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学位授与の題目	Study on Dry Powder Inhaler – Particle Dispersion, Bounce-off and Washout from the Lung（粉末吸入器（ＤＰＩ）に関する研究－粒子の分散・跳ね返りと肺からのウォッシュアウト）
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学位論文要旨

The application of medication via inhalation is the first choice of therapy worldwide for Chronic Obstructive Pulmonary Disease (COPD). For aerosol inhalation therapy, drug particle sizes must be in a relatively narrow range (typically 1-5μm) in order to provide efficient delivery to the lungs. In general, drug particles are generated by three different types of devices for inhalation therapy: Dry Powder Inhaler (DPI), Metered Dose Inhaler (MDI), and Nebulizer. The inhalation device should be simple to use, portable, un-obstructive and cons-effective. The DPI satisfies the previously mentioned requirements. In the previous study, DPIs are usually evaluated under a steady flow condition using Andersen impactor. However, the dose and the aerosol characteristics are dependent on the patient's ability to inspire at the minimum required flow rate. Furthermore, there are some limitations in applying impactors due to occurrences of particle bounce-off, re-entrainment, and break-up upon impaction substrate. Therefore, in order to evaluate more accurate dispersion performance of DPIs, it is necessary to simulate a condition of inspiration pattern with COPD subject and to prevent occurrence of particle bounce-off, re-dispersion, and break-up. Furthermore, to reduce damage by environmental tobacco smoke (ETS) because it is main cause of COPD, it is necessary to elucidate the characteristics of ETS. Due to an increase in the non-smoking area, non-smokers are pretty might feel still unsafe. This is because they could possibly inhale smokers' breathed-out mainstream smoke, which is residual in their lungs after they smoke and return to non-smoking area. Therefore, to reduce the damage by mainstream smoke from the lung,

a good understanding on the inhaled cigarette smoke from the lung is necessary.

The dispersion performance of DPIs is evaluated by applying gravitational settling chamber. The generated particles were introduced into the settling chamber for performing free sedimentation during a certain time, and particle size distribution is measured with optical microscope. By applying this technique, the occurrence of particle bounce-off, re-dispersion, and break-up due to the fact that the agglomerated particles collide with the impaction substrates during measurement, by using an Andersen impactor, can be prevented. Moreover, the inhalation patterns of healthy and COPD subjects using a DPI with different resistant flows were measured. Based on the results of inspiration patterns, an inspiration pattern simulator is constructed and applied to evaluate the DPIs. Furthermore, this study investigated the effects of micronization by particle bounce-off, re-dispersion, and break-up in the impactor in order to control the particle bounce-off, re-dispersion and effects of micronization in the impactor. In general, the impaction substrate coated with an adhesive material can reduce particle bounce-off, which is the main cause of performance deterioration in the impactor. However, these coating methods may cause a problem of chemical and elemental interference with collected particles. Therefore, in order to prevent particle bounce-off, a new impaction substrate without an adhesive material is necessary. This work adopts an impaction substrate with a soft material, and it would be of great interest to investigate the effect of particle bounce-off on the rubber sheet, and if it will lead to inelastic collisions between impaction substrate and particles. Furthermore, we focus on characteristics of rubber sheets as an impaction substrate in order to increase the deformation between impaction substrate and particles.

In order to collect fundamental data on the concentration level of an exhaled MS from smokers, the smoking patterns of smokers are evaluated by using an anemometer while the particle concentration and the size distribution of SS and the exhaled MS are measured with SMPS and ELPI. However, exhaled air is saturated when it leaves from the mouth. Therefore, water vapor condensation on particles as well as the coagulation of particles may significantly alter the size distribution of particles after the exhalation. In order to find the effect of water vapor condensation on the size distribution measurements, the exhaled MS during the first puff are filled into a gasbag with and without passing it through a diffusion dryer packed with silica gel and the size distributions are measured after aging for a given time in the gas bag. Furthermore, in order to measure the exhaled MS after smoking, the exhaled MS from the lung at each puff is collected directly into a gasbag through a mouthpiece with and without passing the exhaled smoke through a diffusion dryer. The conclusions obtained in the present study are as follows;

1. Dispersion performance of drug particles by dry powder inhaler

The flow resistance of DPIs markedly affects the peak flow rate more than the inspiration volume, regardless of sex or subject type. For evaluating the dispersion performance of DPIs using a steady flow condition, the dispersion performance of DPIs is underestimated in the case of a peak flow rate with simulated condition larger than the simulated flow condition, while it overestimate for a peak flow rate smaller than simulated flow condition. Therefore, the larger the peak flow rate, better the particles are micronized under steady flow condition. Consequently, the dispersion performance of DPIs largely depends on inspiration pattern.

