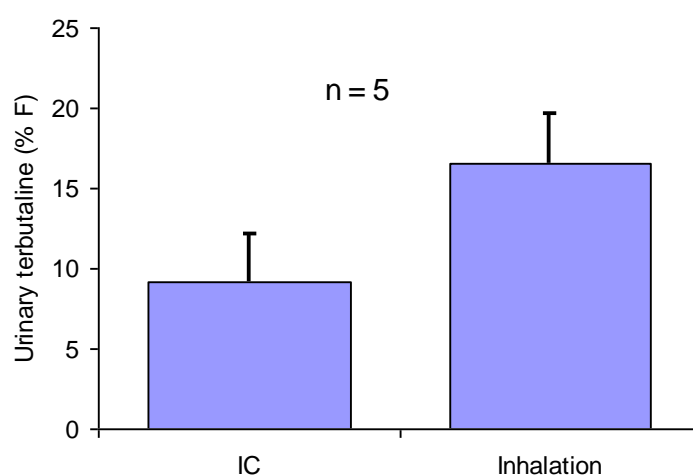


Figure 2. Average quantity of terbutaline excreted in the urine after 36 hours from inhalation with and without charcoal

The medication deposited in the lungs is determined by measuring either its concentration in plasma or the amount excreted in urine after inhalation during the lag period of the medication fraction administered orally. Plasma sampling is recommended after 5, 10, and 20 minutes after inhalation [2], while urine sample is recommended to be taken at 30 minutes after inhalation [6]. Since the amount of inhaled medication is low and the medication distribution volume is enormous, the drug concentrations in plasma are very limited, particularly for “polar” medications that are removed from the blood very quickly [7].

Hindle and Chrystyn had established a pharmacokinetic approach to evaluate pulmonary and total body bioavailability of inhaled salbutamol. They discovered that the excreted urine salbutamol 30 minutes following dose administration is a marker of lung bioavailability, while urine salbutamol produced within one day (24 hours) following dose administration is a marker of total body bioavailability. As shown in **Figure 3**, there is a significant difference in the amount excreted 30 minutes after inhalation and that following the ingested dose ($p < 0.001$). This approach is simple and does not require invasive intervention. This approach has been developed continuously in order to appraise pulmonary bioavailability with the use of inhaled sodium cromoglycate [2], nedocromil [8], gentamicin [9], tobramycin [10], and formoterol [11].

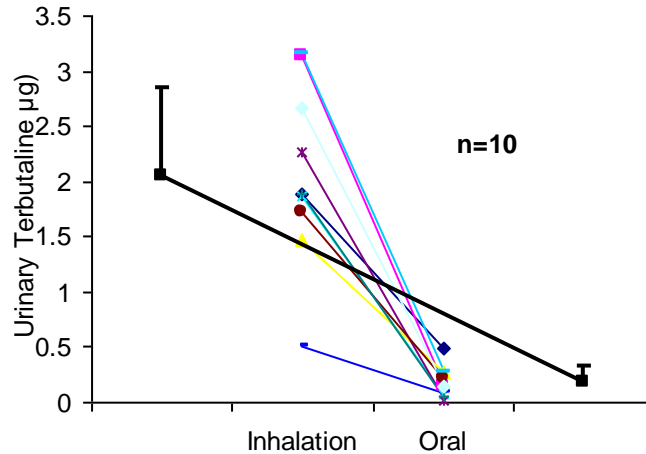


Figure 3. Average amount of salbutamol excreted in urine 30 minutes following inhaled and ingested dose

This pharmacokinetic approach provides valuable information about the percentage of drug deposition in the lungs and the percentage of medication transported throughout the body, so as to compare alternative approaches, technologies, and techniques. The necessity to distinguish the amount of medication ingested and inhaled is one of the drawbacks of pharmacokinetic approaches. They do not distinguish the dosage sedimentations in different parts of the lungs, and some assays are not sensitive enough to detect low amounts [3].

2.2. Gamma scintigraphy

There are two main types of gamma scintigraphy: bi-dimensional imaging method and three-dimensional imaging method [5,12].

