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Lactose Engineering for Better Performance in Dry Powder Inhalers

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ABSTRACT

Dry powder *inhaler* (DPI) is generally formulated as a powder mixture of coarse carrier particles and micronized drug with aerodynamic diameters of 1-5 μm. Carrier particles are used to improve drug particle flowability, thus improving dosing accuracy, minimizing the dose variability compared with drug alone and making them easier to handle during manufacturing operations. Lactose is the most common and frequently used carrier in DPIs formulations and nowadays various inhalation grades of lactose with different physico-chemical properties are available on the market. Therefore, the purpose of this manuscript is to review evolution of lactose as a carrier in inhalable formulations, their production and the impact of its physico-chemical properties on drug dispersion. This review offers a perspective on the current reported studies to modify lactose for better performance in DPIs.

Introduction

Pressurized metered-dose inhaler (MDI), nebulizer and dry powder inhaler (DPI) are main delivery systems in pulmonary delivery.[1] Among these, DPI appears to be the most promising for future use.[2] They are propellant-free, portable, easy to operate and low-cost devices with improved stability of the formulation as a result of the dry state.[3-5] Spinhaler®, the first dry powder inhaler, came into the market in 1970 and since then a new are started in the subject of pulmonary drug delivery. DPIs and dry powder inhalation technology became the second most frequently used inhalation devices for pulmonary drug administration after Montreal Protocol in 1987 in limitation of using CFC in products. DPIs have even become the first choice of inhalation devices in European countries.[6] They are a widely accepted inhaled delivery dosage form where they are currently used by an estimated 40% of patients to treat asthma and chronic obstructive pulmonary disease.[7] Using the DPI system, respiratory delivery of potent drugs such as insulin,[8] antibiotics,[9,10] drugs for neurological disorders like Parkinson's disease,[11] antihypertensive nifedipine,[12] anticoagulant heparin,[13] opioids and fentanyl for cancer pain[14-16] and delivery of atropine sulphate nanoparticle as an antidote for organophosphorus poisoning with better bioavailability[17] have been studied. DPIs have to overcome various physical difficulties for effective drug delivery either local or systemic purposes.[4] First, small size of inhalable particles subjected them to forces of agglomeration and cohesion, resulting in poor flow and non-uniform dispersion.[18] Drug deposition in the lung is mainly controlled by its aerodynamic diameter.[19] Particles larger than 5 μm are mostly trapped by oropharyngeal deposition and incapable of reaching the lungs while smaller than 1 μm are mostly exhaled without deposition.[20,21] Particles with aerodynamic diameters between 1 and 5 μm are expected to efficiently deposit in the lung periphery.[22] The effective inhalation performance of dry-powder products is dependent on the drug formulation and the inhaler device. Dry powder formulations are usually prepared by mixing the micronized drug particles with larger carrier particles. The aerosolization efficiency of a powder is highly dependent on the carrier characteristics, such as particle size distribution, shape and surface properties. The main objective in the inhalation field is to achieve reproducible, high pulmonary deposition. This could be achieved by successful carrier selection and careful process optimization.[23]

The role of carrier on DPI performance

DPI is generally formulated as a powder mixture of coarse carrier particles and micronized drug particles with aerodynamic particle diameters of 1–5 μm.[24] Carrier particles are used to improve drug particle flowability, thus improving dosing accuracy and minimizing the dose variability observed with drug formulations alone while making them easier to handle during manufacturing operations.[1,25] With the use of carrier particles, drug particles are emitted from capsules and devices more readily, hence, the inhalation efficiency increases.[26] Moreover, usually no more than a few milligrammes of a drug needs to be

