Analysis on the Delivery and Formulations of Inhaled Drugs

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Abstract: Inhalation or aerosol administration is an area that deserves more research. It is a helpful way to deliver the drugs that are hard to administrated by other routes. It is also promising for delivering biomacromolecule drugs such as insulin and peptide drugs. Aerosol administration is a multidisciplinary topic that includes physics, chemistry, engineering, and physiology. The relationship between the respiratory system and aerosol drugs is essential when studying aerosol administration. In order to get desirable effects, inhalation devices, drug formulations, and the patient are three significant factors to consider. This paper includes three commonly used delivery devices: metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers. Research has found that most of the aerosol administration devices have low lung depositions, but nebulizers can reach a relatively higher lung deposition than other devices. All of them have advantages and disadvantages, but each of them possesses distinct characteristics. These three devices have different mechanisms and require different formulations.

1 INTRODUCTION

Inhalation or aerosol administration is one of the common drug administration routes and has been widely used. It is mainly used to treat respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and lung fibrosis. Research has shown that aerosol administration can also be used to treat some systemic diseases such as diabetes, anticoagulation, headache, and osteoporosis (Groneberg et al., 2003). This paper mainly talks about the drug delivery to the reparatory system, three commonly used inhalation devices, and drug formulations used in different devices.

The delivery pathway of aerosol administrated drugs is the respiratory tract. There are two types of respiratory epithelial cells that contribute to the absorption of inhaled drugs: type I and type II pneumocytes (Groneberg et al., 2003). In these two types of cells, type I pneumocytes predominate in the surface area of the lungs, so they play an important role in inhaled drug absorption (Ehrhardt et al., 2002). Through the epithelial cells, drugs can go to the circulatory systems and exhibit target or systemic effects. Besides, different devices are used by different patients to treat various diseases. Three common inhalation devices are MDIs, DPIs, and nebulizers. Each of them has different but significant functions. It is important to consider the patients' conditions and drug formulations before choosing the devices. Also, different devices require different drug formulations to ensure their performances.

Compare to other common drug administration routes, such as oral and intravenous administration, aerosol administration shows significant advantages over other administration routes. When a drug is delivered by oral and intravenous routes, it circulates throughout the whole body. In contrast, most aerosol administrated drugs would directly have effects on the target organ, the lungs. Only a small concentration would go to the systemic circulation, which can reduce the off-target effects (Rau, J. L., 2005). Aerosol administration is also a promising way to deliver the macromolecule drugs to human bodies (Choy & Prausnitz, 2010).

2 CONSIDERATIONS OF AEROSOL ADMINISTRATION

From the first use of inhalation of epinephrine in 1929 to the present day, problems and challenges of aerosol administration have shown up (Rau, 2005). The development of aerosol administrated drugs is a

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multidisciplinary challenge—it needs considerations from physics, physiology, engineering, and chemistry aspects. Scientists need to consider the interactions between the respiratory system and the drug particles. In order to achieve successful delivery and absorption of the drugs into our system, it is important for the manufacturers to consider the drug products' particle shape and size, humidity, hygroscopy, excipient, and density (Groneberg et al., 2003). Individual difference is also a critical factor to consider during drug delivery. Gender, body weight, age, and tidal volume might influence the dosing and efficacy of the drugs.

Compare to oral and intravenous administration, aerosol administration is more complicated. It needs devices to help the administration. The three common aerosol delivery devices are dry powder inhalers (DPIs), metered-dose inhalers (MDIs), and nebulizers (Rau, 2005). Not only the drugs, but also the devices are costly for both the patients and researchers (Milgrom et al., 2001).

As shown in Figure 1, there are inseparable relationships among patients, formulation, and devices of inhaled drugs (Hou et al., 2015). Patients need to take effective drug formulations by using available inhalation devices. The drug formulation needs to fit into the devices and must be delivered by the devices. Meanwhile, the drug formulation needs to achieve efficacy in patients. Also, the devices should be compatible with the drugs and usable by the patients. The development of pharmaceutical engineering technologies of inhaled drugs is crucial to obtain a desirable relationship among these three considerations.

