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Research paper

A sugar cane native dextran as an innovative functional excipient for the development of pharmaceutical tablets

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Abstract

We reported the physical chemical characterization of a new series of native dextran (B110-1-2). The chemical structure of the polymer was characterized by IR, ^{1}H and ^{13}C NMR spectroscopy and compared with that of a commercial native dextran B512-F obtained from Sigma Company. Molecular weights of the product and different commercial dextran fractions of *Leuconostoc mesenteroides* from 43 000 to 170 000 average molecular weight (M_w) were established by the analysis of intrinsic viscosity in aqueous solutions and compared with those obtained by gel permeation chromatography (GPC). The critical overlap concentration around 9 g/L was obtained. No interactions of powder mixtures with different commercial excipients (lactose, cetyl alcohol, HPMC) and drugs (propranolol hydrochloride, acetyl salicyclic acid, isosorbide dinitrate, lobenzarit disodium, and nifedipine) were demonstrated by differential scanning calorimetry (DSC) analysis. Tablets obtained by direct compression showed good physical–mechanical and technological properties. Dextran B110-1-2 has similar physical chemical properties as commercial Sigma B512-F. Water uptake, erosion and dissolution profile studies for dextran tablets established that glucose polymer with molecular weight $M_w \geqslant 2 \times 10^6$ is suitable for the development of controlled release solid dosage forms (soluble drugs). Fraction of dextran (M_w 40 000–170 000) could be more useful for immediate release tablets.

Keywords: Native dextran; Molecular weight; Intrinsic viscosity; Tablets; Dissolution profiles

1. Introduction

Dextrans are composed of D-glucan chains ($1–20 \times 10^6$) with α-1,6 as the main chain linkage and variable numbers of α-1,2 α-1,3, or α-1,4 branched chain linkages. Dextran is synthesized from sucrose by dextransucrases, glucansucrases, and glucosyltransferases, produced by Leuconostoc or Streptococci. These bacteria growing in sugar juice produce dextran. High concentrations of dextran in sugar juice (>1000 ppm) can produce severe financial loss to the sugar industry [1,2].

A brief search in the Chemical Abstracts database for dextran and dextran-related titles leaves one in little doubt of the prolific interest in this area; an interest which may be attributed to the continuing clinical, scientific and technical importance of dextran and its derivatives. Currently, more than 1000 publications dealing with dextran appear each year. Almost none of them refer to native dextrans (M_w more than 2 000 000) as matrix excipients for solid controlled release system. Reviews in this field are published with impressing regularity. Certain limitations had to be imposed on those reviews and thus, it has been restricted to dextrans of commercial interest, in particular *Leuconostoc mesenteroides* B512-F; other dextrans and the cariogenic glucans are almost not referred since they are not commercially relevant [3].

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Dextran fractions obtained from enzymatic hydrolysis of native dextrans are supplied in molecular weights from 1000 to 2 000 000 Daltons. The molecular weight of the fraction is, in most cases, a key property and is defined in terms of the average molecular weight (M_w) and the average molecular weight number (M_n). The molecular weight distribution curve for each fraction obtained by gel chromatography offers a unique method for characterizing the dextran fraction [4].

Recently, we demonstrated the ability of a new series of native dextran (B110-1-2) in the use of solid controlled release dosage forms [5]. By using different techniques, the aim of the present work is to characterize this polymer and compare it *versus* the commercial native dextran B512-F (M_w 5 000 000–40 000 000) and its fractions. At the same time, the functionality of this new raw material for controlling drug release is also studied as a function of molecular weights.

2. Materials and methods

2.1. Materials

Racemic propranolol hydrochloride (PPL), commercial native Dextran B512-F (M_w 5 000 000–40 000 000) and its fractions (M_w 430 000, 71 327, and 170 000) were obtained from Sigma (Saint Louis, USA). High molecular weight native dextran (B110-1-2, M_w 2 000 000) was obtained from the Center of Studies of Sugar Cane (Havana, Cuba). Lobenzarit disodium (LBZ) was prepared in the Synthesis Laboratory at the Center of Pharmaceutical Chemistry (Cuba). Hydroxypropyl methylcellulose (HPMC) with a viscosity grade 4000 cps (Methocel K4M) was obtained from Colorcon (Kent, England). Nifedipine, aspirin, dinitrate isosorbide and other excipients were USP 25/NFXX quality [6]. Other chemicals and reagents were of analytical grade.

