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Supramolecular elucidation of the quality attributes of microcrystalline cellulose and isomalt composite pellet cores

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ABSTRACT

The major objective of this study was to disclose the relationships between the physical quality attributes and supramolecular structure of novel composite pellet cores containing microcrystalline cellulose (MCC) and isomalt in different ratios.

The novel composite pellet cores were manufactured by an extrusion/spheronisation process. The micro or supramolecular structure of pellets was tracked by positron annihilation lifetime spectroscopy (PALS) based on the o-Ps lifetime values. The results indicate a correlation between the examined macro and microstructural properties of the inert cores. The higher free volume holes indicated by the higher o-Ps lifetime values resulted in a more mobile micro- and supramolecular structure of MCC cores thus increasing the plastic deformation and the tensile strength of the cores. A physical interaction was found between the microcrystalline cellulose and isomalt which supports the osmotic effect of the water soluble sugar alcohol in the composite pellet cores regarding drug release.

1. Introduction

The layering technique usually starts with inert spherical cores (starters, beads, seeds, spheres, nonpareils). Nowadays, basically pure types of inert cores have been commercially available for the layering process. Beads are traditionally formed from pharmaceutically acceptable materials such as water-insoluble MCC or water-soluble carbohydrates (e.g., sugar, isomalt), which present different characteristics and processability [1,2]. Inert cores produced from MCC possess a number of advantages when used as excipient for pelletization. This includes good sphericity, low friability, high density, smooth surface properties and relatively easy manufacture with excellent yield [3]. On the other hand disadvantages of MCC based matrix pellets include drug adsorption to the surface of MCC fibres [4,5] chemical incompatibility with a number of drugs [6,7] and lack of disintegration and osmotic activity. The latter may result in less bioavailable when formulated with some poorly water soluble drugs [8].

Isomalt is a water soluble polyol produced from sucrose [9,10]. Although up to the present it has not been widely used in pelletization, this sugar alcohol is promising for pharmaceutical purposes because of its multiple potential health benefits [11,12].

In our previous study we demonstrated that the dissolution kinetics of sodium diclofenac from coated pellets applying composite MCC/isomalt inert cores was significantly different compared to pure MCC or isomalt cores [13]. It was concluded that the increase in osmotic activity within the MCC/isomalt pellet was induced by an increase of isomalt concentration which decreased the vulnerability of the dissolution profile to the changes in the osmotic environment.

The aim of this study was to manufacture spherical shape inert composite cores comprising different ratios of MCC/isomalt in lab scale which exhibit acceptable size, size distribution and good mechanical strength, and to compare the most important characteristics of these cores to the pure isomalt and pure MCC based spheres. Moreover, our purpose was to elucidate the quality attributes of the pellet cores comparing the most important macrostructural characteristics with the supramolecular structure of the cores. The supramolecular structure of cores was tracked by PALS which is a unique method since it is exceptionally sensitive

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to the free volume of polymers incorporated as excipients into the dosage forms [14,15]. In polymeric systems and in semisolid/solid dosage forms the changes of these free volumes can indicate the changes of the supramolecular structure during storage conditions, heating, wetting or other circumstances [16,17].

2. Materials and methods

2.1. Materials

Marketed cores were isomalt pellets (galenIQ™ 980, 700–1000 μm; Beneo-Palatinit GmbH, Mannheim, Germany) and MCC spheres (Ethispheres® 850, 710–1000 μm; NP-Pharm Ltd., Bazainville, France). Milled isomalt (galenIQ™ 800, d_{90}:41 μm; Beneo-Palatinit GmbH) and powder grade MCC (Vivapur® 101, average size: 65 μm; JRS Pharma GmbH & Co., Rosenberg, Germany) were used for the preparation of MCC/isomalt cores.

2.2. Preparation of MCC/isomalt cores

MCC/isomalt cores were produced by an extrusion/spheronisation process. Different ratios of galenIQ™ 800 and Vivapur® 101 were blended (batch size: 5 kg) at 105 rpm for 3 min in a Lödige mixer (M20, Gebrüder Lödige Maschinenbau GmbH, Paderborn, Germany). This blend was wetted with an appropriate amount of purified water (Table 1) at 105 rpm using the equipment described above. The wet mass was extruded through a die (d = 1 mm) utilizing a twin-screw co-rotating extruder (DE-40-T-10D, Gabler GmbH & Co. KG, Ettlingen, Germany) at a feeding speed of 60 rpm. The extrudates were subsequently rounded in a spheroniser (R-600, Gabler GmbH & Co. KG) fitted with a cross hatched friction plate rotating for 6 min at 550 rpm. The wet pellets were dried in a fluid-bed dryer (Aeromatic Strea 7; Aeromatic-Fielder AG, Bubendorf, Switzerland) at 50 °C for 2.5 h and sieved through 1000 μm and 700 μm mesh.

