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The tableting properties of melibiose monohydrate

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ABSTRACT

In this research, the tableting properties of α-melibiose monohydrate were studied. Melibiose is a disaccharide which bears structural resemblance to lactose, because they both consist of galactose and glucose monosaccharide subunits. Compactibility and deformation behavior of two melibiose batches from different suppliers were studied and compared with α-lactose monohydrate and some other typical tableting excipients. Differences in the deformation behavior were determined comparing the shape of the Heckel plots, the yield pressure values and the strain rate sensitivity (SRS) indexes. In addition, the effect of moisture on the tabletability was studied. According to the yield pressures and SRS indexes melibiose was concluded to be fragmenting, even at higher degree than lactose monohydrate. However, the overall deformation behavior of melibiose was found to be similar to that of lactose monohydrate. Increase in moisture content resulted in higher tensile strengths of tablets for both melibiose batches, but it seemed to have more effect on compactibility of the other batch. In conclusion, melibiose has potential to be used as an excipient in tablet formulations.

1. Introduction

Lactose is a disaccharide which is one of the most used excipient in the field of pharmacy. Lactose has many advantages in tablet formulations: it is inexpensive, has excellent solubility, low hygroscopicity, mild taste and good tableting properties (Bolhuis and Zuurman, 1995). Although lactose is thoroughly characterized and available in many different forms, there is a need to find a replacer for lactose as a filler/binder in tablet formulations, because it has some downsides. Prevalence of lactose intolerance is for example up to 23% in central Europe and even 100% in some Asian populations (Patel and Minocha, 2000). Further, lactose is incompatible with primary amines due to Maillard reaction (Wirth et al., 1998).

Melibiose is a disaccharide consisting of the same two monosaccharides as lactose, glucose and galactose, but unlike in lactose, the monosaccharide subunits are linked together by an alpha glycosidic bond (Fig. 1). Melibiose has two polymorphs, α- and β-melibiose, and is also stable in amorphous form (Fletcher and Diehl, 1952). Both crystalline forms of melibiose have excellent water solubility, 2500 g/l. During crystallization α-melibiose forms monohydrate and β-melibiose usually dihydrate form (Fletcher and Diehl, 1952). As free sugar, melibiose is a mixture of α-melibiose and β-melibiose (4:1 ratio, respectively).

Although there is no toxicological data available for melibiose, it is supposed to be safe for oral consumption, because it can be found in many foods. For example soybeans and honey contain small amounts of melibiose (Doner, 1977). Humans cannot digest melibiose due to absence of α-galactosidase (Ramalingam et al., 2010), but some bacteria in gut microbial flora can break down melibiose to galactose and glucose (Van Laere et al., 1999). Therefore, as all indigestible disaccharides, melibiose can cause flatulence and other GI symptoms (Ramalingam et al., 2010). Melibiose is also a reducing sugar and therefore can undergo Maillard reaction as well as lactose (Kato et al., 1989).

Examples for melibiose in a pharmaceutical use are quite limited. Melibiose has been used as an ingredient in topical cosmetic formulations as a hydrophilic skin permeation enhancing agent (Kung et al., 2002). There are patents that mention the use of melibiose in tablet formulations, but they do not give information about tableting properties (Daisy and Tourek, 1998; Zalit et al., 2007). In addition, there are no published research articles about compression properties and tabletability of melibiose to be found. However, the effect of humidity on the physical properties of melibiose monohydrate was studied quite recently (Heljo et al., 2013). It has been shown that dietary melibiose affects the T-helper cell responses to an ingested antigen with mice (Tomita et al., 2007).

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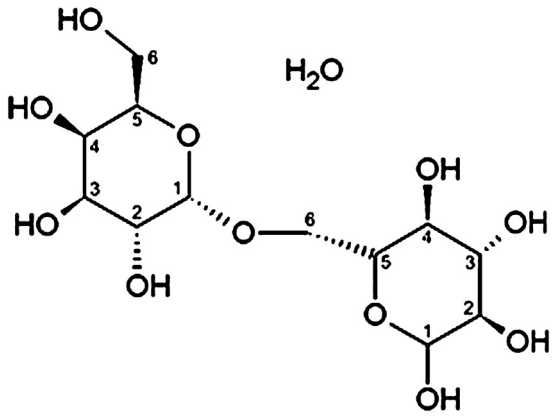

Fig. 1. The molecular structure of melibiose monohydrate, where the galactose and glucose subunits have been marked, along with the rank order of their carbon atoms (separately for both monosaccharide units).

Therefore, there is a possibility that melibiose could be useful for reducing the symptoms of allergic disease.