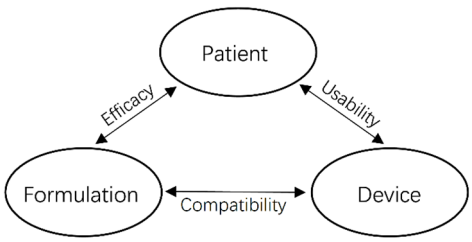

Figure 1: Considerations of aerosol administered drugs (Hou et al., 2015).

3 DRUG DELIVERY TO THE RESPIRATORY SYSTEM

The delivery and absorption of aerosol drugs are mainly through the lower respiratory tract, including small bronchioles and alveoli (Groneberg et al., 2003). Between type I and type II pneumocytes, type I pneumocytes are in charge of drug absorption (Groneberg et al., 2003). In addition, type I pneumocytes epithelial cells are the rate-limiting step of absorption because they have smaller pore size and tight junction depth compare to endothelial cells (Wangensteen et al., 1969). In order to be absorbed through the epithelial cells, particle size is a significant characteristic to consider. Aerodynamic diameter, dA, is used to describe the particle size of inhaled drugs. Research has shown that particles with dA smaller than 5 μm can reach small bronchioles and alveoli to exhibit local effects (Chow et al., 2007). Meanwhile, particles with dA that are between 1-2 μm can go to the systemic circulation, which might lead to off-target effects (Chow et al., 2007). Different excipients are used to manufacture different drugs, and they might also influence the relationship between particle size and absorption. For example, research has shown that the aerodynamic diameter for solution-based aerosol drugs are usually 2 μm, while the one for suspension-based aerosol drugs are usually 4 μm (Chow et al., 2007).

Hygroscopy is also a vital characteristic to consider. The humidity of the environment might influence the particle size of drugs. When the environment reaches a humidity of about 44 μg/cm3, hygroscopic growth of the drug particles can happen (Groneberg et al., 2003). Therefore, the administrated particle size might increase in the respiratory tract. The hygroscopicity of excipients is one of the major reasons that lead to an increase in particle size. Water vapors in the human respiratory tract would bind with the hygroscopic excipients to increase the size (Worth Longest & Hindle, 2011). Thus, during drug delivery, the final particle size after exposure to water vapor is also an essential factor to consider.

Aerosol administration would have different effects on different individuals because each patient has different physiological conditions. Tidal volume, breath pattern, and flow rates would all affect the drug efficacy (Groneberg et al., 2003). Age and gender would lead to individual differences in these three parameters. Therefore, it is crucial to administer aerosol drugs differently to different groups of people.

4 DEVICES

4.1 Metered-Dose Inhalers (MDIs)

MDIs are commonly used by asthma and chronic obstructive pulmonary disease (COPD) patients for treating bronchospasm (Hou et al., 2015). MDI containers have three parts, which are metering valve,

canister, and actuator. The metering valve controls the volume of a single dose. The canister contains pressurized drug formulation. Then the drug formulation is decompressed and released by the actuator (Lavorini, 2013). One of the advantages of MDI devices is that a single device can contain multiple doses, so that it can be used for a long time. It has shown that one MDI device contains at least two hundred doses (Lavorini, 2013). Since every dose has an equal volume, there is no worry for overdose. Comparably, MDI devices are also portable and low-cost. However, MDI devices require good coordination between patients and the devices. Patients need to breathe while releasing the drug and hold breath for a few seconds to increase lungs deposition (Lavorini, 2013). In addition, the materials of the metering valve, canister, and actuator would affect the drug properties. The inner walls of the MDI container are usually coated with polymers, such as perfluoroalkoxy (PFA), fluorinated ethylene propylene–polyether sulphone (FEP–PES), and polytetrafluoroethylene (PTFE), to prevent changes in drug properties (Traini et al., 2006).

