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 enable the stability of the therapeutics to be improved and for them to be delivered in a controlled manner, via either the parenteral and 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

Dextran are a family of high-molecular-weight polymers composed of D-glucose units interconnected 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 5-33%. Commercial dextran are about 95% α-1,6 linked and 5% α-1,3 linked [1].

Dextran 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<sub>w</sub>) and degree of branching, which in turn depend on the source of production [3].

In the last few decades dextran have been mainly used as plasma volume expanders [2, 3]. However recently, dextran 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 cyclodextrins (β type) grafted dextran to solubilize hydrocortisone. Dextran 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, dextran have been extensively utilized as controlled release polymer excipients in the preparation of oral hydrophilic matrix tablets [19-23].

Korner et al. [23], compared dextran (M<sub>w</sub> 70, 500 and 2000 kDa) to polyethylene oxides (PEOs) and hydroxypropyl methylcelluloses (HMPCs), analyzing 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 and co-workers (2006, 2007 and 2008) showed the potential of medium molecular weight dextrans (40-170 kDa) for immediate release, whilst 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. 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 others 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 weight 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 analyzed 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 x 1536 pixels) were analyzed 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 analyzed 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 particles size distributions.

### 2.3 Density and flowability

The bulk ($\rho_b$) and tapped ($\rho_t$) 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 equation 1.

$$CI = \frac{\rho_t - \rho_b}{\rho_t} \cdot 100$$  \hspace{1cm} \text{Equation 1}

Bulk and tapped densities were determined in triplicate.

### 2.3 Hygroscopicity

Dextran hygroscopicities were determined by leaving the samples at ambient conditions and measuring water content at predetermined time intervals using a moisture analyzer (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 percentage were monitored twice a day during both experiments, giving the following average conditions:

1. $18.4 \pm 0.6$ °C and $67.5 \pm 3.8$ % during the experiments performed at ambient conditions;
2. $20.7 \pm 1.1$ °C and $6.1 \pm 1.4$ % 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.

2.4 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 analyzed using a hardness tester (TBH30, Erweka, DE) and the obtained crushing forces (H) were converted into tensile strength (TS) using the following equation:

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

Equation 1

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.

2.5 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 were monitored. For each time point 5 tablets were analyzed.
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.

2.6 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 of magnesium stearate (lubricant). All tablets were characterized by the same hardness, equal to 30 N (effective values were 30.9 ± 2.5).

Dissolution studies were performed at 37 ± 0.5 °C using an USP dissolution apparatus 1 (AT7 smart, Sotax, CH) with rotation speed of 50 rpm. Potassium phosphate buffer (50 mM) pH 6.8 (700 ml) was selected as medium according to previously reported studies concerning tramadol release [26, 27]. For each batch 3 tablets were tested and drug release was monitored spectrophotometrically at 271 nm (UV-1800, Shimadzu Corporation, JP) for a period of 4 hours.

2.7 Tablet swelling

The analysis of tablet swelling was performed using the same procedure followed by Roberts at al. (2007) to study HPMC matrix tablets [28]. Briefly, each tablet was placed vertically in a small glass Petri dish, and 10 ml of dissolution medium was added at ambient temperature. The Petri dish was placed on a plane surface and the digital camera was placed above. The analysis was performed on tablets composed of 99 % dextran (or HPMC) and 1 % of magnesium stearate, having a hardness of 30 N. Images were obtained at 0, 5, 10, 15, 30, 45, 60 and 90 minutes. Each image was calibrated using a graduated ruler and analyzed with the software Image Pro Plus (MediaCybernetics Inc., USA). The analysis was performed in triplicate.
3. Results and discussion

3.1 Particle size and flowability analysis

Microscopic images of the different dextran powders are reported in Figure 1. They appear to be characterised by differently shaped fine particles, with sizes lower than 50 µm. Specifically, all the samples provided by Pharmacosmos, D_1kDa, D_40kDa and D_500kDa, showed a perfect circular shape with a darker inner core, while the sample D_2300kDa was made up by particles of irregular shape. The observation of particles with smaller size and perfectly round shape suggests that low molecular weight dextrans were probably produced by spray drying, this is supported by comparison of similar images reported in the previous literature [29]. On the other hand, the particles images of the sample with highest molecular weight suggest that it was probably obtained through a milling process.

