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Dextran and its potential use as tablet excipient

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ABSTRACT

Dextrans are a class of carbohydrate polymers extensively applied in pharmaceutical applications, particularly as drug conjugate macromolecular carriers or drug delivery systems. These polysaccharides improve the stability of the therapeutics enabling also the control of their release, via either the parenteral and or oral routes. In the latter case, due to their gel forming ability they may have potential as hydrophilic matrix tablets for sustained drug release.

In this paper, we investigated the behaviour of different molecular weight (1, 40, 500 and 2300 kDa) dextrans as tabletting excipients. Powder particle size and hygroscopic studies have been reported, together with tabletability, tablet stability and tablet swelling. Moreover we use tramadol as model compound to evaluate the ability of dextrans to control drug dissolution. The results suggest that dextrans with lower molecular weights may be a promising excipient to be used as filler for immediate release tablets, due to their good tabletability and fast dissolution rate, while dextrans with higher molecular weights could be an efficient disintegrant due to their swelling ability.

1. Introduction

Dextrans are a family of high-molecular-weight polymers composed of D-glucose units inter-connected with α-1,6 linkages, with a variable degree of side branches via α-1,2, α-1,3, or α-1,4 linkages. In most cases the length of the side chains is short, and branched residues vary between 5 and 33%. Commercial dextrans are about 95% α-1,6 linked and 5% α-1,3 linked [1].

Dextrans are biosynthesised from sucrose by several species of bacteria (e.g. *Leuconostoc* and *Streptococcus*), through the use of specific enzymes like *glucansucrases* [2]. Their physicochemical properties are mainly related to molecular weight (M_w) and degree of branching, which in turn depend on the source of production [3].

In the last few decades dextrans have been mainly used as plasma volume expanders [2,3]. However recently, dextrans have shown the potential to be used in several drug and gene delivery systems [4–6]. Therapeutics have been formulated as polymer-drug conjugates or in the form of hydrogels or particulate drug delivery systems [3,6–10]. Fülöp et al. [11] described the use of cyclodextrin (β type) grafted dextrans to solubilize hydrocortisone. Dextrans have been also evaluated for the preparation of targeting carrier systems particularly to deliver the drug into the colon [12–15]. A further application of this class of polysaccharides is their use as oral tablet excipient. A commercial tablet formulation based on Limaprost (e.g. Opalmon®), an alprostadil (prostaglandin E1) analogue, employing dextran (40 kDa) and dextrin as excipients, has been marketed in Japan. A series of studies demonstrated how the presence of the carbohydrates could improve the stability of the Limaprost under high levels of humidity [16–18].

Moreover, dextrans have been extensively utilized as controlled release polymer excipients in the preparation of oral hydrophilic matrix tablets [19–23].

Korner et al. [23], compared dextrans (M_w 70, 500 and 2000 kDa) to polyethylene oxides (PEOs) and hydroxypropyl methylcelluloses (HMPCs), analysing the release and swelling mechanisms in correlation with the intrinsic viscosity (which in this case is an indirect measure of molecular weight) of the polymer. Gil et al. [19–21] showed the potential of medium molecular weight dextrans (40–170 kDa) for immediate release, while the higher molecular weight (more than 2000 kDa) was more suitable in the formulation of extended drug release tablets.

Based on these promising results, it has been decided to integrate the knowledge concerning the use of dextrans as excipients in the formulation of matrix tablets, taking into account the mechanical properties of the powders and how they are affected by the production speed and storage conditions.

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Dextrans with different molecular weights (1, 40, 500 and 2300 kDa) were selected from within those approved for pharmaceutical use, with the only exception of that of the highest molecular weight, which is at this time only approved as a food ingredient.

All the dextrans were characterized in terms of their powder properties and tabletability. Moreover, their ability to act as controlled release agents was evaluated through dissolution studies, using hydroxypropyl methylcellulose (4000 cps), a common polymer used in controlled release systems, as reference material. The dissolution profiles, using tramadol as model drug, were explained in terms of the swelling ability of the formulated tablets.

2. Materials and methods

2.1. Materials

Dextrans with molecular weight of 1 kDa (Dextran 1 EP), 40 kDa (Dextran 40 EP) and 500 kDa (Dextran 500 pharmaceutical quality) were provided by Pharmacosmos A/S (Holbaek, DK), while a dextran of 2300 kDa was supplied by BIOerg srl (Jesi, IT). Hydroxypropyl methylcellulose 4000 cps (Methocel K4M) was provided by Colorcon (Dartford, UK). Microcrystalline cellulose (Avicel PH 101) was provided by FMC BioPolymers (Brussels, BE) and tramadol hydrochloride was generously donated by the company Janssen-Cilag SpA (Borgo San Michele, IT). All the other materials were reagents of standard grade and were supplied by Sigma-Aldrich (St. Louis, USA).