The bi-dimensional gamma scintigraphy, also known as planar imaging, often incorporates the use of technetium-99m attached to drug particles present in the formulation; this is known as physical attachment. Upon inhaling the combined formulation, a quick radionuclide imaging is done to determine the accumulation of drug inside the lungs [2]. The planar images obtained from using this method do not depend on the amount of medication deposited in different parts of the lungs.

Imaging methods were invented recently to solve the existing problems in planar imaging. These methods are categorized as three-dimensional methods. Apart from the fact that the gamma camera rotates 360°, the single photon emission computed tomography (SPECT) bears a resemblance to bi-dimensional gamma scintigraphy. This lengthens the time for data collection. Positron emission tomography (PET) is a technique that involves embedding a radiolabel directly into a medication molecule, which is known as chemical attachment. Positron emitters such as 11C, which has a short half-life, and 18F, which has a long half-life, have been employed lately. Since current positron emitters have limited half-lives, the method is quite costly. Triamcinolone acetonide now contains 11C, and researches have shown that using a spacer with an MDI increases peripheral deposition [13]. This is because the overall medication quantity accumulated inside the lungs increased significantly (13.6% with spacer, and 4.9% without spacer). Fluticasone has also been administered using this method [14].

Gamma scintigraphy provides information about the overall quantity absorbed in the lungs and excreted out via mucociliary clearance. The charcoal approach, which includes the secretion of terbutaline in urine [4], is compared with the overall accumulation or deposition in lungs calculated by using gamma scintigraphy [15]. After inhalation and with concurrent charcoal administration, the mean SD of terbutaline excreted in the urine was 21.1, accounting for 3.2% of the nominal dose, whereas gamma scintigraphy revealed overall pulmonary accumulation of 26.9 (3.8%). The disadvantages of this approach include safety

issues in the long run and costly research [3]. Furthermore, the labelling technique entails changes to the formulation [16].

Particle size ranges should likewise be represented in terms of excreted amounts, and ex vivo measurements should use the same number of quantified doses as in scintigraphy studies. The Food and Drug Administration (FDA), for example, is very cautious about using imaging research data to demonstrate bioequivalence [17].

2.3. Clinical research

Research studies that use spirometry or bronchoprovocation tests are prevalent in determining the difference in bioequivalence, which may be present with different brands of inhaled medication [18,19].

The protective effect on methacholine or histamine-induced pulmonary constriction is a common method used for assessing the efficacy of inhaled medications [20,21]. Inhaling aerosolized SABA increases the provocative quantity of inhaled methacholine or histamine by 1.1 to 3.9 times [22,23].

Almost all clinical studies are done by using calculations for dose correlation between introduced dose and response. For example, increasing the therapeutic dose of inhaled fluticasone by 2 times has been found to elevate PEFR by 4.3 L/min [24]. Concerning beclomethasone, FEV₁ is elevated by 0.18 L and 0.21 L above the baseline after inhaling 200 mg and 400 mg two times per day, respectively [25]. For beta 2-agonists, the highest possible response after inhaled medication was investigated in a study [26]. It was found that in normal individuals, the highest response from the airway to inhaled salbutamol can be attained when the overall accumulated quantity is 110 µg. The required drug quantity to achieve maximal bronchodilation effect is significantly higher with a higher degree of bronchial constriction [26]. Except for the use of gamma scintigraphy to measure deposition in lungs, the same approach was used in an asthmatic investigation. The overall percentages of pulmonary accumulation were 12.3% and 23.1%, respectively, when the participants inhaled salbutamol labelled with radioactive element via MDI with and without a large-sized spacer; however, there were no changes in spirometry measurements [27]. In addition, the bronchoprovocation challenge is not able to distinguish between different inhalation methods as a result of a large variability in the method [28]. Clinical trials have a significant level of interpatient variability. Hence, the sensitivity to identify a difference is limited, thus necessitating the incorporation of a larger number of subjects in the study [1].