All the images acquired were further processed using image analysis software in order to measure the size of each single particle and obtain the particle size distributions of the different batches. These results are summarized in the Figure 2 using the box plots. Although the dextran samples were produced using different techniques, they show very similar results. The median particle size ranged from a value of 15.9 µm for the D_1kDa to 22.8 µm for D_2300kDa (table 1), while the width of the distributions, calculated as the interquartile range, varied between 7.6 µm to 13.4 µm for the samples D_1kDa and D_500kDa, respectively (table 1). All the particle size distributions were slightly asymmetric, having the right tail longer than the left one (the values of skewness were in the interval 0.5 to 1.3 for all the samples).

All the detxtran samples were characterized also in term of particles flowability using the Carr index. The results, reported in table 1, ranged from 20.5 to 27.7. According to the United States Pharmacopoeia (USP) and the European Pharmacopoeia (EP), the obtained values of Carr index indicate a flowability behaviour defined as “passable” (Carr index in the range 21-25) or “poor” (Carr index in the range 26-31). Such behaviour is related to the low values of particles size. Carr
index results reported in the literature for samples having a particle size in the range of around 10-20 \( \mu \text{m} \) and obtained troughs spray drying are in the range 18-48 [30, 31], comparable with the values found for dextran samples.

### 3.2 Hygroscopicity

The ability to take up water from the environment is a central attribute of any powdered material that strongly influences its storage and handling conditions. The water bound to the hydrophilic groups of a substance acts as a plasticizer and can markedly change its properties (e.g. tabletability, flowability and stability) [32, 33].

All polymeric materials with a high number of hydrophilic groups along their backbone, whilst being glassy or possessing glassy regions (e.g. dextrans), are able to adsorb high amounts of water and consequently change their physical properties [32, 34].

The kinetics of water absorption and desorption when the powders were stored at ambient and dry conditions are reported in Figure 3A and Figure 3B respectively. The dextran samples showed different initial moistures; the powders with the lower molecular weights, \( i.e. \) those below 500 kDa, had moisture contents in the range of 6-7 \%, while the remaining sample, the 2300 kDa, had a moisture content of approximately 10 \%. All the dextrans quickly absorbed environmental water, reaching a stable moisture value in 2-4 days (Figure 3A). The amount of water sorbed is apparently dependent upon the polymer molecular weight; where materials with a lower M\(_w\) show the higher amount of moisture content. The only exception is the dextran 1_kDa.

This result can be explained by observing the images (supplementary material SF1) of all the materials analysed at the start of the test and then after 8 days. All the dextrans remain in the powder form during their exposure at ambient conditions, with the only exception being the 1_kDa. This sample becomes a “rubbery block” as it absorbs water. In this condition, the moisture analyser was not be able to accurately determinate the weight loss since the water is more strongly bound. The change of the powder 1_kDa into a block makes it virtually useless for the preparation of solid
dosage forms. Thus for dextrans of lower molecular weight the storage and handling conditions have to be rigorously controlled.

Water absorption was revealed to be a reversible phenomenon, as is evident from Figure 3B. When the samples were stored at around 6 % environmental humidity, they slowly released the absorbed water (most of the samples returned back at the initial moisture values after 15 days). All the samples had a similar behaviour, with water desorption curves almost overlapping. The sample 1_kDa always remained as a “block”. However, its consistency changed from rubbery to rigid and friable.

The control materials showed similar absorption kinetics than dextrans, even if the total amount of absorbed moisture was lower. Also in this case, the process appeared to be reversible when the samples was stored at dry conditions.

3.3 Tabletability and tablets stability.

Tabletability is one the most relevant features of excipients intended for the preparation of pharmaceutical solid dosage forms. It represents the ability of a material in powder form to produce tablets with good mechanical properties.

In this work, all the dextrans were characterized in terms of tabletability highlighting the effect of molecular weight, compaction speed and moisture absorbed. These results are summarized in Figure 4.

In Figure 4A the curves of the samples with the initial moisture content (the values at time zero in Figure 3A) are reported. Dextrans showed good tabletability, being able to produce tablets with tensile strength in the range 5-12 MPa when compressed at 200 MPa. Such results suggest that dextrans have a tabletability almost comparable with that of microcrystalline cellulose and much higher than many other pharmaceutical excipients used as diluents or controlled release polymers in the direct compression process [35, 36]. There is no apparent trend taking into account the molecular weights. Samples with a weight of 40 kDa and 500 kDa had the higher tabletability. It is
interesting to observe that up to 100 MPa, all the samples have the same behaviour, with data almost overlapped, while it is only at higher pressure that polymers with different M_w begin to show a variable tabletability. There is no effect of production speed, with the exception of the D_2300kDa. Such a difference is most probably due to the different moisture content (10 % versus 6-7 % for the others polymers), as previously discussed. Figure 4B presents the tabletability of the samples exposed at ambient conditions for 8 days (they have a moisture content as defined at the time point “8 days” in Figure 3A). There is no data for the sample D_1kDa since it was no longer in a suitable state to be loaded into the rotary tableting instrument. At higher moisture content dextran powders were more tabletable, but only at the lower compaction pressure (50-100 MPa). Moreover, also the production speed begins to affect the tablet behaviour. In fact, the tablets produced at the lower speed are slightly harder, even if only at the higher compaction pressure applied. These results are not unexpected; water acts as plasticizer increasing the material’s viscoelasticity. This results in higher ductility (better tabletability) and also more strain rate sensitivity (higher tabletability at low production speed) [37-39]. These results show that dextran powders are characterized by a certain hygroscopicity, which affects their compaction behaviour.

