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Comparative study of erythritol and lactose monohydrate as carriers for inhalation: Atomic force microscopy and in vitro correlation

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ABSTRACT

The adhesion of micronised salbutamol sulphate to two carrier excipients, lactose monohydrate and erythritol, was investigated using the atomic force microscope (AFM) colloid probe technique and correlated with their respective physico-mechanical properties and aerosolisation performance. The particle size, morphology and moisture sorption properties of the carriers were similar thereby allowing direct comparison of functionality. AFM force measurements ($n = 1024$ force curves) were obtained between salbutamol sulphate drug probes ($n = 4$) and the excipients, as 63–90 μm sieve fractions and atomically smooth crystals. In general, significant differences in drug adhesion to lactose monohydrate and erythritol were observed (ANOVA, $p < 0.05$), with erythritol exhibiting relatively greater adhesiveness. A linear relationship between drug probe adhesion to lactose monohydrate and drug probe adhesion to erythritol was established with salbutamol sulphate–lactose monohydrate adhesion being 60–70% of that of the erythritol system. In vitro analysis suggested good correlation with the adhesion measurements. The aerosolisation of salbutamol sulphate from erythritol carrier particles was significantly less (ANOVA, $p < 0.05$) than from lactose monohydrate, with a fine particle dose (<6.4 μm) of 41.9 ± 7.4 μg and 24.9 ± 3.1 μg for the lactose monohydrate and erythritol carriers, respectively ($n = 3$).

1. Introduction

The successful delivery of medicaments to the respiratory tract can be achieved through the engineering and processing of drug particles. In general, milled or micronised drug particles of a suitably respirable size range (<5 μm) are required (Pritchard, 2001; Ganderton and Kassem, 1992). However, the use of such powders is fraught with technological difficulties since they are inherently cohesive and exhibit poor flow properties which invariably prevents their use in dry powder inhaler (DPI) devices. To overcome such constraints, the micronised drug is often blended with a larger inert carrier, lactose monohydrate, to improve processing, flowability, content uniformity, stability and metering.

Historically, lactose monohydrate was an obvious choice for use as a carrier excipient. A natural product, recovered from whey during the cheese making process, lactose can be mass produced, has low toxicity, is water soluble and is available from many suppliers in a variety of particle size ranges. However, even though lactose is a relatively simple disaccharide which has been used in many DPI products, efforts are continuing to design improved lactose and alternate DPI car-

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rier materials. In terms of developing improved lactose carriers, an option would be to modify the particle shape and lactose form. However, for lactose monohydrate, the tomohawk crystal shape cannot be easily modified since it is a consequence of the inhibition of the fast growth face due to the mutarotation of the α to β form in aqueous solution (Raghavan et al., 2001). Lactose, like many organic compounds can exist in several forms, the stable ones being alpha monohydrate, stable alpha anhydrous, beta anhydrous and mixed crystal. Additionally, amorphous lactose and an unstable alpha anhydrous exist (Bolhuis and Chowhan, 1996). The possible existence of multiple lactose forms in lactose products raises obvious questions about purity, especially since DPI lactose monohydrate can be considered as an active pharmaceutical ingredient (API). For example, commercially available anhydrous lactose contains approximately 80% anhydrous β-lactose, the remainder being anhydrous α-lactose (Bolhuis and Chowhan, 1996). This may be particularly important for low dose DPI formulations where any variations in the surface structure of the carrier may have a profound effect on the formulation performance. Furthermore, lactose may interact with drug/protein functional groups due to its reducing sugar function (Patton and Platz, 1992). In addition, a significant proportion of people have a degree of lactose intolerance (Solomons, 1996), therefore making the use of lactose carrier based devices an issue. More recently, there have been reports of milk protein being present in such devices, fuelled by the past BSE scare (Nowak-Wegrzyn et al., 2004).