2.4. In vitro approaches

In vitro studies determine the characteristics of the inhaled product, including the total discharged dose, dose uniformity, and drug particle size distribution. These studies are frequently expanded to estimate in vivo deposition. Inertial separation approach and laser diffraction approach are the most often employed approaches. Microscopic techniques are also utilized. The mass median aerodynamic diameter (MMAD) is the diameter value that divides the mass of the aerosolized particles into two equal halves.

2.4.1. Total (overall) discharged dose

2.4.1.1. MDI dose emission unit

The total discharged dose is the overall amount of medication discharged from the drug-containing device. Its uniformity is very important for the safety and efficacy of all inhaled medications. The MDI dose emission unit, as illustrated in **Figure 4** [2], has been built to assess MDIs. The system is mainly composed of a filter made from glass (25 mm), which can keep nearly 99.98% of aerosolized drug particles. The pore of the filter has a diameter of one micron, and the filter is placed in the sample collection tube.

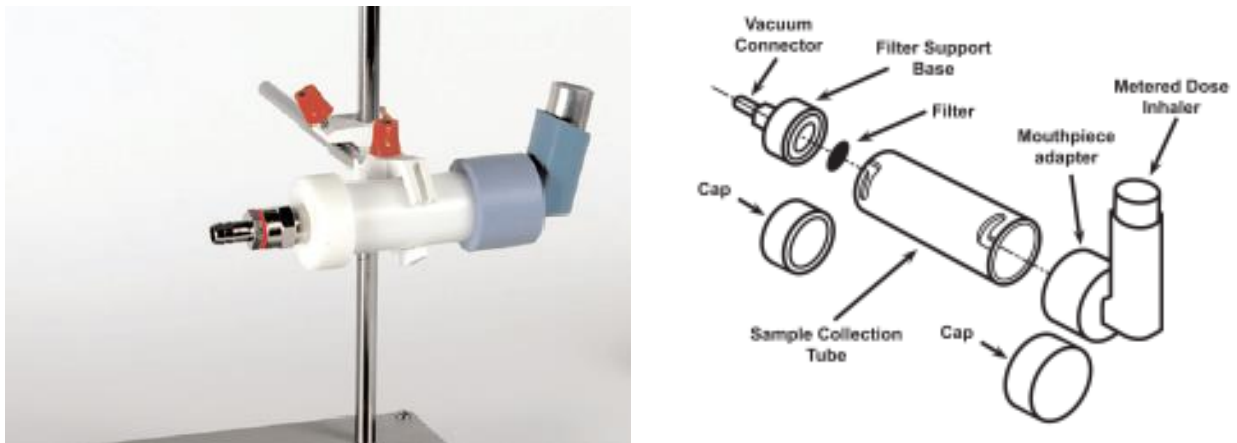


Figure 4. Constituents and method of adjusting the MDI dose emission unit

2.4.1.2. DPI dose emission unit

The DPI dose emission unit is similar to that of the MDI (**Figure 5**) [2]. The duration of inspiration and inspiration power influence the generated and small particle dose while using DPIs [29,30]. Additionally, various inhalers have different levels of flow resistance. As a result, according to compendial methodologies, it is crucial to identify the optimum test flow and duration depending on the pressure drop created over the inhaler, especially during evaluation of DPIs, which have medium to high resistance to flow [2]. Following that, it is necessary to ensure that sonic flow takes place in the system's valve, which regulates the flow. This guarantees that the flow through the DPI dose emission unit is operating properly. The resulting airflow, which creates a pressure drop over the inhaler being evaluated, should then be utilized to measure the given quantified dose and also the particle size distribution based on compendial methodologies [2].

Low resistance DPIs that create a flow greater than 100 L/min are the only exceptions to this rule. It is important to use a critical flow controller when the DPI unit is utilized to estimate the lowering in pressure and to ascertain sonic flow conditions.

