Inhalable levodopa: from laboratory to the patient

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APPENDIX A

SUMMARY
Chapter 1: Introduction: Inhaled drugs for systemic action

There is a growing interest in using the pulmonary route for the administration of systemically acting drugs as this route may have certain advantages (such as a rapid absorption or limited first-pass metabolism) in comparison to other administration routes. However, in spite of the advantages, systemic drug delivery using inhaled aerosols is accompanied by several specific requirements and challenges too. Chapter 1 describes these challenges. It starts with defining the target site for deposition of the inhaled aerosol, which may be different for different applications, but for systemically acting drugs is often considered to be in the most peripheral airways, including the alveoli. Whether drug delivery to the alveolar region is necessary may depend on the type of drug. Whether, and to what extent it is possible to administer drugs systemically via the lung, is amongst others determined by the drug formulation, the inhaler technology as well as by how the inhaler is used. Device design and instruction for use are, therefore, of utmost importance to the success of the delivery. And even after successful delivery to the (peripheral) lung, the fate of the particles after deposition at the site of absorption is often still uncertain. Metabolism and clearance mechanisms in the lungs may be effective in degradation and removal respectively, thereby diminishing the bioavailability of the drug. This all makes the entire process from drug aerosolization to systemic therapeutic effect very complex. It involves many different steps of which many are insufficiently explored and poorly understood.

It is of great interest to understand and control (for as good as possible) the steps that are directly related to the technical measures that can be taken to administer the drug to the desired target area. In this chapter we take a critical view on the efficacy that may be expected for pulmonary delivery of systemically acting drugs when using classical DPI and formulation designs and some new developments, and what technical measures can be taken for further optimisation. Having adequate knowledge about lung architecture (numbers and sizes of airways), the lung’s defence system against invading particles and the conditions of the deposition area for inhaled particles is of utmost importance to the optimisation of respiratory drug delivery with dry powder inhalers. We also present the state of the art regarding systemically acting drugs for pulmonary delivery and summarise the arguments for considering dry powder inhalers as the most appropriate type of administration device for these drugs.

Chapter 2: Can patients with Parkinson’s disease use dry powder inhalers during off periods?

Levodopa is effective in alleviating the motor symptoms of Parkinson’s disease, but a high variability in levodopa absorption from the gastrointestinal tract after oral administration causes fluctuations in the levodopa plasma concentration. In more advanced Parkinson’s disease, fluctuations in the levodopa plasma concentration often result in an irregular occurrence of off periods, when symptoms are poorly controlled. Off periods are characterised by an extensive variety of complaints, such as decreased mobility, bradykinesia, tremor, autonomic symptoms, sensory symptoms and psychiatric disorders. Pulmonary administration of levodopa may offer an attractive alternative to oral administration, due to the larger size of the absorption membrane.
and the relatively low metabolic activity in the lungs. However, hardly anything is known about Parkinson’s disease patients’ abilities to operate a dry powder inhaler. For that reason, we assessed the ability of Parkinson’s disease patients to use a disposable dry powder inhaler (Cyclops) suitable for the administration of a high dose of levodopa during an off period. A test inhaler with three different resistances to air flow around the resistance of the Cyclops inhaler was used in order to investigate whether this dry powder inhaler needed further optimisation on resistance. We monitored how the test inhaler was handled and we recorded the inspiratory flow curves generated by 13 Parkinson’s disease patients while they were in an off period. Pressure drops across the inhaler, inhalation times, inhaled volume and breath holding periods after inhalation were recorded and evaluated by comparing them with the requirements for adequate operation of the Cyclops and achieving efficient aerosol deposition in the respiratory tract respectively. It was observed that all patients were able to generate pressure drops > 2 kPa over the highest resistance to airflow and 10 out of 13 patients achieved at least 4 kPa. Inhaled volumes (all resistances) varied between 1.2 and 3.5 L. Twelve out of thirteen patients could hold their breath for at least five seconds after inhalation and nine could extend this to ten seconds. As will become clear from the next chapter, a pressure drop of 2 to 4 kPa is sufficient for complete dose emission and powder the dispersion by the Cyclops for the levodopa formulation developed, and this indicates that patients with Parkinson’s disease will indeed be able to use this device in an off period.

Chapter 3: Development of a levodopa dry powder formulation for the Cyclops
As described in the previous chapter, during an off period, pulmonary administration of levodopa may be an interesting alternative to levodopa taken via the oral route. Our objective was to develop a levodopa inhalation powder by mean of simple particle preparation techniques such as micronization and spray drying of the drug, either as pure active substance or with a minimum amount of excipients. Screening and selection on dispersion behaviour of the developed levodopa inhalation powders was performed with using laser diffraction analysis. Thereafter, the most promising formulation of levodopa, co-micronized with 2% l-leucine, was characterized in vitro using cascade impactor analysis over a range of pressure drops (2 – 6 kPa) and doses (20, 30 and 40 mg) being representative for those to be expected in practice. This formulation used in combination with the Cyclops inhaler showed good aerosolization properties for inhalation over the entire range of pressure drops and up to a dose of 30 mg. It also showed highly consistent delivered dose at the same pressure drop, yielding fine particle fractions between 40 and 60% of the metered dose. We therefore concluded that the formulation of levodopa with 2% l-leucine used in the Cyclops inhaler is a promising candidate for the use in off periods.