The next step is to verify whether the environmental conditions have a similar effect on the mechanical properties of dextran tablets, which were produced with the polymer “as received” and then stored at ambient conditions. The test was only performed on the sample D_1kDa, since this material was more sensitive to the absorbed moisture and to the D_500kDa sample, which was used as a “typical” dextran as it had a comparable behaviour to that of all the other dextrans.

The amount of sorbed moisture, expressed as variation of tablet weight, and the tablet hardness are reported in Figure 5. Tablets prepared with the two dextrans, D_1kDa and D_500kDa, showed almost superimposed weight increase profiles, with about 6 % water absorbed during the 35 days of the test. These results are consistent with those reported in the hygroscopicity section. However, the results in terms of tablet hardness were completely different. The D_500kDa tablets had a constant value of hardness for the first 15 days with a remarkable increase in the following week, which has
been kept constant up to the end of experiment. On the other hand, D_1kDa tablets had a
completely different behaviour; their hardness constantly decreased during the experiment time and
was detectable only for the first 15 days (the hardness of D_500kDa tablets has been easily
monitored for the whole duration of the experiment). After this period, the D_1kDa tablets turned
into a “plastic” mass, which deformed instead of breaking during the hardness measurement. The
images of the tablets during the 35 days of the test clearly show how it is strong the effect of
moisture on D_1kDa tablets (Figure SF2 on supplementary materials).

3.4 Dissolution testing

To evaluate the ability of dextrans to work as controlled release excipients, matrices containing
tramadol hydrochloride as model drug were prepared with the four different dextrans and with
HPMC K4M as model controlled release polymer. Dissolution profiles and dissolution rate traces are shown in Figures 6A and B, respectively. Dextran controls the drug dissolution as a function of their molecular weight, with the 50 % of tramadol released at 3, 6.5, 9 and 42 minutes for the D_1kDa, D_40kDa, D_500kDa and D_2300kDa, respectively.

In any case, their ability to prolong drug dissolution was less effective than HPMC. The sample D_2300kDa provided an anomalous dissolution profile; the release of the drug was very slow and superimposable to that of HPMC matrices during the first 30 minutes and then accelerates to finish after 2 hours. This aspect is clearly visible analysing the dissolution rates (Figure 6B). All the samples, including HPMC, have a maximum dissolution rate at 5 minutes and then the process slows down up to a rate of zero in a time dependent manner for each polymer type. The only exception is the sample D_2300kDa, which show 2 peaks in the dissolution rate profiles, one at 5 minutes and the other at 45 minutes.

3.5 Tablets swelling
To explain the results obtained during the dissolution studies, all the tablets were tested in terms of the variation of their axial and radial dimensions. Percent normalised size variation was calculated as the axial or radial length increase/decrease with respect to the initial value.

Results (Figure 7) showed marked differences in the swelling behaviour of the tablets as a function of dextran molecular weight both in the axial and radial direction. The main behaviour of the polymers moves from a completely erosive mechanism for the D_1kDa to an almost predominantly swelling mechanism for the D_2300kDa.

In the first case, the tablets dissolve in less than 20 minutes while in the latter there is a size increase of more than double with respect to the initial dimensions. The polymers with a molecular weight of 40 kDa and 500 kDa show an intermediate behaviour. In the Figure 7, all the traces end at different times without reaching the -100 value (tablet dissolved). This is due to the breakage of tablets in to pieces, which made it impossible to measurement the size increase. For sample D_500kDa and especially D_2300kDa, after a certain time, the tablets lost their rectangular shape and consequently the parameters reported in Figure 7 are only an estimation (in the traces of Figure 7 a dotted line indicates the estimated values, while the solid line the value correctly measured). The differences in the swelling ability of the different materials are clearly evident observing Figure 8, where the images of all the tablets are compared during the first 30 minutes of the test.