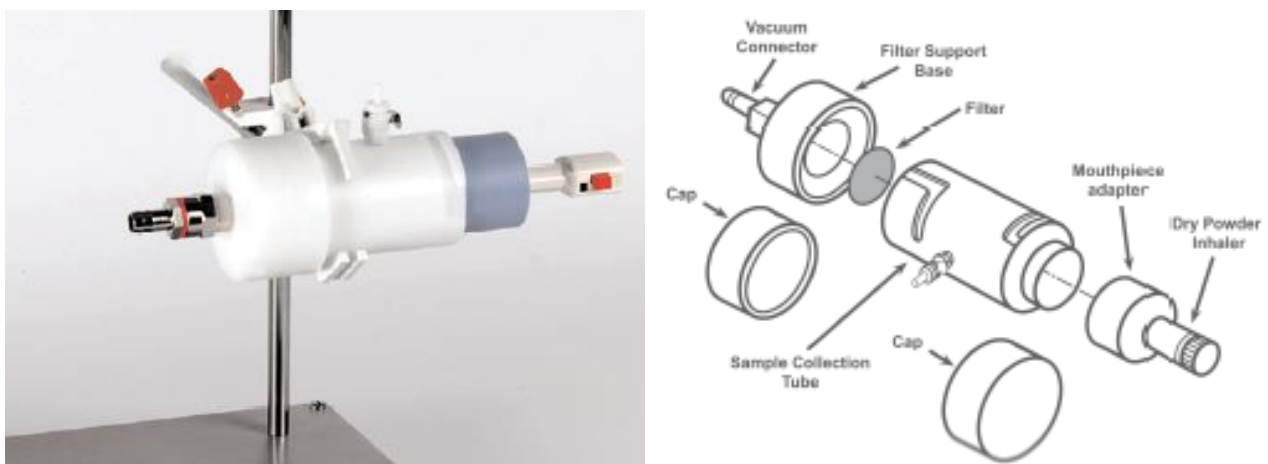


Figure 5. Constituents and method of adjusting the DPI dose emission unit

2.4.2. Characterisation of the discharged dose

Inertial impaction is used to determine the streamlined properties of medication doses produced from inhalers [2].

2.4.2.1. Twin-stage impinger

The device shown in **Figure 6** ^[31] can be employed while using an estimated inspiration flow rate between 30 and 90 L/min. In consideration of its value as a basic and cheap quality control appliance, it has been preserved in pharmacopeias. However, if an impinger is used to present detailed data about the distribution of particle diameter, it is generally acknowledged that it should be equipped with at least five phases, or ideally more than that. A twin-stage impinger is most likely to be phased out of compendial testing. Despite its effectiveness in quick fine particle fraction (FPF) quantification, it lacks size resolution in the critical range of 0.5 to 5.0 μm in diameters ^[32].



Figure 6. Twin-stage impinger

2.4.2.2. Multiple-stage liquid impinger

The multiple-stage liquid impinger (MSLI) comprises of a metal gullet, the stages of impaction, and a terminal filter (**Figure 7**). It provides more specific data concerning the distribution of particle size compared to the twin-stage impinger.



Figure 7. Multiple-stage liquid impinger

2.4.2.3. Anderson cascade impactor

As shown in **Figure 8**, the Anderson cascade impactor (ACI) is made of a barrel with eight platters; and each platter includes a series filters and pores ^[2]. The diameter of the pore becomes smaller along the stages. As a particle passes through the impactor, the jet velocity increases. The ACI has cut-off diameters of 9, 5.8, 4.7, 3.3, 2.1, 1.1, 0.65, and 0.43 μ m, and it runs at a flow rate of 28.3 L/min. This approach, unlike the MSLI or the twin-stage impinger, allows for a more complete description of particle size distribution. Stages 0 and 7 are removed from the top of the ACI and substituted with stages -1 and -0 for a 60 L/min inhalation flow. Stages 0, 6, and 7 are removed from the top of the ACI and replaced with stages -2, -1, and -0 for a 90 L/min inhalation flow.



Figure 8. A: MDI Anderson cascade impactor; B: DPI Anderson cascade impactor

High flow rates at which these devices operate may cause substantial evaporation of aqueous particles, such as nebulized aerosols, resulting in incorrect particle size calculations ^[33]. Under the influence of humidity, temperature, and disease alterations, the pulmonary tract has a very complex structure. As a result, such in vitro approaches are unable to determine the deposition in lungs effectively. Particle size may vary as a result of changes in relative humidity and temperature inside the respiratory tract.