Chapter 4: Pharmacokinetics and tolerability of inhaled levodopa from a new dry powder inhaler in Parkinson’s disease patients
In this chapter, we describe the results of a pilot study where we assessed the pharmacokinetics and tolerability of the levodopa with 2% l-leucine inhalation powder from the Cyclops inhaler. We performed a single centre, single ascending, dose response study. Eight Parkinson’s disease
patients (not in an off state) visited the hospital three times. During these three visits they received levodopa by inhalation; 30 mg (1st visit) and 60 mg as 2 x 30 mg (2nd visits) or their regular oral levodopa (3rd visit). During pulmonary administration, the inhalation curve was recorded and characteristic flow parameters were computed. Predose and at \( T = \text{predose}, 0, 5, 10, 15, 20, 30, 45, 60, 90 \) and \( 180 \) min after the levodopa administration blood samples were drawn. Predose, 35 and 100 minutes after levodopa administration spirometry was performed to assess the pulmonary function.

It was observed that, after inhalation, the levodopa \( T_{\text{max}} \) occurred between 5 to 15 minutes in all participants, with an overall mean value of 10 minutes. After oral administration, \( T_{\text{max}} \) varied considerably more and ranged from 20 to 90 minutes. The bioavailability of inhaled levodopa without decarboxylase inhibitor calculated from the emitted dose was 53% relative to oral levodopa with decarboxylase inhibitor. None of the patients experienced cough or dyspnea and no change in pulmonary function parameters was measured. We could not show correlations between measured inhalation parameters and the levodopa pharmacokinetic parameters. This indicates that the bioavailability of inhaled levodopa is not dominated by the inhaled flow rate and volume, which suggests that effective absorption occurs in a large deposition area, meaning that the drug can be robustly administered over a wide range of inhalation flow profiles. Based on this pilot study, it is concluded that inhaled levodopa with 2% L-leucine administered with the Cyclops inhaler is absorbed faster than oral levodopa and that it is well tolerated too. The formulation from the Cyclops inhaler therefore appears to be suitable for the treatment of off periods in Parkinson’s disease.

Chapter 5: Learning from Parkinson’s patients: usability of the Cyclops dry powder inhaler

Effective inhaler therapy requires correct operation of the inhaler, including all the preparations that are required before the drug can be inhaled. It is known that usability is a key factor in ensuring safe and efficacious medication use by patients. The levodopa inhalation powder in the Cyclops inhaler is intended for use during off periods. In daily practice, this means that patients in an off period must be able to prepare the inhaler correctly for use. For this reason, we assessed the user ability and convenience of the Cyclops inhaler in 30 Parkinson’s disease patients in an off period. We also assessed opening of the pouch in which the inhaler is packed for protection of the inhalation powder against light and moisture. Additionally, we were interested if there exists a difference in handling ability between patients in an off period and patients in an on period. Therefore, 30 patients in an on period were assessed too. Correct opening of the pouch was defined as opening the pouch the way it was designed for. For both pouches this meant using the tear notch. The pouch is wrapped around the inhaler and provided with two ‘end seals’ and one ‘fin seal’ over the length of the inhaler. The tear notch position of pouch 1 was acentric, opposite to the side were the fin seal has been folded, one third from the right corner. The tear notch position of pouch 2 was centric, thus located in the middle of the upper side of the pouch.
By choosing different process parameters regarding the sealing of the foil on the dose compartment, Cyclops inhalers with a variable sealing of the dose compartment were developed. The peel resistance that is needed to pull the foil from the dose compartment and out of the inhaler is higher for Cyclops B than for Cyclops A. Correct opening of the inhaler was defined as holding the inhaler on a flat area with one hand and pulling out the complete foil with the other hand.

The results show the relevance of testing the ability and user convenience, since, especially for the pouches, several patients did not open the pouch the way it was designed to be opened. Pouch 2 was more often opened correctly than pouch 1, but more participants defined opening pouch 2 as hard or difficult. For future use, it may be worth improving the pouch by developing a pouch with two tear notches. Based on suggestions of the participants, the visibility of the tear notches may be improved too.

For the inhaler > 95% of the on state participants and > 90% of the off state participants were able to prepare the inhaler by pulling the foil from the dose compartment. Since Cyclops A was easier to open for both on and off state participants, this one is preferred over Cyclops B for use in daily practice.