Swelling results appear to be related with the thickening ability of the different dextrans, as reported in the supplementary materials SMT_2. Thus, a purely erosive behaviour is observed with the only polymer having a virtually zero thickening power while the degree of swelling is associated with a particular dextran’s ability to build up viscosity.

It is interesting to note as there is correlation between the dissolution profiles and the swelling data of the D_2300kDa. This sample, showed an increase of the drug release in the time range 30 and 60 minutes, which correspond to the time interval where the sample completely lost its regular shape (30 minutes) and break into pieces (60 minutes) during the swelling analysis. A completely
irregular swollen tablet has a surface area much higher and consequently the drug is quickly released.

These results also allow an easy comparison between dextrans and HPMC. Dextrans suddenly swell or erode ending up to dissolve completely or break into pieces in less than 1 hour, while HPMC shows a constant and regular swelling which takes place during the entire duration of test. This difference can be attributed to the different properties of the gelled layer around the tablets and consequently to the thickening ability of the polymers (SMT_2). As the thickening power of the polymers decrease, the gelled layer around the tablets will be less compact, allowing an easier water diffusion, faster polymers hydration and dissolution.

The data obtained analysing the axial swelling was qualitatively similar to those of the radial swelling. The only difference was in the absolute values of normalized size increase. In the axial parameters, for each time point the swelling was roughly the double respect to those measured in the radial direction. Such a result is consistent with the previously published paper on HPMC swelling [28, 40, 41].

4. Conclusions

Dextrans of molecular weights in the range of 1 kDa to 2300 kDa were tested in terms of their ability to produce tablets and to control tramadol release. All dextrans showed good tabletability, almost comparable with that of microcrystalline cellulose and much higher than many other pharmaceutical excipients. However, their use as controlled release polymer for the preparation of matrix tablets does not appear particularly promising. Dextran polymeric chains showed fast hydration kinetics with high amount of water absorbed, which turned into fast dissolution or fast swelling as a function of the molecular weight.

Nevertheless, these results suggest other uses for dextrans in tablet formulation both in pharmaceutical and nutraceutical products. Specifically, the sample with lowest molecular weight is
a very promising candidate to be used as filler for immediate release tablets, thanks to its good tabletability and fast dissolution rate, while the sample with highest molecular weight could be an efficient disintegrant due to its swelling ability.

Acknowledgments

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References


### Table 1: Density, flowability and particle size of dextran samples.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Bulk density (g/cm³)</th>
<th>Tap density (g/cm³)</th>
<th>Carr index</th>
<th>D₅₀ (µm)/ IQR (µm)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₁kDa</td>
<td>0.47±0.00</td>
<td>0.61±0.00</td>
<td>22.89±0.00</td>
<td>15.92 / 7.64</td>
</tr>
<tr>
<td>D₄₀kDa</td>
<td>0.40±0.01</td>
<td>0.53±0.01</td>
<td>25.00±0.42</td>
<td>21.64 / 11.46</td>
</tr>
<tr>
<td>D₅₀₀kDa</td>
<td>0.41±0.02</td>
<td>0.57±0.00</td>
<td>27.74±3.88</td>
<td>21.66 / 13.38</td>
</tr>
<tr>
<td>D₂₃₀₀kDa</td>
<td>0.53±0.00</td>
<td>0.67±0.01</td>
<td>20.49±0.69</td>
<td>22.78 / 13.32</td>
</tr>
</tbody>
</table>

a D₅₀ represents the median diameter and IQR the interquartile range
Figures and table captions

**Figure 1:** Optical microscope images of dextran.

1. D$_{1}$kDa
2. D$_{40}$kDa
3. D$_{500}$kDa
4. D$_{2300}$kDa
Figure 2: Box plot of the particle size distributions of the dextran powders. In the box plot the box horizontal borders represent the 25th and 75th percentile, the horizontal lines in the middle of the box represents the median value, the black circle the mean value and the two whiskers the 5th and 95th percentile respectively.
Figure 3: Variation of moisture content of dextrans and control material when exposed at A) ambient conditions (18.4±0.6 °C and 67.5±3.8 % UR) and at B) dry environmental conditions (20.7±1.1 °C and 6.1±1.4 % UR).
Figure 4: Tabletability curves (mean ± SD n = 10) of dextrans at a production speed of 5 (open symbols) and 30 rpm (closed symbols) and with a moisture content equal to (A) the value of the “as received samples” and to (B) the value reach after 8 days of exposure to environmental conditions (18.4±0.6 °C and 67.5±3.8 % UR).
Figure 5: Variation of tablets hardness and weight during their exposure at ambient conditions (20.3 ± 1.2 °C and 65.2±2.6 % UR). (mean ± SD n = 5)
Figure 6: The effect of molecular weight on A) the release of tramadol hydrochloride B) the release rate of tramadol hydrochloride from dextrans matrices. HPMC is reported as control (mean ± SD n = 5).
Figure 7: The effect of molecular weight on the percent normalised axial (A) and radial (B) size variation for dextran matrices. HPMC is reported as control. (mean ± SD n = 3).
Figure 8: The effect of time on the size variation of dextran matrices at various time points (the units are minutes). HPMC is reported as control.
Figure SF1: Images of dextran powders (A) as received and (B) after 8 days of exposure to environmental conditions (18.4±0.6 °C and 67.5±3.8 % UR).
Figure SF2: Images of dextran tablets during their exposure to the environmental conditions (20.3 ± 1.2 °C and 65.2±2.6 % UR) at the different time points (the units are days).