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delivered (e.g., between 20 μg and 500 μg of corticosteroids for asthma therapy), and thus carrier provides bulk, which improves the handling, dispensing, and metering of the drug.[23] The presence of the carrier material is the taste/sensation on inhaling, which can assure the patient that a dose has been taken.[4] Consequently, the carrier forms an important component of the formulation and any change in the physico-chemical properties of the carrier particles has the potential to alter the drug deposition profile.[27] Therefore, the design of the carrier particle is important for the development of DPIs.[28] Carrier particles should have several characteristics such as physico-chemical stability, biocompatibility and biodegradability, compatible with the drug substance and must be inert, available and economical. During insufflation, the drug particles are detached from the surface of the carrier particles by the energy of the inspired air flow that overcomes the adhesion forces between drug and carrier. The larger carrier particles impact in the upper airways, while the small drug particles go through the lower parts of lungs.[23] Unsatisfactory detachment of drug from the carrier due to strong inter-particulate forces may be one of the main reasons of inefficient drug delivery encountered with most DPIs.[29,30] Therefore, in the best case, the adjusted balance between adhesive and cohesive forces provides enough adhesion between drug and carrier to produce a stable formulation (homogeneous mixture with no powder segregation and proper content uniformity) yet allows for easy separation during inhalation. Consequently, it has been stated that the efficiency of a DPI formulation is extremely dependent on the carrier characteristics and the selection of carrier is a crucial determinant of the overall DPI performance.[23] Obviously, the effect of the carrier material on DPI formulation should be carefully evaluated. The range of materials which can be proposed to be as carriers in inhaled products are restricted for toxicological reasons. Lactose and other sugars have been studied and used, therefore modifications to these materials may allow further formulation optimization.[4]

Lactose as the most frequently used carrier in DPIs

Lactose, 4-(b-D-galactosido-)-D-glucose, can be obtained in either two basic isomeric forms, α and β-lactose, or as an amorphous form.[31] Historically, lactose monohydrate was an obvious choice for use as a carrier excipient. Lactose accompanying with glucose and mannitol is allowed as carriers in DPIs by the US Food and Drug Administration department.[32] Lactose is the most common and frequently used carrier in DPI formulations accordingly nowadays various inhalation grades of lactose with different physico-chemical properties are available on the market. The advantages of lactose are its well-investigated toxicity profile, physical and chemical stability, compatibility with the drug substance, its broad availability and relatively low price.[33,34] α-lactose monohydrate is the most common lactose grade used in the inhalation field. Almost all DPI formulations on the market are based on α-lactose monohydrate as a carrier. Therefore, wealth of literatures refers to the optimization of lactose carrier particles for better inhalation performance. More than 250 articles have been published in the past 40 years regarding the role of lactose in adhesive mixtures used in DPIs. However, in spite of these extensive investigations, the relationship between physico-chemical properties of the lactose in adhesive mixtures and the performance of the DPIs remains largely indistinct.[6]

Lactose engineering for application in DPIs

Surface modification

Iida et al. prepared lactose carrier particles for dry powder inhalations by its surface modification with aqueous ethanol solution and evaluated the inhalation efficiency of salbutamol sulfate from its mixture with modified lactose. The degree of adhesion between drug particles and carrier particles and the separation characteristics of drug particles from carrier particles in air flow were assessed by the ultracentrifuge separation and the air jet sieve methods, respectively. It was shown that the average adhesion force between the surface-treated lactose carrier and drug particles was considerably lower than that of powder mixed with the un-treated lactose carrier, indicating better drug separation from carrier and consequently an improvement of in vitro inhalation properties. The authors claimed that surface-smoothing of lactose by aqueous ethanol solution resulted a well balanced drug-carrier adhesion force so that the drug particles could be emitted together with the carrier particles and efficiently separated in airflow after emission.[35] Fine lactose particles were immobilized on the lactose surface by spray coating with liquid suspensions consisting of micronized lactose dispersed in isopropyl alcohol and/or water mixtures to modify surface of lactose. The produced lactose was used as a carrier in the formulation of inhalable salbutamol sulfate powder. It was found that the roughness of the lactose surface established by immobilization of fine lactose increased the FPF and dispersibility of the drug. The authors claimed that unlike crevices and valleys, these microscopic undulations did not accommodate the drug particles and instead enhanced the detachment of drug from the lactose surface and improved the drug inhalation efficiency.[36] Spray dried amorphous, spray dried crystallized and fluidized bed granulated lactose were prepared and used as carrier for inhalation of pranlukast hydrate. Fluidized bed granulated lactose emitted drug particles effectively from the inhalation device, whereas most part of drug captured in the upper stage of twin impinger, resulting in lower inhalation efficiency, due to strong adhesion of drug to the carrier lactose. The spray dried amorphous lactose, smoothed sphere particle, did not so improve the inhalation efficiency as expected, because of fairly strong