For both pouches and both inhalers, more on state patients than off state patients were able to correctly open it. Also, more on state participants defined opening as being easy. These results indicate that differences exist in the experienced and measured suitability for use between off state and on state participants, and although the differences were small, in our opinion the worst-case assessment is the best for rating the usability. Therefore, we suggest to assess the effects of further packaging optimisation in off state patients. The data obtained in this study will help the developers to further improve the packaging of the Cyclops inhaler.

Chapter 6: Therapeutic effects of an inhaled levodopa dry powder formulation on the recovery from off periods in patients with Parkinson’s disease

As described in chapter 4, the levodopa dry powder formulation administered with the Cyclops inhaler was rapidly absorbed and well tolerated after inhalation. Chapter 6 describes the study protocol for a currently ongoing study for assessing the therapeutic effects of that levodopa dry powder formulation. For this purpose, nine Parkinson’s disease patients with predictable off periods recognizable for themselves and others, with a morning oral levodopa dose of 100 mg and at least 2 years of levodopa use will be asked to participate in this trial. The study has a single arm cross over design; one arm consists of administration of 90 mg of inhaled levodopa and the other arm of oral administration of 1 tablet levodopa / benserazide 100 / 25 mg. Study medication is administered after a levodopa free period of at least 5 times the half-life time.

The primary outcome of this study will be the levodopa efficacy measured with the timed up and go test and the finger tapping test. Secondary outcomes are the pharmacokinetics and the time to maximum effect assessed by the MDS-UPDRS III motor function score. Further, pulmonary safety is assessed before and after admission.

The results of this study will show whether levodopa with 2% L-leucine is effective in the recovery from off periods.
Chapter 7: general discussion

In this thesis, we focused on the development of a levodopa containing dry powder inhaler (Cyclops) for use by Parkinson’s disease patients. We were able to successfully develop a levodopa inhalation powder with only 2% l-leucine as excipient, for this inhaler. Co-micronization of levodopa with the l-leucine significantly improved the dispersion behaviour of the drug. L-leucine is a branched-chain aliphatic amino acid and an essential constituent to the human diet. It is also an ingredient of several pharmaceutical preparations for oral administration and injection. If a patient with Parkinson’s disease has 8 off periods per day and uses 8 times 60 mg levodopa inhalation powder, the total maximum daily-administered l-leucine dose is only 9.6 mg. This is a minute amount compared to the daily intake of l-leucine from food and supplements, estimated at 6.1 gram per day or compared to the recommended daily intake of L-leucine (2380 mg to 2730 mg per day). However, in literature, very little is described regarding the pulmonary safety of l-leucine and there are currently no marketed drug formulations containing l-leucine. Although the available studies in literature indicate that the inhalation of l-leucine may be considered as safe, the intended upscaling and marketing authorisation of the inhalation powder require that the tolerability profile of l-leucine should be assessed in more detail, to prove the suitability of the excipient for pulmonary administration.

When using the lung as portal of entry for systemic drug delivery, it is important to realize that abnormal lung function and lung anatomy may influence absorption. Previous studies have provided inconsistent results about abnormalities in Parkinson’s disease patients, since obstructive as well as restrictive defects have been described. We assessed the spirometry data of all Parkinson’s disease patients in the Lifelines cohort. Parkinson’s disease patients were excluded if they had no clinically reliable spirometry results (e.g. if they were not able to generate reproducible curves) and when they had COPD, chronic bronchitis, asthma or emphysema. From the cohort of 152,180 participants, 131 patients had Parkinson’s disease and 82 patients were eligible for analysis. We did not find differences between Parkinson’s disease patients and non-Parkinson’s disease controls. However, the number and mean age of Parkinson’s disease patients was lower than expected and this indicates that the results are not fully representative. However, our results clearly show that there are no major concerns regarding pulmonary function defects in the fast majority of Parkinson’s disease patients.

Next to l-leucine, the pulmonary safety of levodopa needs to be proven too. Since a commercially available inhaled levodopa (Inbrija ®; Accorda) was recently allowed on the US market (December 2018), it can be assumed that extensive safety data have already been obtained for that purpose. However, since Inbrija ® is under data protection, these results are not yet available in the public domain. It is, therefore, expected that our development team may have to perform these safety studies too, although it must be questioned whether it is ethical to perform animal safety studies in two mammalian species while knowing that levodopa is safe.
In conclusion, a levodopa dry powder formulation with 2% L-leucine as excipient in the Cyclops seems suitable for use in Parkinson’s disease patients. A currently ongoing clinical trial on effect should confirm the positive results from the pharmacokinetic and tolerability study and show whether inhalation of our levodopa formulation indeed results in a rapid reversal of the off period. For a correct and effective use of the Cyclops inhaler, it is suggested to optimize the pouch and the lidding foil for the dose compartment based on the suggestions of the Parkinson’s disease patients. Finally, it should be discussed with the Dutch registration authority whether and to what extent safety studies are needed, in order to prevent unnecessary testing in both animals and humans.