2.4.2.4. Next generation impactor (NGI)

This impactor has seven successive stages and the ability to work when the inspiratory flow is in the range of 30 to 100 L/min (**Figure 9**).

NGI offers many different features to improve its utilization for the testing of inhalers:

- (1) Particles accumulated on assemblage tanks are collected as a single unit in a tray from the impactor, which allows for faster sample turnaround time when numerous trays are used.
- (2) For more efficient drug recovery, the user can fill up to 40 ml solvent.

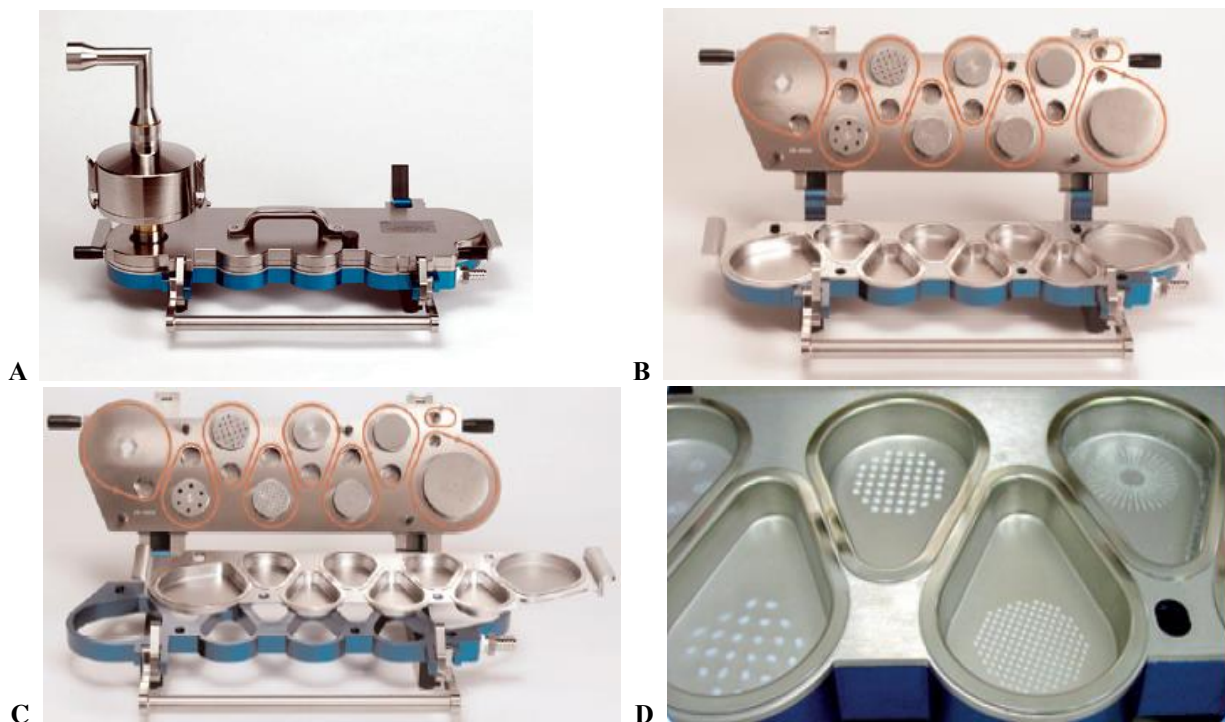


Figure 9. Next generation impactor; **A:** NGI with both pre-separator and inauguration port; **B:** NGI assumes nozzles and assemblage cups; **C:** NGI with its tray removed; **D:** Assemblage cups showing the standard pattern of sedimentation

2.4.2.5. The mechanism of operating cascade impactors

Each stage includes a sole nozzle or a group of successive jets or nozzles (**Figure 10**), through which the sample is pulled by air flow, pulling in any volatile molecules toward the direction of the collection plate of that stage. The size of an aerodynamic particle influences its impact on that stage. Particles with enough inertia will collide with that stage's collection plate, whereas smaller particles with inadequate inertia will continue entrained in the airstream and move on to the next stage, where the operation restarts.