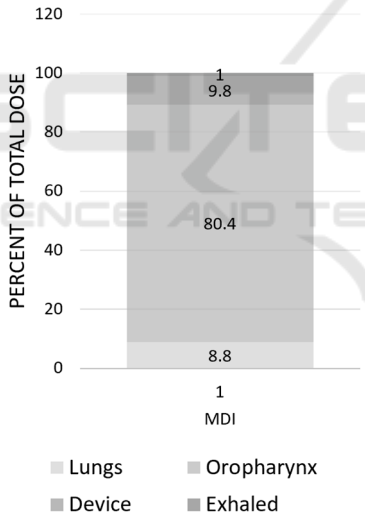

Figure 2: Drug deposition for patients who use MDI devices (Newman et al., 1981).

Newman et al. has measured drug depositions and the data is shown in figure 2. When delivered by MDI, most of the drugs, about 80.4%, would lost in the oropharynx. Only 8.8% of the total amount would be delivered to the lungs (Newman et al., 1981). There are also other studies showed that the lung deposition when using MDI with good techniques can reach to 11.2% (Newman et al., 1986).

4.2 Dry Powder Inhalers (DPIs)

Similar to MDI devices, DPI devices are portable and convenient. A DPI device can have only one dose or multiple doses. If one DPI device is single-dosed, it is a disposable inhaler (Hou et al., 2015). Recent research shows that disposable DPIs are suitable for inhaled COVID-19 vaccines because they can prevent reuse and contamination (Heida et al., 2021). Furthermore, unlike MDIs, DPI devices do not require coordination between patients and devices. Drug delivery of DPIs only relies on patients' breath independently (Hou et al., 2015). However, this leads to a drawback of this kind of device: DPIs require a certain amount of inspiratory flow rate to get an effective dosage (Lavorini, 2013). For example, Newman et al. conducted an experiment that measures the drug deposition in patients who use a DPI device, SpinHaler.

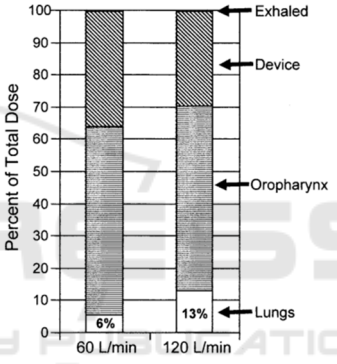

Figure 3: Drug deposition for patients who use SpinHaler with a high inspiratory flow rate (120 L/min) and with a low inspiratory flow rate (60 L/min) (Newman et al., 1994).

As shown in Figure 3, the experiment illustrated that drug deposition in lungs for patients with a higher inspiratory flow rate and those with a lower inspiratory flow rate are significantly different (Newman et al., 1994). The drug deposition in the lungs is doubled when the inspiratory flow rate is doubled (Newman et al., 1994). Thus, some patients might not use them correctly and efficiently. Research has found that 94% of the patients do not use the DPI devices correctly (Lavorini et al., 2008).

4.3 Nebulizers

Nebulizers are relatively larger and less portable than MDIs and DPIs. They can provide continuous drug delivery, which is especially useful for the delivery of large-dosed drugs (Hou et al., 2015). This also leads to a longer time duration of drug delivery, so some nebulizers require outside energy sources to conduct

drug delivery (Lavorini, 2013). However, nebulizers are easier for patients to use. Nebulizers usually need mouthpieces or facemasks to delivery drugs to patients (Lavorini, 2013). Patients only need to perform their normal breathing pattern to use nebulizers, which is especially helpful for incoordinate patients such as infants and elderly patients (Lavorini, 2013). Tidal volume determines the amount of drug delivered, so there might be individual differences in terms of efficacy. On the other hand, nebulizers are not disposable, so the drugs need to be loaded into the devices. Thus, compare to MDIs and DPIs, nebulizers have a higher chance of causing drug contamination (Lavorini, 2013).