SMT_1: High performance size exclusion chromatography coupled to multi-angle light scattering (HPSEC-MALS)

2 mg/mL of sample was dissolved in distilled. High performance size exclusion chromatography (HPSEC) was performed at room temperature on a system consisting of a PL aquagel guard column (Polymer Labs, Amherst, U.S.A.) followed by in series (PL aquagel-OH 60, PL aquagel-OH 50 and PL aquagel-OH 40) eluted with distilled water at a flow rate of 42 mL/h. The eluent was detected on-line by:

1. DAWN EOS light scattering (LS) detector (Wyatt, Santa Barbara, U.S.A.)
2. T-270 differential pressure viscometer (DPV) (Viscotek, Huston, U.S.A.)
3. rEX differential refractometer (RI) (Wyatt, Santa Barbara, U.S.A.)

The refractive index increment, $dn/dc$ was taken to be 0.15 ml/g.
From the analysis by SEC-MALS the water-soluble portion of the dextran provided by BIOerg was estimated to have a weight-average molecular weight of $2.3 \times 10^6$ g/mol (2300 kDa) and a polydispersity ($M_w/M_n$) of 2.4.

SMT_2: Viscosity of the dextran and HPMC solutions

All the dextran solutions were prepared by dispersing the polymer in water under magnetic stirring, while the HPMC solutions were prepared through the “hot/cold” technique. Briefly, the HPMC powder was dispersed in 1/3 of the required amount of hot water (70°C) adding then the remaining amount of medium during the cooling phase at ambient temperature under magnetic stirring. All the solutions were left at 5°C for at least 24 hours before being analysed.

All the solutions were prepared in different range of concentrations (% w/w) in order to take into account their different thickening properties and consequently obtain comparable viscosity values (in the range of 0-1 Pa*sec).

Flow curves were determined with a controlled stress rheometer (Stress Tech, Reologica) by a steel cone–plate geometry (C40/4). Shear rate was increased from 1 to 150 sec$^{-1}$ and the corresponding shear stress measured, at a constant temperature of 25 and 37°C.

Each sample was tested in triplicate.

The flow curves were then analysed to obtain the viscosity by the Power-law equation:

$$\sigma = k\dot{\gamma}^n$$

Where $\sigma$ is the shear stress, $\dot{\gamma}$ the shear rate, $k$ the consistency index and $n$ the power law index.

Power law equation is an easy rheological model able to describe the flow of Newtonian and many non-Newtonian systems. The consistency index $k$, also called power law viscosity, is related to the system viscosity while the power law index $n$ is related to the flow patterns. $n$ values equal to 1 indicate a Newtonian behaviour while values lower and higher than 1 suggest shear thinning and thickening behaviour respectively.

The results of power law analysis are reported in the following figure SMT_2. All the analysed polymers showed very different thickening ability and the following rank of viscosity (power law viscosity) values are observed: D2300_kDa >> D500_kDa > D40_kDa >> D1_kDa. It need to be highlighted that the sample D1_kDa had viscosity values comparable with that of pure water and consequently its thickening power is virtually nil, at least in the concentration range analysed (5-30%). The sample D2300 kDa showed definitely higher viscosity values among all the tested...
dextrans, even if its thickening ability is not comparable with that of HPMC. In addition, all the samples are Newtonian except the HPMC and the D2300_kDa at the higher concentrations, where a pseudoplastic behaviour is observed.

No differences were observed at the two tested temperature, 25 and 37°C.

**Figure SMT_2:** Effect of polymer type, polymer concentration and temperature on the power law viscosity (consistency index $k$) and the power law index ($n$) of aqueous dispersions.