Micronization of particles mainly occurs in the orifice of the impactor, whereas micronization (particle bounce-off, re-dispersion, and break-up) as well as collection of particle occur at the impaction substrate. The micronization effect of the 0^{th} orifice and impaction substrate of impactor equals the dispersion of DPI.

For these reasons, in order to develop an effective DPI system and to control the dosage, it can be said that the performance of a DPI has to be evaluated using simulated inspiration patterns of a patient with a DPI. Furthermore, for measuring the dispersion performance of DPI, it is necessary to use a measurement method without particle bounce-off, re-dispersion and break-up.

2. Particle bounce-off on various rubber sheets

In general, the rubber characteristics changes for different temperatures and frequencies. The characteristics of rubber are usually measured at a frequency of 10 Hz by varying the temperature. However, the time scale of particle-wall collisions is much shorter than 10Hz. Therefore, the rubber state changes to the glassy region due to the increase of the frequency and it can be said that the glassy region extends to the high temperature zone. Consequently, the particle bounce-off can be prevented by applying rubber sheets of silicone and Gelnic with a low glass transition temperature at room temperature. Furthermore, the rubber state changes to the rubber region due to the increase of the temperature. Therefore, by controlling the temperature of the rubber sheets, the particle bounce-off can be prevented for various kinds of rubber sheets.

For these reasons, in order to control a particle bounce-off without adhesive materials, this study found that the particle bounce-off can be controlled by using a rubber with different glass transition temperature under the room temperature. Furthermore, various rubber sheets are applicable to prevent the particle bounce-off by controlling the temperature of the rubber sheets.

3. Washout characteristics of inhaled cigarette smoke from human lung

Vital capacities of smokers do not affect the inspiration pattern of cigarette smoke, and the air inspired through a cigarette by a smoker during a puff, which is obtained by integrating the inspiration curves is about 80 cm^3 without a significant difference between the smokers. Human lung constantly generates particles with a median size smaller than 0.01 μm at the concentration of about 1.6×10^4 cm^{-3}, and residual particles in the lung are washed out after 20 times of deep breathing. The effect of water vapor condensation on the size distribution measurements, the particles in the size range 0.3 to 0.7 μm are scavenged by the coagulation with the larger particles at a faster rate in case without the diffusion dryer since the initial number concentration of larger particles without the diffusion dryer is higher than that with the diffusion dryer. Furthermore, the concentrations of particles smaller than 0.3 μm in exhaled MS are little influenced by the water vapor condensation. Consequently, in the washout experiments, the exhaled MS from the lung are measured with the diffusion dryer using the SMPS and ELPI. Mainstream smoke exhaled from the lung has a bimodal distribution with the concentration of about 2.5×10^7 cm^{-3}, and after smoking, complete washout of residual smoke in the lung requires normal breathing for 20 min.

For these reasons, the control of exhaled mainstream smoke as well as the sidestream smoke is necessary to prevent passive smoking because they are nearly the same both in concentration and in size.

学位論文審査結果の要旨

平成18年8月1日に口頭発表と質疑応答を行い、その後に開催した学位論文審査会において以下のように決定した。

本論文は、喘息などの呼吸器疾患の吸入療法に用いられる粉末薬剤吸入器（DPI）に関するもので、吸入パターンとDPIの粒子分散性能の関係について検討するだけでなく、DPIの粒子分散機構の一つと考えられる壁面での粒子の跳ね返り、吸入された粒子の肺からのウォッシュアウトについてもたばこ煙を用いて詳細な検討を行った。その結果、DPIの通気抵抗が大きくなると吸気時のピーク流量が大幅に低下すること、そして吸入パターンによってDPIの分散性能が大きく変化することを明らかにした。また、粒子の壁面での跳ね返りに関し、粒子の付着効率は粒子の運動量によってほぼまとめることができ、ガラス転移温度の低いゴムを用いることにより粒子の跳ね返りを抑制できることを示した。さらに、肺からの粒子のウォッシュアウト実験により、通常呼吸の場合、0.1μm程度の小さな粒子は吸入後15分以上も肺内に残存し、呼気とともに排出されることが明らかになった。

以上のように、本論文は、DPIを用いてエアロゾル吸入療法を効果的に実施するために不可欠な、DPIの分散性能、分散機構、肺内でのエアロゾルの挙動について工学的な見地から検討を加えて重要な知見を与えており、博士（工学）の学位に値すると判断する。