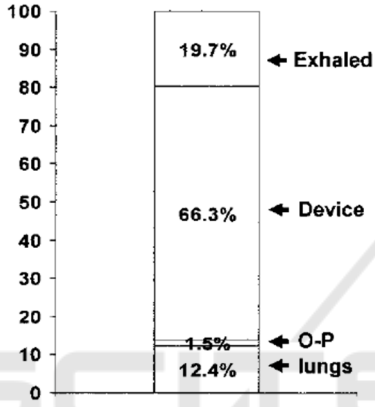

Figure 4: Drug deposition for patients who use Inspiron Mini-Neb. O-P=oropharyngeal (Lewis & Fleming, 1985).

Experiment has found that nebulizers can reach a lung deposition of 12.4%, which is higher than the one for MDIs (Lewis & Fleming, 1985). In addition, compare to MDIs and DPIs, most of the drugs, about 66.3%, would lost in nebulizer devices (Lewis & Fleming, 1985).

5 FORMULATIONS

Different devices utilize different drug formulations. MDIs and nebulizers are usually used to deliver suspension or aqueous solution formulated drugs, while DPIs, as the name indicates, are usually used to deliver drug powders (Hou et al., 2015). Also, MDIs contain propellants while DPIs and nebulizers do not (Lavorini, 2013). Since different delivery devices possess different mechanisms, different excipients and formulations are needed to ensure the desired performance of each kind of device.

5.1 Metered-Dose Inhalers (MDIs)

Drug particles are conserved with propellants in MDIs and delivered together. Different propellants were used since the first use of MDIs. One of the previously used propellants is chlorofluorocarbons (CFC), but it is no longer in use since the Montreal Protocol in 1987 because of ozone-depleting effects (Hou et al., 2015). The commonly used propellants now are hydrofluoroalkane (HFA), which includes HFA 134a and 227ca, which are less likely to cause global warming than CFC (Lavorini, 2013). Except for propellants, MDIs also need surfactants and cosolvents (Lavorini, 2013). Some common surfactants are sorbitan trioleate, lecithin, oleic acid, and polyethylene glycol (PEG), which mainly serve as valve lubricants and inhibit particle aggregation. It is also shown that some surfactants contribute to the taste (Lavorini, 2013). However, the solubility of some surfactants is not ideal in HFA propellants (Vervaet & Byron, 1999). Cosolvents such as ethanol would help to improve the solubility of surfactants (Hou et al., 2015).

5.2 Dry Powder Inhalers (DPIs)

DPIs are used to deliver solid drug powders into human body systems. The commonly used excipient or carrier of DPI drugs is lactose. Micronized drugs first blend with lactose particles with diameters of 30-60 μm; they are granulated into micronized particles using wet or dry granulation (Chow et al., 2007). Meanwhile, particle size and shape are important parameters to consider when formulating dry powder inhaler drugs. Amorphous particles are less efficient during delivery because of their high-energy surface (Kawashima et al., 1998). Research has shown that lung deposition is higher when the particles are elongated and pollen-shaped (Fults et al., 1997). Various techniques can be used in DPI drugs formulation, such as spray drying, freeze-drying, and roller drying (Hou et al., 2015). Among these techniques, in vitro research has shown that anhydrous β-lactose by using roller drying might be more efficient and doable (Chow et al., 2007). Trehalose, mannitol, and menthol could be other excipient carriers that can replace lactose (Chow et al., 2007).