2.2. Infrared spectroscopy

The IR spectra of native dextrans B110-1-2, B512-F and fractions were obtained using a Perkin-Elmer 983-G spectrophotometer (Beaconsfield, Bucks, UK) employing KBr disks.

2.3. ^{1}H and ^{13}C NMR spectroscopy

The ^{13}C NMR and ^{1}H NMR spectra for native dextran B512-F and B110-1-2 were determined in D_2O using Bruker spectrometer, 300 MHz (Germany).

2.4. Differential scanning calorimetry (DSC) and thermogravimetric analyzer (TGA)

Differential scanning calorimetry studies were carried out using a DSC6 calorimeter (Perkin-Elmer Instruments, Beaconsfield, Bucks, UK). Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples (dextrans, different drugs and mixtures) were tightly sealed in aluminium pans and heated at a constant rate of 20 °C/min over a temperature 20–175 °C under nitrogen purge. Thermogravimetric analysis was carried out using a TGA6 equipment (Perkin-Elmer Instruments series, UK).

2.5. Viscometry

Viscometric measurements with aqueous polymer solutions (up to 70 g/L) were carried out using the Schott autodilution viscometer K105373 with Ubbelohde capillary tubes. Temperature was regulated by circulating bath. Prior to measurements, the aqueous solutions were filtered through 0.2 μm filters. Polymer concentration was corrected by the results obtained in the TGA. All experiments were performed at 37 °C, and the variation of flow time of water at different temperatures (20 and 37 °C) was checked and consistent with the literature data [7]. Milli-Q water was used for all the experiments.

2.6. Preparation of tablets

Constant weighing (300 mg, 150–280 μm particle size) of dextran samples was compressed with a Perkin-Elmer hydraulic press fitted with a 10 mm diameter punch. After some time the formed tablets were ejected from the punch. The influence of compression force (from 6 to 30 kN) was studied as a function of the tablet hardness. Furthermore matrix tablets (300 mg) containing binary mixture dextran:LBZ and dextran:PPL (1:1, w/w) were prepared by direct compression without any further excipient at 14 kN compression force.

The hardness of tablets ($n = 10$) was measured using a Pharma Test PTB-311 instrument (Germany). Its friability was measured according to the USP 25 [6] using 20 tablets and 100 rotations during 4 min.

2.7. In vitro drug release studies

Dissolution studies were carried out at 37 ± 0.5 °C in 1000 ml of distilled water, in a USP 25 apparatus (Sotax-AT7 Smart, Teknokroma, Spain) using the paddle method. The rotation speed was kept constant at 100 rpm. Release of LBZ and PPL was detected by UV spectrophotometer method at 360 nm (for LBZ) and 290 nm (for PPL) during 8 h. Three replicates of filtered samples, taken at different times, were performed for each determination and the mean values were used to obtain the release profiles. The total amount of drug present in the tablets was calculated as the sum of the cumulative mass of drug released in the last sample and the mass of drug remaining (residue). The techniques were previously validated. The validation method for LBZ was carried out by analyzing solution containing several concentrations of LBZ in five replicates.

Furthermore, these solutions were analyzed by triplicate on five different days ($n = 15$). The results showed a good linearity ($r^2 = 0.9940$), with appropriate precision (CV < 2%) and accuracy values (⩾98.98%). The absence of interference of dextran was checked by comparing the data obtained from pure substance LBZ or PPL and from samples spiked with polymer (for PPL, see [1]).

2.8. Wet and dry weight studies

The method used was based on those of Tahara and Jamzad [8,9]. Swelling and erosion of dextran polymers of differing molecular weights were examined by measuring the wet and subsequent dry weights of matrices.

The experiment consisted of allowing the tablet (dextran alone) to dissolve in the medium (in the same condition described in drug release studies) for certain time periods (15, 30, 60 and 90 min) before they were removed into a pre-weighed weighing boat. The excess dissolution medium was drained and measure blotted from around the tablet without touching it. The tablet and boat were then weighed to establish the wet weight of the tablet. The tablets were then dried to a constant weight in an oven at 105 °C. Every determination at each time point was performed in triplicate and mean values were expressed. The dissolution medium uptake per weight of polymer remaining was calculated at each time point for a particular matrix to correct the effect of erosion and dissolution in the measurement of degree of dissolution medium uptake Eq. (1). Eroded dextran was measured according to the equation described by Jamzad et al. Eq. (2).

$$\text{Water uptake per unit polymer remaining } (\%) = \frac{\text{wet weight} - \text{remaining dry weight}}{\text{dry weight}} \times 100 \quad (1)$$

$$\text{Mass polymer loss } (\%) = \frac{\text{Original weight} - \text{remaining dry weight}}{\text{original weight}} \times 100 \quad (2)$$

The Davidsons and Peppas model Eq. (3) was applied to these data to study the mechanism and the rate of water uptake [10].

$$w = K_s \cdot t^n \quad (3)$$

Being w the weight gained of the swelled matrix (water/dry polymer); K_s, the kinetic constant of water penetration; t, the penetration time; n, the exponent which depends on the water penetration mechanism.