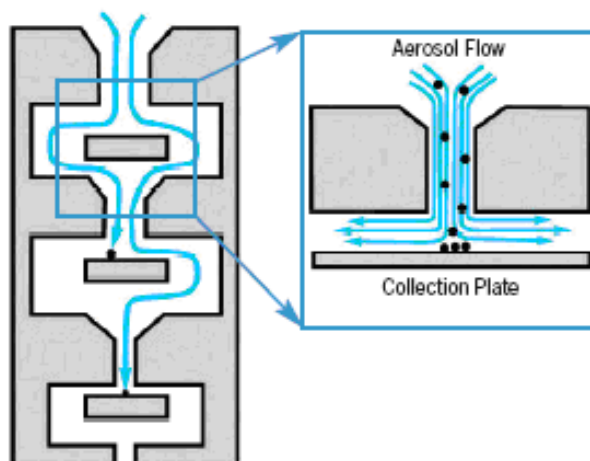


Figure 10. The mechanism of operating cascade impactors

The stages are arranged in a stack in order of decreasing particle size. The air speed increases as the jet becomes smaller and finer particles are gathered. The final filter collects any residual particles. The particle mass corresponding to each stage is extracted using an appropriate solvent at the end of the test and analyzed using HPLC to measure the actual amount of active drug.

Both impactors and impingers are affected by the basic principles of inertial impaction. When particles hit the collection plate, they may bounce back in reaction to the impact. In this case, they recommence into the airflow and are transferred to the earlier stage. This action can be minimized by using a proper surface coating on the collection plate [34].

2.4.3. In vitro identification of discharged dose from nebulizers

The European Respiratory Society Guidelines encourage the use of the Comité Européen Normalisation method to determine the dynamic size and properties of aerosolized particles in the drug dose discharged from nebulizers [35,36]. The Marple 298X Cascade Impactor, as shown in **Figure 11**, is used in this in vitro approach, because it operates at stunted rates of flow, which are similar to those of human natural breathe. However due to the restricted load-bearing capacity in successive stages of filter fitting, desorption, and compatibility issues, only a small proportion from the discharged dose can be sampled [37,38].



Figure 11. Marple 298X Cascade Impactor

3. Medications

3.1. β_2 -agonists

β_1 , β_2 , and β_3 are the three different subtypes of β -receptors, which are mostly found in cardiac muscles, involuntary muscles, and fatty tissues, respectively [39]. Following the stimulation of β_2 -adrenoceptors, cyclic AMP is generated, thus giving rise to intracellular signaling, which results in the relaxation of airways via phosphorylation and changes in cellular concentrations (Ca_2^+) [2]. As shown in **Figure 12**, β_2 -agonists can be divided into three categories: those that directly activate the receptor (e.g., salbutamol and terbutaline); those that are absorbed into a membrane depot (e.g., formoterol), from which they are thought to gradually diffuse out and interact with β_2 -receptors; and those that interact with a receptor-specific auxiliary binding site, remain in the external layer, and diffuse slowly from the membrane (e.g., salmeterol) [39,40]. The kinetics of relaxation and bronchial dilatation reflect these changes in the mechanism of action. Various polymorphisms in β_2 -receptors have been found, which tend to affect the receptor's behavior, such as the degree of downregulation (causing resistance to β_2 -agonists), and the reactivity towards β_2 -agonists [2].