5.3 Nebulizers

Nebulizers are usually used to deliver drugs with suspension or aqueous solution formulations. A common solvent of nebulizer drugs is sterile water,

which is the same solvent for intravenous injection (Hou et al., 2015). Similar to MDI drugs formulation, ethanol can be the cosolvent for nebulizer drugs as well (Hou et al., 2015). Furthermore, the physical properties of drug formulations are essential because they might lead to change in delivery efficiency and result in side effects (Labiris & Dolovich, 2003). For example, a low pH would lead to bronchoconstriction, which might result in irritation (Labiris & Dolovich, 2003). In this case, the pH can be increased by adding sodium hydroxide, while similarly, hydrochloric acid can be added if the pH is too high (Hou et al., 2015). Besides, solution viscosity can influence the size of particles—the larger the viscosity, the smaller the particle size (Hou et al., 2015). Therefore, physical properties are crucial factors to consider in nebulizer drug formulation. In addition, since nebulizers are not disposable and have a higher chance of getting contaminated, preservatives are needed. Benzalkonium chloride can be an antimicrobial preservative (Hou et al., 2015).

6 CONCLUSIONS

Aerosol administration is a promising area of drug delivery and still needs more research. It is not as common as other administration routes, such as oral and intravenous administration, but it is a helpful way of drug delivery. Aerosol administration has benefits when the local administration is wanted. Meanwhile, some aerosol drugs also have systemic effects. Inhaled drugs are mainly absorbed by type I pneumocytes to exhibit local or systemic effects.

There are three most commonly used inhalation devices: metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers. Each of them has advantages and drawbacks compared to others. We need to put drug formulation and patient conditions into account when using these devices. Different drugs and devices need different excipients and formulations. The inhaled drugs and formulations need to be compatible with specific devices. There also might be individual differences in aerosol administration because each patient has different physiological conditions. Devices, formulations, and patients together are three crucial factors to consider for the development of aerosol administration (Hou et al., 2015).

There are many approved inhalation devices. This paper focuses on three common ones with different formulation requirements. MDIs and nebulizers require suspension or solution formulations, while DPIs require drug powder formulations. There are many aspects to consider in drug formulation, such as propellant, excipients, and physical properties. More studies on the specific effects of different formulations and the optimal devices and formulations for specific systems are still needed.

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REFERENCES

Chow, A. H. L., Tong, H. H. Y., Chattopadhyay, P., & Shekunov, B. Y. (2007). Particle Engineering for Pulmonary Drug Delivery. Pharmaceutical Research, 24(3), 411–437. https://doi.org/10.1007/s11095-006-9174-3

Choy, Y. B., & Prausnitz, M. R. (2010). The Rule of Five for Non-Oral Routes of Drug Delivery: Ophthalmic, Inhalation and Transdermal. Pharmaceutical Research, 28(5), 943–948. https://doi.org/10.1007/s11095-010-0292-6

Ehrhardt, C., Fiegel, J., Fuchs, S., Abu-Dahab, R., Schaefer, U. F., Hanes, J., & Lehr, C.-M.. (2002). Drug Absorption by the Respiratory Mucosa: Cell Culture Models and Particulate Drug Carriers. Journal of Aerosol Medicine, 15(2), 131–139. https://doi.org/10.1089/089426802320282257

Fults, K. A., Miller, I. F., & Hickey, A. J. (1997). Effect of Particle Morphology on Emitted Dose of Fatty Acid-Treated Disodium Cromoglycate Powder Aerosols. Pharmaceutical Development and Technology, 2(1), 67–79. https://doi.org/10.3109/10837459709022610

GRONEBERG, D. A., WITT, C., WAGNER, U., CHUNG, K. F., & FISCHER, A. (2003). Fundamentals of pulmonary drug delivery. Respiratory Medicine, 97(4), 382–387. https://doi.org/10.1053/rmed.2002.1457

Heida, R., Hinrichs, W. L., & Frijlink, H. W. (2021). Inhaled vaccine delivery in the combat against respiratory viruses: a 2021 overview of recent developments and implications for COVID-19. Expert Review of Vaccines. https://doi.org/10.1080/14760584.2021.1903878

Hou, S., Wu, J., Li, X., & Shu, H. (2015). Practical, regulatory and clinical considerations for development of inhalation drug products. Asian Journal of

Pharmaceutical Sciences, 10(6), 490–500. https://doi.org/10.1016/j.ajps.2015.08.008