adhesion between drug and lactose particles. But the spray dried crystallized lactose having lots of microscopical projection on its surface increased the respirable particle percent of the emitted particles. The conclusion was that the surface roughness should be optimized to gain improved inhalation efficiency of particles.[37] In the other study, a Wurster fluidized bed was used for surface-coating of lactose particles with lactose aqueous solution containing hydroxypropyl methyl cellulose. The authors could be able to increase the inhalation performance of salbutamol sulfate 2.5 times more than commercial lactose (Pharmatose®200M) and reported that surface coating of carrier particles may be an effective technique for improving the inhalation performance of DPI.[38] Lactose carrier particles were layered with vegetable magnesium stearate by physical mixing and their effect of on the dry powder inhalation properties of salbutamol sulfate was investigated. The in vitro inhalation performance of drug was enhanced compared with the powder mixed with unlayered lactose carrier. It was stated that using this surface layering system would thus be valuable for increasing the inhalation properties of dry powder inhalation.[39] For example, increasing the surface smoothness of lactose carrier particles was shown to improve the potentially respirable fraction of albuterol sulfate from the Rotahaler®.[40]

Shape modification

Lactose crystallization from Carbopol gel in different conditions (named Carbo lactose) produced a more regular shape lactose with smoother surface as compared with the control lactose. The Carbo lactose caused a higher and reproducible salbutamol sulphate emission and fine particle fraction after aerosolisation via a Rotahaler® tested in multi-stage impinge. It was concluded that engineered crystal growth under controlled conditions can enhance the potential inhalable fraction of drug from dry powder inhalers.[41] More recently, the use of more elongated crystals of lactose was also found to produce a higher inhalation efficiency of albuterol sulfate.[29] However, the improvement in drug dispersion that can be achieved by increasing the elongation ratio of the carrier particles is limited.[42]

Composite lactose

Lactose carrier particles were prepared by fusing sub units of lactose (either 2, 6 or 10 μm prepared by spray drying) in saturated lactose slurry, sieve fractioned to obtain a 63–90 μm carriers and used for inhalation of salbutamol sulfate. The surface morphology and physico-chemical properties of the composite carriers were considerably different from regular α-lactose monohydrate. In all cases, the composite carriers resulted in improved drug aerosol performance. It was suggested that composite based carriers are a potential route to control drug-carrier adhesion forces and variability thus allowing more precise control of formulation performance.[43]

Engineered lactose-mannitol mixture

Mannitol and lactose were co-crystallised to prepare crystals with more desirable characteristics than either lactose or mannitol alone appropriate for application as carriers in the formulations of salbutamol sulfate DPIs. In vitro deposition evaluation showed that crystallized carriers resulted more efficient delivery of salbutamol sulphate compared to formulations containing commercial grade carriers. It was concluded that simultaneous crystallization of lactose-mannitol can be a new approach to enhance inhalation performance of DPI formulations.[44]

Expert Opinion and Final Remarks

Interest in DPIs has increased in the last decade due to its numerous advantages over other pulmonary drug delivery dosage forms. Currently, the inhalation performance of DPIs are being improved by changing formulation strategy, drug and carrier particle engineering. Regarding formulation development, micronized drug particles are cohesive with poor flow properties. Addition of large carrier particles, mostly lactose, into powders to enhance their flow characteristics has been an appropriate approach. The main goal in the inhalation field is to obtain reproducible, high pulmonary deposition which can be highly effected by physico-chemical characteristics of lactose. Technologies for engineering lactose particle shape, density, and size will continue to develop to enhance the effectiveness of pulmonary drug formulations. This approach may enable more drugs to be delivered through this route for local treatment of lung diseases or systemic therapy.

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