In order to address such issues, researchers have investigated other materials, in particular sugar alcohols (polyols), as potential carrier alternatives (Tee et al., 2000; Steckel and Bolzen, 2004; Endo et al., 2005). For example, Tee et al. (2000) reported increased aerosolisation performance of salbutamol sulphate when using mannitol as an alternative carrier to lactose. Interestingly, in a parallel study, the group found the use of sorbitol (an isomer of mannitol) as a carrier resulted in little difference when compared to lactose (Tee et al., 2000). In a different study, Steckel and Bolzen (2004) reported that the use of different carrier excipients (mannitol, glucose, sorbitol, maltitol and xylitol) significantly influenced the aerosolisation efficiency of budesonide. It is interesting to note, however, that Steckel and Bolzen also reported variations between different grades of some of the excipients, attributing these to physical—mechanical properties of the carrier surfaces. Clearly, variation in particle size, morphology, chemical structure and roughness is of importance when comparing carrier-based systems (Kawashima et al., 1998; Zeng et al., 2001).

Any potential carrier for DPI applications should exhibit the following desirable characteristics: it should be non-toxic, crystalline, have no polymorphs or metastable structures, be stable during processing and available from more than one supplier. One such candidate is erythritol. This material satisfies many of the above desirable characteristics and is especially attractive in that it is a symmetrical molecule and therefore only exists as a *meso* form, reducing possible stereochemistry issues compared to, for example, mannitol and sorbitol which both have several polymorphic forms. Additionally, erythritol was recently entered in the European Pharmacopoiea. Here, the authors investigate the potential of erythritol as a carrier excipient. Erythritol is a non-calorific polyol, which has similar moisture sorption and physico-mechanical properties to lactose (Michaaud and Haest, 2003). Although, recently, Endo et al. (2005) have reported the use of erythritol to deliver glucagons to the respiratory tract, a specific study comparing the excipient with similar sized lactose carriers, in terms of physico-mechanical and aerosolisation properties, has yet to be reported.

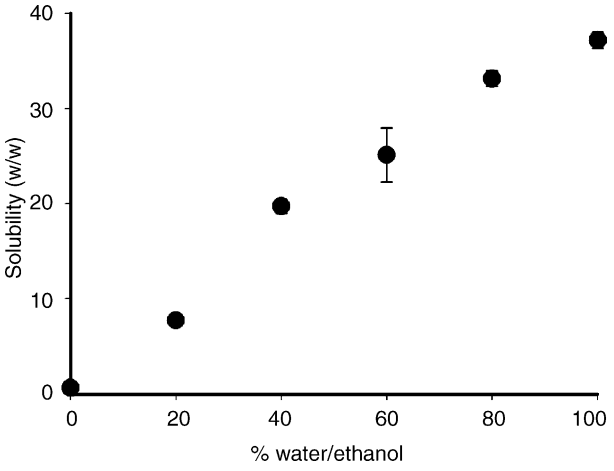

Fig. 1 – Solubility of erythritol in water/ethanol mixtures in a controlled water bath at 25 °C.

Since the respiratory deposition of drug from a carrier based system will be directly related to its efficiency at liberating drug particles from the carrier surface, particle adhesion measurements may be a useful way of predicting performance. In this study, the atomic force microscope (AFM) colloid probe technique was utilised to directly measure drug adhesion to erythritol and lactose monohydrate surfaces. These fundamental measurements were then correlated with in vitro deposition studies. Salbutamol sulphate was chosen as a model drug.

2. Materials and methods

2.1. *Materials*

Micronised salbutamol sulphate was used as supplied. Lactose monohydrate (Lactochem crystals, batch: BN 329009/S) was supplied by Boroculo Domo (Netherlands). Erythritol (Eridex 16592, batch GS3100) was supplied by Cerestar (Mechelen, Belgium). Water was purified by reverse osmosis (MilliQ, Millipore, France). All solvents were supplied by BDH (Dorset, UK) and were of at least analytical grade.

2.2. *Methods*

2.2.1. *Solubility of erythritol in water/ethanol solvent mixtures*

The solubility profile of erythritol in ethanol/water mixtures was determined gravimetrically (see Fig. 1). Saturated solutions were prepared in 0–100% (w/w) ethanol/water (20% increments) in triplicate. All samples were shaken in a controlled