α-Lactose monohydrate (LMH) is known to be mainly fragmenting excipient. Also other disaccharides are known to be brittle, such as maltose (Picker, 2004) and sucrose (Roberts and Rowe, 1987; Eriksson and Alderborn, 1995; Nordström et al., 2009) depending on initial particle size (Kendall, 1978; Roberts and Rowe, 2000) and moisture content (Armstrong et al., 1986; Shukla and Price, 1991). When the moisture content increases these materials become more ductile as water acts as plasticizer (Armstrong et al., 1986; Shukla and Price, 1991; Garr and Rubinstein, 1992). Monosaccharide D-glucose, i.e. dextrose is known to be fragmenting and elastic (Armstrong et al., 1986). Since melibiose monohydrate consists of the same monosaccharides than LMH, the hypothesis is that its deformation mechanism would be similar to LMH.

Aim of this work was to study the tableting properties of α-melibiose monohydrate. The potential of melibiose as a pharmaceutical tablet excipient is evaluated. Compactibility and deformation behavior of melibiose is studied and compared with LMH and other typical tableting excipients. This is the first time when the tableting behavior of melibiose is studied.

2. Materials and methods

2.1. Materials

Melibiose was purchased from two different suppliers. α-Melibiose monohydrate (purity>98% HPLC) was obtained from Sigma–Aldrich (St Louis, MO) and Senn Chemicals (Dielsdorf, Switzerland). These different batches of melibiose are referred in this study as Sigma and Senn, respectively. Both suppliers claimed their product to contain only α-melibiose monohydrate. α-Lactose monohydrate (LMH, Pharmatose 80M; DMV-Fonterra Excipients, Veghel, Netherlands) was used as reference excipient in this study. Microcrystalline cellulose (MCC, Avicel PH-200; FMC Biopolymers, Cork, Ireland) was used as a plastically deforming reference and calcium dihydrogen phosphate (DCP, Emcompress; Edward Mendell CO Inc., New York, NY), as a fragmenting reference material. In addition, magnesium stearate (Ph. Eur.) and acetone (Ph. Eur.) were used to lubricate the tableting die.

2.2. Scanning electron microscopy

Scanning electron microscopy (SEM) was used to investigate the particle size, shape and morphology of the melibiose batches. Rough estimates of a median particle size and particle size range were also made according to SEM images. The powder was sprinkled on top of carbon tape and loose particles were removed with pressurized air. Samples were then coated with platinum in vacuum evaporation coater. The images were acquired using an acceleration voltage of 10 kV and magnification of 100× and 200× with FEI Quanta 250 FEG (FEI Inc., Hillsboro, OR).

2.3. Density measurements

Bulk density of powders was measured by filling a 250 ml cylinder with a 50 g in the case of both melibiose batches and 100 g in the case of the LMH batch and measuring the volume of the powder. Tapped density was then measured for the samples according to European Pharmacopeia with a standard apparatus (Erweka SVM 1UZ, Erweka Apparatebau GmbH, Heusenstamm, Germany). The measurements were done in triplicate. Samples were stored in room humidity (RH 35 ± 5%) and temperature (23 ± 2 °C) prior to density measurements.

True density of melibioses and LMH was measured with a helium pycnometry (Multivolume pycnometer 1305, Micromeritics Inst. Corp., Norcross, GA). Three samples of each material were measured in triplicate. Sample cup was filled with 2/3 of material and sample was weighed. Helium flow through every fresh sample was used to remove moisture from samples. The flow pressure of helium was 5 Pa and it was sustained for 5 min. Pressure in the system was allowed to stabilize for 30 s and the pressure values were used to calculate the true volume of the sample. Average values of the true density was calculated from mass of the sample and from the true volume, and used for this study.

2.4. Flowability of materials, Hausner ratio and Carr index

Flow properties of melibioses and LMH were studied using FlowPro instrument (SAY Group, Helsinki, Finland). The operational principle of the apparatus has been described previously by Soppela et al. (2010). All materials were stored and the testing was performed under controlled temperature and humidity conditions (RH 40–45%, 25 °C). Metallic cylinder with a volume of 5 ml was filled with powder and placed in the apparatus. 5 measurements for each of the materials were performed. The Hausner ratio and the Carr index values calculated from the bulk and tapped densities of the materials were also used to estimate the flow properties of the powders.

2.5. Compression studies

Differences in the densification behavior were determined comparing the shape of the Heckel plots, the yield pressure values (P_y) and the strain rate sensitivity (SRS) indexes. In addition, energy utilization in compaction and elastic recovery (ER) of tablets was determined.

Before tableting the powders were sieved to obtain particle size fraction between 125 and 355 μm. An automatic sieve shaker (Fritsch Analysette, Idar-Oberstein, Germany) was used to sieve each power sample for 5 min using an amplitude setting of 6. The same sieve fraction of each material was used in the compression experiments, so that initial differences in particle size distributions would not affect the tableting properties of the samples.

Comparing the compression force and the mechanical strength of the resulting tablet is a simple one point estimate for compactibility (Fell and Newton, 1970; Sonnergaard, 2006). The slope of the compression force versus tensile strength profile is individual for each material. The compactibility of the two batches of melibiose, DCP, LMH and MCC was studied with instrumented eccentric tableting machine (Korsch EK0, Erweka Apparatebau, Heusenstamm, Germany). Flat-faced punches with diameter of