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Novel dry powder inhaler formulation containing antibiotic using combined technology to improve aerodynamic properties

Rita Ambrus[a,*], Edit Benke[a], Árpád Farkas[b], Imre Balásházy[b], Piroska Szabó-Révész[a]

[a] Faculty of Pharmacy, Institute of Pharmaceutical Technology and Regulatory Affairs, University of Szeged, Szeged, Hungary
[b] Centre for Energy Research, Hungarian Academy of Sciences, Budapest, Hungary

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ABSTRACT

Dry Powder Inhaler (DPI) could offer a propellant-free, easy-to-use powder form ensuring better stability than liquid dosage forms. Therefore the development of traditional carrier-based and carrier-free new generation systems is a determinative factor in the field of DPI formulation. The purpose of our research work was to combine these two systems, utilizing their beneficial properties to produce a novel pulmonary drug delivery system containing ciprofloxacin hydrochloride (CIP). Co-spray drying, surface smoothing and the preparation of an interactive physical mixture were applied as the technological procedures of sample preparation. The carrier-based and carrier-free formulations, as well as the developed novel product were compared to each other. Structural investigations were made by X-ray powder diffraction and micrometric properties (habit, bulk density) were determined. Particle interactions were also evaluated to investigate surface free energy, cohesive-adhesive forces, and spreading coefficient. *In vitro* aerodynamic properties (mass median aerodynamic diameter), fine particle fraction (FPF) and emitted dose of DPIs were measured using Andersen Cascade Impactor. A novel *in silico* Stochastic Lung Model was also used to quantify the amount of particles deposited at the target area. The novel-formulated composition presented amorphous spherical particles with an average size of about 2 µm. The *in vitro* aerodynamic investigations showed a variance in FPF as a function of formulation method (carrier-based: 24%, carrier-free: 54% and applying the novel combination method: 63%). The *in silico* deposition results were in line with the *in vitro* measurements and yielded increased lung doses for the sample prepared by the combined technology. This novel DPI formulation provides an opportunity for a more effective therapy with deeper deposition of CIP.

1. Introduction

Pulmonary drug administration enables to target drugs directly to the lung for local or systemic therapy. DPI compositions can be divided into two main categories, conventional carrier-based and carrier-free (new generation) systems (Benke et al., 2017). The marketed products belong to the traditional carrier-based formulations, applying a large carrier (*e.g.* lactose) and a micronized active pharmaceutical ingredient (Lee et al., 2018; Peng et al., 2016). Using a carrier is advantageous for active compounds with strong cohesive properties that have a positive effect on the flow properties of the product, the dosage of a small amount of drug can be refined or the taste of the carrier in the oral cavity during inhalation confirms the successful use of the product in the patient. However, most of these marketed products still have low pulmonary deposition values (~20–30% FPF, fine particle fraction value), hence only a small percentage of the active ingredient can reach the proper lung segments because a large mass will be deposited in the upper respiratory tract. Only the modification of interparticle interaction (Tüske, 2005) (decrease of cohesive-adhesive forces by technological methods) could result in higher lung deposition. The role of the carrier and special additives applied in the designing phase is to prepare particles easy to handle during manufacturing and to provide an enhanced aerosolization property for inhalation (Velaga et al., 2018; Della Bella et al., 2017). Inhalac® series (different-sized lactose monohydrate, MEGGLE Group, Wasserburg, Germany) offer high quality drug transport to the lung (Pilcer et al., 2012). Lactose particles entering the lungs are rapidly absorbed, then metabolized and finally excreted in the urine. The processing of DPI formulation with a minimum concentration of magnesium stearate (MgSt) is an effective means of improving the de-agglomeration and aerosolization of cohesive powders (Coccini et al., 2012). Making a thin film with this excipient could produce better aerosolization properties. It could be applied in a wide range

* Corresponding author.
E-mail address: arita@pharm.u-szeged.hu (R. Ambrus).

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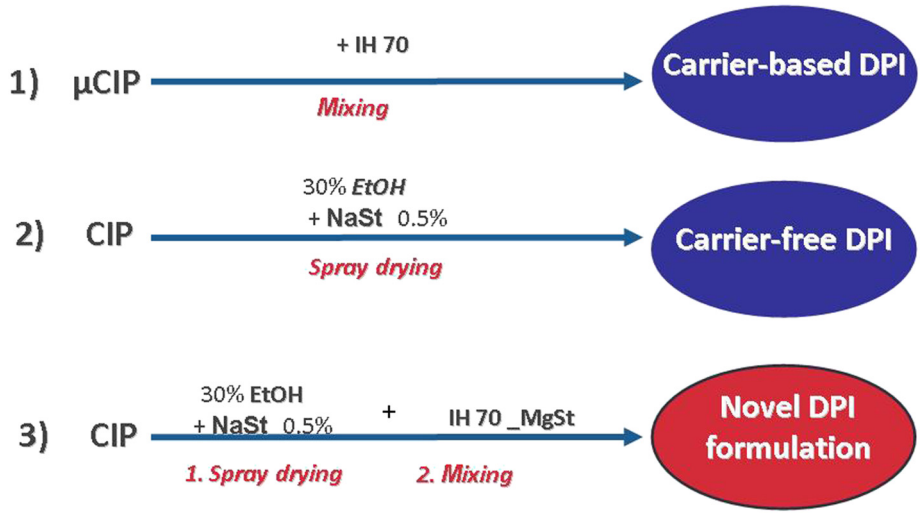

Fig. 1. Preparation protocol for different types of DPI formulations.

between 0.001 and 10.0 w/w%. In the lower segments of the lung, only an insignificant amount of MgSt is released, which does not have negative effects and therefore many marketed products have a MgSt content (Palistra, 2008; Hazare and Menon, 2009; Keller and Müller-Walz, 2003).