2.9. Studies of mechanism of LBZ and PPL release from dextran tablets

The mechanism of drug release was analyzed according to Higuchi Eq. (4), Hixson-Crowell Eq. (5), Korsmeyer Eq. (6) and Peppas-Sahlin Eq. (7) equations:

$$\frac{Q_t}{Q_\infty} = k_1 \cdot t^{1/2} \quad (4)$$

$$\frac{Q_t}{Q_\infty} = (1 - k_2 \cdot t)^{1/3} \quad (5)$$

$$\frac{Q_t}{Q_\infty} = k_3 \cdot t^n \quad (6)$$

where Q_t/Q_∞ is the fraction of drug released; k_1, k_2 and k_3 are kinetic constants; n is a diffusional exponent that depends on the release mechanism and on the shape of the swelling device tested. Values of $n = 0.5$ indicate Fickian release, values of $0.5 < n < 1.0$ indicate an anomalous (non-Fickian or couple diffusion/relaxation) drug release, whereas values of $n = 1.0$ show a case II (purely relaxation controlled) drug release.

$$\frac{Q_t}{Q_\infty} = K_d \cdot t^m + K_r \cdot t^{2m} \quad (7)$$

where Q_t/Q_∞ is the fraction of drug released; K_d is the diffusional constant; K_r is the relaxational constant and m is the diffusional exponent that depends on geometric shape of the releasing device through its aspect ratio [11].

A comparative study of dissolution profile for PPL and LBZ was established as the analysis of a similarity factor. It can be defined as:

$$f_2 = 50 \cdot \log\left\{\left[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \cdot 100\right\} \quad (8)$$

In the equation above f_2 is the similarity factor, n is the number of time points, $R(t)$ is the mean percent drug dissolved of the current formulation, and $T(t)$ is the mean percent drug dissolved of, e.g. the changed composition.

The evaluation of similarity is based on the conditions of:

- a minimum of three time points
- 12 individual values for every time point
- not more than one mean value of >85% dissolved
- that the standard deviation of the mean should be less than 10% from the second to last time point.

An f_2 value between 50 and 100 suggests that two dissolution profiles are similar [12]. In this study, experimental data corresponding to 30, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min were considered.

3. Results and discussion

3.1. IR spectroscopy analysis

IR spectra of native dextrans are shown in Fig. 1 (IR spectra for **F1**, **F2** and **F3** are similar to native dextrans). The IR spectra for glucose polymers (dextran B110-1-2 and B512-F) are overloads suggesting that two series of dextran are similar. The attribution of signals was established over glucose monomer [13,14]. The low-wave

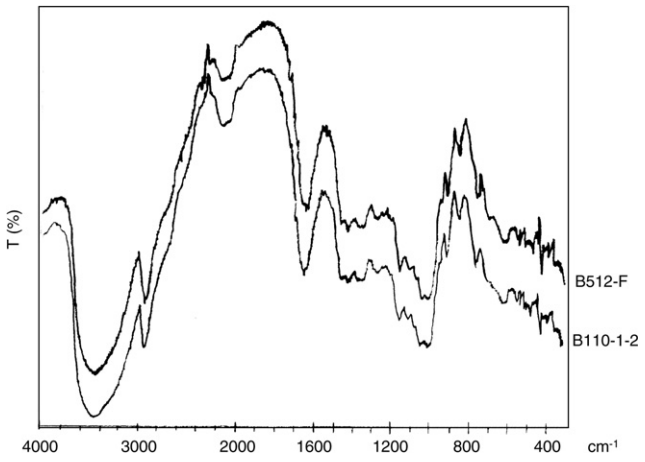


Fig. 1. IR spectra for native dextran B110-1-2, B 512-F.

number range 400–700 cm^{-1} shows the skeletal vibrational motions, δ(C–C–C), δ(C–C–O), δ(C–O) and τ(C–C), with a relative intensity as a function of water content.