2.3. Macrostructural physical characterization

2.3.1. Image analysis

Photomicrographs of pellets were taken with a digital camera (Coolpix 4500, Nikon, Tokyo, Japan) linked to a stereomicroscope (SMZ 1000, Nikon). The images were analyzed using Image Pro Plus 4.5 (Media Cynerbetics, Bethesda, U.S.). A standard micrometre scale was used for the calibration (3.05 μm/pixel). 200 individual pellets were analyzed from every batch. The pellet size and shape were characterized as aspect ratio (AR) and Feret diameter.

2.3.2. Scanning electron microscopy (SEM)

The pellets were coated with gold for 60 s under argon atmosphere in a Jeol JFC-1200 Fine Coater (Jeol Ltd., Tokyo, Japan) and then analyzed using a scanning electron microscope (JEOL JSM-6380 LA type, Jeol Ltd.) at 15 kV.

2.3.3. Residual water content

The water content of the dried cores was determined using a Karl Fischer titrator (787KF Titrino, MetrohmAG, Herisau, Switzerland). Prior to the titration of the sample the water equivalency factor of Hydranal was determined using sodium tartarate (Hydranal-water standard, Sigma–Aldrich Chemie GmbH, Taufkirchen, Germany). The solvent was extra dry methanol, which was titrated with Karl Fischer reagent (Hydranal-composite-5) before the measurement. 100 mg pellets were accurately weighed, dispersed (1 min at 15,000 rpm) and titrated with the reagent.

2.3.4. True density

The true density of the inert cores was determined using a helium pycnometer (Ultrapycnometer 1000, Quantachrome, Germany). Sample preparation consisted of storing the beads at 60 °C for 20 h. The pycnometer tested each pellet 15 times and the results were presented as the mean values of the measurements. The sample pellets were examined in triplicate.

2.3.5. Tensile strength

Twenty pellets were measured with a texture analyser (TA-HDi®plus Texture Analyser, Stable Micro System Ltd., UK) operating with a 5 kg load cell. A cylindric punch (diameter = 5 mm) was moved from the top with a speed of 0.1 mm/s towards the pellet. The fracture force (F) and the diameter (d) of each individual pellet were recorded during the test. The tensile strength (σ) was calculated from Eq. (1) [18]:

$$\sigma = \frac{1.6 \times F}{\pi \times d^2} \quad (1)$$

In case of deformation, the practice most widely used in the literature was chosen, namely the strength corresponding to the first maximal peak of the graph was given [19]. The average of 20 values was reported as the tensile strength for each batch.

2.4. Microstructural examination

2.4.1. Positron annihilation lifetime spectroscopy

For positron lifetime measurements a carrier-free ^{22}NaCl positron source was used. Its activity was around 10^5 Bq and the active material was sealed between two thin Ti-foils. Lifetime spectra were measured with a fast-fast coincidence system [20] based on BaF_2/XP2020Q detectors and Ortec electronics. Every spectrum was recorded in 4096 channels of an analyzer card and each contained 2×10^6 coincidence events. 3 spectra were measured at each concentration to increase reliability. All the lifetime spectra were evaluated individually by the RESOLUTION computer code [21]; the indicated errors are the standard deviations of the lifetime parameters obtained. Three lifetime components were found in the pellet cores.

2.4.2. ATR-FTIR and near infrared (NIR) spectroscopy

Fourier transform infrared spectra of inert cores were scanned over wavenumber range of 4000–300 cm^{-1} using Able Jasco FTIR 4200 type A spectrometer (Jasco Europe S.R.L., Cremella, Italy) with ATR Pro470H attenuated total reflection (ATR) single reflection accessory. 32 scans at a resolution of 4 cm^{-1} were co-added by the FTIR software (Spectra Manager-II, Jasco). The diffuse reflectance of cores was measured by a Hitachi U-3501 UV/VIS/NIR spectrophotometer (Hitachi Ltd., Tokyo, Japan) equipped with integrating sphere (d = 60 mm) and PbS detector. The reflectance (R%) was recorded in the range of 200–2500 nm wavelength using a 5 mm layered cell. Second derivative spectra were analyzed for multiple linear regression by Excel2007.

3. Results and discussion

Process parameters used during the manufacture of the cores greatly influenced yield and processability of the pellets. Therefore the main criteria for a successful manufacturing process were defined as >90% yield of spherical particles with an AR value <1.2 combined with acceptable mechanical strength. In order to achieve the latter, the determination of the optimum amount of water respectively extrusion liquid was elaborated first. The optimum water content for each composition is shown in Table 1. The amount of extrusion liquid required for producing pellets under the set