In the case of carrier-free DPI systems, the application of large carriers can be avoided with the use of special excipients and technologies (*e.g.* co-spray drying) (Chvatal et al., 2017; Nandiyanto and Okuyama, 2011; Yang et al., 2015). These systems yield around 50–60% FPF results due to the apparent high cohesive properties between the active ingredient's particles (Kadota et al., 2015). These formulations involve the usage of different amino acids (*e.g.* L-leucine) and polymers (*e.g.* polyvinyl alcohol or polyvinylpyrrolidone) (Pilcer and Amighi, 2010). The most important advantages of these novel formulations are their low density, improved aerodynamic properties and higher lung deposition (Healy et al., 2014). However, the main problem with the microparticles is that they stick to each other because of their high surface free energy. Overcoming this cohesive nature included the incorporation of large amounts of lipophilic adjuncts (such as the mixture of cholesterol and phospholipids *e.g.* sodium stearate) (Buttini et al., 2012). The preliminary analysis of the toxicity effect of sodium stearate on A549 lines showed that the adjunct, in the concentration (maximum 3 w/w%) used, had no effect on cell viability over a 24 h period compared to particles of pure tobramycin.

The use of antibiotics in the treatment of pulmonary fibrosis has long been known since Abbot Laboratories developed the inhaler (Aerohalor) containing penicillin powder in 1948. The most common treatment for bacterial respiratory infections is currently the oral administration of high doses of single or combined antibiotics, which may have serious side effects. With the development of antibiotic-containing DPI systems, the local treatment of these diseases is possible. Thus, high levels of the active substance can be achieved in the lung tissue, smaller doses are sufficient for oral therapy, leading to reduced systemic antibiotic exposure and lower toxicity. Ciprofloxacin hydrochloride (CIP) belongs to fluoroquinolones, it has a 6-fluoro-7-piperazinyl group, which is responsible for its antibacterial effectiveness (Gram− and Gram+ microorganisms) (Karimi et al., 2016). CIP is a major advance in the treatment of bronchopulmonary infection in patients with cystic fibrosis and chronic obstructive lung disease. At present, tobramycin and aztreonam are the only inhaled antibiotics on the market. CIP is also a potential pharmacon for DPI formulation (it is in Phase III as a PulmoSphere® system) (Stass et al., 2008). Therefore it is important to study its newer DPI formulations.

The aim of our work is to develop a novel DPI system using combined technology to formulate CIP containing DPI samples. It was important that all of the formulated DPI samples (carrier-based, carrier-free and novel combined method) will be fulfilling the requirements of effective pulmonary drug delivery (micronized particles with low density for deep lung deposition). Our goal is to exceed the FPF values of the carrier-based and carrier-free DPIs and to find correlations between the interparticle interactions and the lung deposition results and to suggest a novel DPI formulation for pulmonary application of CIP.

2. Materials and methods

2.1. Materials

Micronized ciprofloxacin hydrochloride (µCIP), a fluoroquinolone-type antibiotic, (D50: 5.09 µm) was kindly supplied by Teva Pharmaceutical Works Ltd. (Debrecen, Hungary). Lactose monohydrate, Inhalac® 70 (IH 70) (D50: 215.00 µm) (MEGGLE Group, Wasserburg, Germany) was used as a carrier base. Magnesium stearate (MgSt) was applied as a surface modifier (Sigma-Aldrich, Budapest, Hungary) (D50: 6.92 µm). Sodium stearate (NaSt) (Alfa Aesar, Heysham, United Kingdom) was used for habit modification.

2.2. Methods

2.2.1. Preparation of dry powder formulation

Fig. 1 presents the procedures which were used for carrier-based, carrier-free and their combined method for DPI preparation.

First, we applied a well-known formulation method. According to the preliminary experiments, a large size IH 70 was chosen for the **carrier-based** formulation. These samples were prepared by mixing (Turbula System Schatz; Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland) using 1:10 drug: IH70 ratio at 60 rpm for 30 min (Benke et al., 2017).

The **carrier-free** formulation applied a co-spray-drying method with NaSt and the use of 30% of EtOH as the solvent phase to modify the habit of CIP. CIP solution to be spray-dried was prepared by mixing a 70 g of CIP containing aqueous solution (1.5 w/v%) with a 30 g of NaSt (0.0175% w/v) containing alcoholic solution applying 30 °C. Finally, the prepared solid samples had 99.5% of CIP and 0.5% of NaSt content. The spray drying procedure was carried out using a Büchi B-191 apparatus (Mini Spray Dryer, Büchi, Switzerland). The drying parameters were adjusted as follows, based on our previous experiments, see Table 1 (Pomázi et al., 2014).

A combination of these two methods completed with surface