We also suggested the possible contribution of fairly pure OH proton motions. We assigned the bands present at 537 and 550 cm^{-1} to the δ(C–C–O) bending vibration. The 431 cm^{-1} band could be assigned to a δ(C–C–C) and 481 cm^{-1} band to an endocyclic δ(C–C–O) ring mode.

The spectral range 800–900 cm^{-1} is part of a region often referred to as the ''anomeric region''. In the spectra of crystalline dextran, two absorption peaks at 851 and 914 cm^{-1} are observed and they could be assigned to the υ(C–C) and δ(C–H). While, many works have also suggested υ(C–O), δ(C–C–H), υ(C–C) and δ(C–C–O) contribute most to the vibrations in this region.

The spectral range 1000–1200 cm^{-1} has been suggested to be dominated by contributions from heavy atom, υ(C–C) and υ(C–O) stretching vibration with contributions from δ(C–O–H) motion. We suggested that the band centred at 1159 cm^{-1} could be assigned to δ(C–O–C).

The vibrational bands at 1013 and 1045 cm^{-1} in the spectrum of dextran have been assigned to the υ(C–O) vibration with contributions from υ(C–OH), υ(C–C) and δ(C–O–H) modes. It has been suggested that the absorption bands in spectral range between 1200 and 1500 cm^{-1} may be caused mainly by CH deformation vibrations and δ(COH) bending vibrations. The spectrum shows one mode around 1273 cm^{-1} assigned to the υ(C–O) stretching mode in the ring. The normal mode at 1360 cm^{-1} is an almost pure δ(O–C–H) vibration and the mode at 1429 and 1460 cm^{-1} a pure CH_2 group vibration. We assigned the bands present at 2935 and 3429 cm^{-1} υ(C–H) and υ(O–H) stretching vibration, respectively.

3.2. ^{1}H and ^{13}C NMR spectroscopy analysis

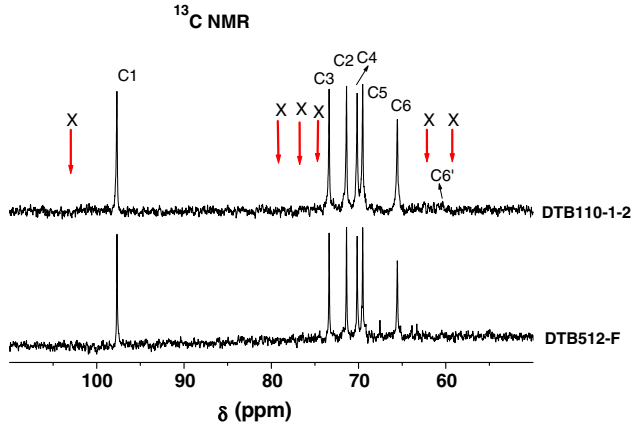
The ^{1}H and ^{13}C NMR spectra afford compelling evidence for the main structural features of dextran. The individual assignments reported in the literature and experimental are shown in Table 1. Fig. 2 shows ^{13}C NMR and ^{1}H NMR spectra of native dextran from *L. mesenteroides* B512-F and B110-1-2 in D_2O.

In our studies impurities of levan neither for commercial native dextran B512-F nor for native dextran B110-1-2 were detected. Spectral obtained for native dextrans were very similar and it was demonstrated by subtractions of spectra (see Fig. 2). According to this result, B512-F and B110-1-2 have a similar structure. This can also be seen in Table 2 that shows the different linkage structures found in all dextran series and reported in the literature [1,15]. The downfield signal at 99.5 ppm is tentatively assigned to α (1-3) anomeric carbon. The signal at 61 ppm, assigned to the C6 atom on the non-reducing glucose units, is of considerable interest as it corresponds to the branching [16]. Some laboratory studies on the determination of the degree of branching of clinical dextran by NMR yield a value of 4.8–5.5%, depending on the integrating technique employed. Since the early studies on dextrans by Pasika and Cragg [17] using ^{1}H NMR, rapid progress has been made in resolution and quality of the spectra. A thorough re-examination of the technique used to dextrans has been published by Gagnaire and Vignon [18] and Seymour et al. [19]. The assignments for the proton signals are included in Table 1. Since the spectra are necessarily much more complex, it has not been possible to resolve and identify all signals, particularly the minor ones. Some authors reported ^{13}C NMR spectroscopy useful for detecting traces of levan in native dextran [3]. Fig. 2 also shows the ^{13}C spectrum signals corresponding to levan (the signals marked X are due to levan).