Throughout the text the material names will be reported with the following abbreviations: D_1kDa, D_40kDa, D_500kDa and D_2300kDa for dextrans with molecular weight of 1, 40, 500 and 2300 kDa, respectively and HPMC and MCC for hydroxypropyl methylcellulose 4000 and microcrystalline cellulose. Molecular weights of the D_1kDa, D_40kDa and D_500kDa were provided by the manufacturer, while for the D_2300kDa was determined using size exclusion chromatography coupled to multi-angle light scattering (SEC-MALS), as described in the Supplementary material SMT_1.

2.2. Particle size analysis

All the dextran powders were analysed using optical microscopy (MT9000 Polarizing Microscope, Meiji Techno Co Ltd, JP) equipped with a 3 megapixel CMOS camera (Invenio 3S, DeltaPix, DK). The acquired images (2048 × 1536 pixels) were analysed through the use of image analysis software (Image Pro Plus, MediaCybernetics Inc., USA), previously calibrated using a specific glass slide with a 5 mm graticule (S2-StageMic, Graticules Ltd, UK). One hundred particles, randomly selected, were analysed in terms of projected area equivalent diameter. The obtained data were analysed using the software Minitab 15 (Minitab Inc., State College, USA), in order to measure the most representative parameters of particle size distributions.

2.3. Density and flowability

The bulk (ρb) and tapped (ρt) densities of the samples were determined by pouring a pre-weighted amount of sample in a cylinder and measuring the volume occupied initially and after 300 taps respectively (after 200 taps the powder volume remained constant).

Carr's index was estimated from the bulk and tap densities according to Eq. (1).

$$CI = \frac{\rho_t - \rho_b}{\rho_t} \cdot 100 \quad (1)$$

Bulk and tapped densities were determined in triplicate.

2.4. Hygroscopicity

Dextran hygroscopicities were determined by leaving the samples at ambient conditions and measuring water content at predetermined time intervals using a moisture analyser (SMO 01, Scaltec, DE).

When the stable moisture content was reached, the powders were placed in a desiccator containing calcium chloride and the water content was monitored as previously described in the tests at ambient conditions.

The temperature and the moisture percentages were monitored twice a day during both experiments, giving the following average conditions:

(i) 18.4 ± 0.6 °C and 67.5 ± 3.8% during the experiments performed at ambient conditions;
(ii) 20.7 ± 1.1 °C and 6.1 ± 1.4% during the experiments performed inside the dessicator.

The tests were also performed on two control polysaccharides, MCC and HPMC. MCC was selected as example of a direct compression excipient while HPMC as controlling release excipient.

2.5. Tabletability

Dextran tablets were prepared using a fully instrumented 10 station rotary tablet press (Ronchi, IT). Details of mounted traducers and their calibration have been previously reported [24,25]. The tableting machine was equipped with 6 mm diameter, round, flat-faced punches. The tabletability of the original dextrans was evaluated by preparing for each sample 10 batches of 100 mg tablets at different pressures, 50, 100, 150, 200 and 250 MPa and at two speeds, 5 and 30 rpm. For each batch, 10 tablets were analysed using a hardness tester (TBH30, Erweka, DE) and the obtained crushing forces (H) were converted into tensile strength (TS) using the following equation:

$$TS = \frac{2 \cdot H}{\pi \cdot D \cdot t} \quad (2)$$

Where D is the tablet diameter and t the tablet thickness, measured using a micrometer (103-137, Mitutoyo, Japan).

The analyses were repeated also for the samples left under ambient conditions for the appropriate times necessary to reach stable moisture contents. The hardness of each batch was determined by measuring 10 tablets.

2.6. Tablet stability

Dextran matrices were prepared by setting the punch penetration in order to produce 100 mg tablets at a pressure of 200 MPa. The tablets were left at ambient conditions for 5 weeks (average temperature and moisture were 20.3 ± 1.2 °C and 65.2 ± 2.6%) during which time the variation in weight and hardness was monitored. For each time point 5 tablets were analysed.

In this analysis, the hardness values were not transformed in tensile strength. During the monitored period, the tablets prepared with D_1kDa lost their regular shape making impossible the measurement of the diameter and thickness values necessary for the calculus of the tensile strength.

2.7. Dissolution testing

Five batches of tablets were prepared by compression of blends composed of 49.5 mg dextran (D_1kDa, D_40kDa, D_500kDa and D_2400kDa) or HPMC (used as control), 49.5 mg tramadol and 1 mg