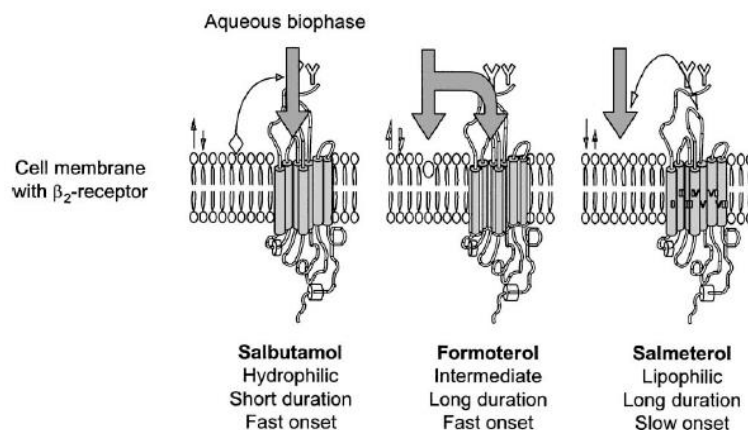


Figure 12. Microkinetic diffusion ^[41]

β_2 -agonists and corticosteroids are the ideal drugs that can be used regularly in the treatment of asthma. β_2 -agonists were found to be effective in the prevention of exercise-induced asthma ^[42], and the inhalation route is preferred to drive the medication directly to its target location for action. SABAs are the preferred drugs for treating acute bronchial constrictions due to their rapid bronchodilatation activity.

Isoprenaline was the first non-selective beta-agonist used to treat asthma symptoms. In the 1960s, after reporting high morbidity and mortality rates among asthmatic patients in association with the use of non-selective beta-agonists, it was discontinued ^[43]. However, even with the use of selective β_2 -agonists, a high morbidity rate among asthmatic patients was reported ^[2]. These cases were reported as a result of using long acting β_2 -agonists (e.g., fenoterol) ^[44]. The same situation also occurred in Canada and Japan for salbutamol ^[2]. However, by analyzing the mortality data in a retrospective study conducted in New Zealand, no evidence was found in which utilizing β_2 -agonists other than fenoterol causes such a hazard ^[44]. A meta-analysis carried out based on accumulated data up to 1992 found that the increase in morbidity due to β_2 -agonist use was inadequate and doubtful ^[45]. Since this event, the prescribed doses of β_2 -agonists were reduced, and selective SABAs were highly recommended.

3.2. Terbutaline sulphate

Terbutaline sulphate is a bronchodilator and β_2 -adrenergic agonist. It is prescribed to treat asthma. It was initially used in the 1970s ^[39,40].

In the commercial market, terbutaline sulphate is available in a racemic combination. As there are two types of crystal form, the melting point range varies depending on the crystal form. The melting point for crystal form A varies from 268 to 271 degree Celsius, whereas that of crystal form B ranges from 258 to 260 degree Celsius ^[46].

Terbutaline sulphate is a bronchodilator that comes in various forms (inhalation, oral solution, injectable, and tablet). There have been several methods developed for determining terbutaline in these dosage compositions ^[2].

Terbutaline (direct-acting selective β_2 -agonist) is introduced in the form of sulphate salt to benefit from its bronchodilatory effect in reversible airway obstruction diseases and COPD. It reduces uterine contractions by rendering the relaxation of uterine muscles. In that way, it can be used to stop premature contractions using a variety of formulations, including vaginal gel ^[2]. However, in the majority of cases, the mother develops pulmonary oedema and other cardiovascular complications as a result of its use. In view of increased danger to the mother after two days and no evidence of benefits from continuing the therapy, the British National Formulary (BNF) does not recommend it as a maintenance therapy in premature labor.

Its bronchodilatory effect often commences in less than five minutes, and lasts for 3 to 4 hours. Its regular dose is one or two inhalations of 250 µg, every 4 to 6 hours, with no more than 8 inhalations per day [47]. Spacers devices can be used in conjunction with MDIs containing terbutaline to improve drug accumulation in the lungs [48]. There are DPIs that deliver 500 µg of terbutaline sulphate in each dose, with a maximum dose of four inhalations per day. It can be taken orally (2.5 to 3 mg) three times a day in three separate doses. The maximum dose allowed for ingestion is 5 to 6 mg daily. In children, the suggested dose is 75 µg/kg. Orally administered terbutaline takes around 30 minutes before showing any effect, and it can last up to eight hours [47].