Table 1
The individual assignments ^{1}H and ^{13}C NMR (native dextran B512-F and B110-1-2) reported by literature and experimental evidence

	B512-F (reported values)		B512-F (experimental)		B110-1-2 (experimental)	
	^{13}C (ppm)[a]	^{1}H (ppm)[a]	^{13}C (ppm)	^{1}H (ppm)	^{13}C (ppm)	^{1}H (ppm)
C1–H	97.8	4.99	97.68	4.91	97.68	4.91
C2–H	71.5	3.6	71.38	3.52	71.37	3.52
C3–H	73.5	3.76	73.37	3.68	73.37	3.68
C4–H	70.3	3.52	70.16	3.48	70.16	3.48
C5–H	70.0	3.88–4.04	69.52	3.93	69.52	3.93
C6–H	66.1	3.88–4.04	65.56	3.87	65.55	3.87
C6′–H	61.0	3.81–3.86	–	3.83	–	3.83

[a] Reported values (Refs. [3,4]).



* The signal marked X are due to levan (not detected in samples)

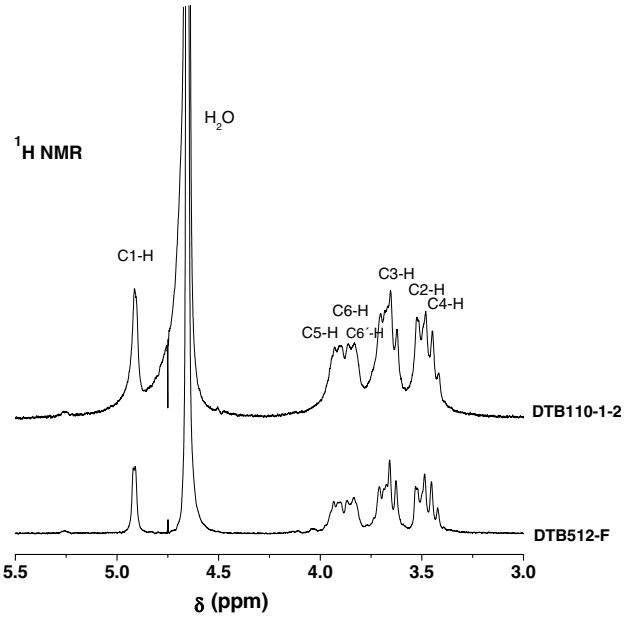


Fig. 2. ^{13}C NMR and ^{1}H NMR spectra of native dextran from *Leuconostoc mesenteroides* B512-F and B110-1-2 in D_2O.

Table 2
The different linkage structures found in all dextran series and reported in the literature

Dextran	Solubility	Linkages (%)				
		α 1-6	α 1-3	α 1-3 Br[c]	α 1-2	α 1-4 Br
L.m. B512-F[a]	**Soluble**	**95**	**5**			
L.m. B742	Soluble	50		50		
L.m. B742	Less soluble	87				13
L.m. B1299	Soluble	65			35	
L.m. B1299	Less soluble	66		1	27	
L.m. B1355	Soluble	54	35	11		
L.m. B1355	Less soluble	95		5		
L.m. B110-1-2	**Soluble**	**93**	**6**			**1**
S.m. 6715[b]	Soluble	64		36		
S.m. 6715	Insoluble	4	94	2		

Source, adapted from Robyt, values for DT B110-1-2 obtained by Brossar.
[a] L.m., *Leuconostoc mesenteroides*.
[b] S.m., *Streptococcus mutans*.
[c] Br, branch linkage.

3.3. Differential scanning calorimetry (DSC)

Pure polymer components showed the characteristic thermal parameters in each case. No endothermic peak was observed in this range as it normally occurs for dextrans and its fractions and other glucose polysaccharides. The DSC thermal parameters for the DT B110-1-2, pure drugs and the physical binary mixtures of these polymers with different drugs as PPL, LBZ, nifedipine (NIFED), isosorbide dinitrate (40% in lactose) (DNI), acetyl salicyclic acid (ASA) were, respectively, analyzed, as presented in Fig. 3 (except for LBZ because no endothermic peak was observed). The thermal parameters of each pure component could be observed in all physical binary mixtures. Furthermore, no thermal signals due to the decomposition products were found in any physical binary and ternary mixtures of dextran and different drugs. These results suggest that no interaction between drugs and polymer has occurred and DT B110-1-2 can be used in solid mixture with PPL, DNI, LBZ, ASA, and NIFED for solid dosage form formulation. Similar results were obtained with pharmaceutical excipients as cetyl alcohol (endothermic peak at 53 °C), lactose (see DNI) and HPMC (no characteristic endothermic peak observed).