Kawashima, Y., Serigano, T., Hino, T., Yamamoto, H., & Takeuchi, H. (1998). Effect of surface morphology of carrier lactose on dry powder inhalation property of pranlukast hydrate. International Journal of Pharmaceutics, 172(1-2), 179–188. https://doi.org/10.1016/s0378-5173(98)00202-6

Labiris, N. R., & Dolovich, M. B. (2003). Pulmonary drug delivery. Part II: The role of inhalant delivery devices and drug formulations in therapeutic effectiveness of aerosolized medications. British Journal of Clinical Pharmacology, 56(6), 600–612. https://doi.org/10.1046/j.1365-2125.2003.01893.x

Lavorini, F. (2013). The Challenge of Delivering Therapeutic Aerosols to Asthma Patients. ISRN Allergy, 2013, 1–17. https://doi.org/10.1155/2013/102418

Lavorini, F., Magnan, A., Dubus, J. C., Voshaar, T., Corbetta, L., Broeders, M., Dekhuijzen, R., Sanchis, J., Viejo, J. L., Barnes, P., Corrigan, C., Levy, M., & Crompton, G. K. (2008). Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. Respiratory Medicine, 102(4), 593–604. https://doi.org/10.1016/j.rmed.2007.11.003

Lewis, R. A., & Fleming, J. S. (1985). Fractional deposition from a jet nebulizer: How it differs from a metered dose inhaler. British Journal of Diseases of the Chest, 79(4), 361–367. https://doi.org/10.1016/0007-0971(85)90069-5

Milgrom, H., Skoner, D. P., Bensch, G., Kim, K. T., Claus, R., & Baumgartner, R. A. (2001). Low-dose levalbuterol in children with asthma: Safety and efficacy in comparison with placebo and racemic albuterol. Journal of Allergy and Clinical Immunology, 108(6), 938–945. https://doi.org/10.1067/mai.2001.120134

Newman, S. P., Hollingworth, A., & Clark, A. R. (1994). Effect of different modes of inhalation on drug delivery from a dry powder inhaler. International Journal of Pharmaceutics, 102(1-3), 127–132. https://doi.org/10.1016/0378-5173(94)90047-7

Newman, S. P., Pavia, D., Moren, F., Sheahan, N. F., & Clarke, S. W. (1981). Deposition of pressurised aerosols in the human respiratory tract. Thorax, 36(1), 52–55. https://doi.org/10.1136/thx.36.1.52

Newman, S. P., Woodman, G., Clarke, S. W., & Sackner, M. A. (1986). Effect of InspirEase on the Deposition of Metered-Dose Aerosols in the Human Respiratory Tract. Chest, 89(4), 551–556. https://doi.org/10.1378/chest.89.4.551

Rau, J. L. (2005). The Inhalation of Drugs: Advantages and Problems. Respiratory Care, 50(3), 367–382.

Traini, D., Young, P. M., Rogueda, P., & Price, R. (2006). The Use of AFM and Surface Energy Measurements to Investigate Drug-Canister Material Interactions in a Model Pressurized Metered Dose Inhaler Formulation. Aerosol Science and Technology, 40(4), 227–236. https://doi.org/10.1080/02786820500543316

Vervaet, C., & Byron, P. R. (1999). Drug–surfactant–propellant interactions in HFA-formulations. International Journal of Pharmaceutics, 186(1), 13–30. https://doi.org/10.1016/s0378-5173(99)00134-9

Wangensteen, O. D., Wittmers, L. E., & Johnson, J. A. (1969). Permeability of the mammalian blood-gas barrier and its components. American Journal of Physiology-Legacy Content, 216(4), 719–727. https://doi.org/10.1152/ajplegacy.1969.216.4.719

Worth Longest, P., & Hindle, M. (2011). Numerical Model to Characterize the Size Increase of Combination Drug and Hygroscopic Excipient Nanoparticle Aerosols. Aerosol Science and Technology, 45(7), 884–899. https://doi.org/10.1080/02786826.2011.566592