The gastrointestinal system absorbs terbutaline sulphate in various ways. Sixty percent of terbutaline absorbed is metabolized in the liver [47]. Terbutaline, alike the majority of sympathomimetics, is a racemic combination. The pharmacologically active part in this mixture is the negative enantiomer. The racemic combination has a 14.8% oral bioavailability. Several studies have attempted to isolate the enantiomers from one another to determine their concentrations in various formulations and biological samples [2].

The distribution volume of terbutaline sulphate is 1.6 L/kg [49]. Its tendency for conjugation with proteins in the plasma is poor (14-25%), but its binding to erythrocytes is stronger, resulting in a terbutaline-erythrocyte plasma concentration ratio of 2 to 2.5 [46].

Terbutaline and other β-agonists, particularly when given at large doses, may cause fine tremors in skeletal muscles (particularly, in the hands), peripheral vasodilation, palpitations, increased heart rate (tachycardia), headaches, and rarely, muscle cramps [40]. Hypokalemia, as a side effect, has been observed with substantial doses, especially following parental or nebulized routes, and it is exacerbated by the concurrent use of glucocorticoids, diuretics, and xanthines [50]. When administering large amounts of potassium, serum potassium concentrations should be observed in severe asthmatic patients as hypokalemia might lead to arrhythmias. When terbutaline is administered with monoamine oxidase inhibitors (MAOIs), such as toloxatone, it can cause symptoms similar to those in pheochromocytoma, and this drug interaction is common with less selective MAOIs, which are older and irreversible [47]. Due to a pH of less than 5.5, certain powdered formulations of inhaled bronchodilators, comprising of terbutaline, have been observed to cause tooth decay [51].

According to several studies, the tolerance from regular inhalation of short acting β₂-agonist promotes the overstimulation of lung airways, which lessens its shielding effect from bronchospasm induced by triggers, such as allergens [52,53]. The enhancement of interleukin-8 production has also been found to be one of the routes by which β₂-adrenergic agonists might alter inflammatory responses. As a result, anti-inflammatory medications, such as corticosteroids, are required [54].

Terbutaline has an inactive prodrug called bambuterol. It is categorized under LABA as it hydrolyzes in the blood circulation when taken orally at bedtime. According to preliminary studies, the average half-life of terbutaline is around 21 hours [55].

Another pro-drug of terbutaline is ibuterol, in which it is three times more effective than terbutaline after inhalation. Clinical studies have revealed that the absorption of ibuterol takes a shorter time compared to terbutaline. However, the concentrations of terbutaline in blood and inside lung tissues are less with inhaled ibuterol compared to administering free terbutaline alone [56].

4. Conclusion

Drug absorption and deposition in the lungs can be studied using a multitude of approaches. Pharmacokinetic and pharmacodynamic studies, gamma scintigraphy approach, and ex vivo research are the main approaches used. Similarly, in order to evaluate the characteristics of different inhaled aerosolized medications, several pharmacokinetic research methods can be used. The effective lung dose and total systemic transportation (delivery) can be determined by using pharmacokinetic analyzing methods based

on plasma and urine samples. Gamma scintigraphy can be classified into two main approaches: two-dimensional imaging approach (planar imaging) and three-dimensional imaging approach. Gamma scintigraphy provides critical data concerning the overall medication dose accumulated in the lungs and expelled via mucociliary clearance. Clinical studies have used bronchoprovocation to determine the bioequivalence of two aerosolized medications. In vitro methods, including inertial separation method and laser diffraction method, are used to determine the quality of the inhaled drug. Inertial impaction is the optimal method for the identification of the dynamic properties of the discharged dose. Cascade impactors are operated on the basis of inertial impaction. Using inhaled medications containing β_2 -agonist derivatives, such as terbutaline sulphate, is a controversial issue as it can be beneficial for asthma and COPD patients owing to its bronchodilatory effect; however, some studies have revealed that the continuous use of these drugs will induce hyperresponsive airways. In addition, other than its numerous drug interactions with other medications, it may cause serious adverse effects when used in high doses.

Disclosure statement

The authors declare no conflict of interest.

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