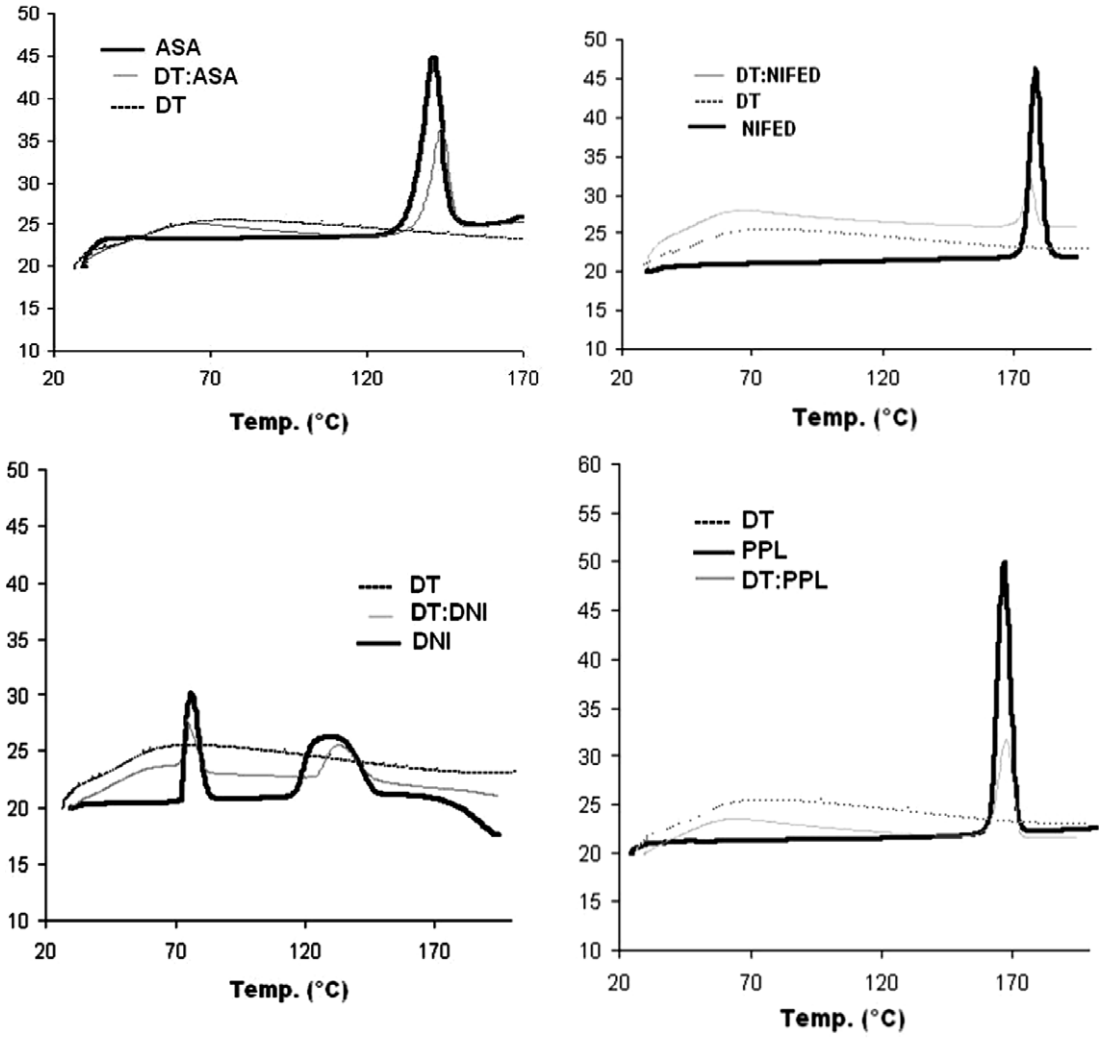
3.4. Viscometry of dextrans

Researchers have studied the rheological properties of aqueous solutions of dextran for a number of years. Several interesting behaviours, which depend on the structure and nature of the dextran samples used, have emerged from these studies. The intrinsic viscosity $[\eta_{int}]$ of dextran solutions has been a topic of a lot of research dating back to the 1950s, and results vary slightly amongst different researchers. The dependence of the intrinsic viscosity on molecular weight M_w can be represented by:

$$[\eta_{int}] = KM_w^a \quad (9)$$

where the constant K and exponent a are independent of molecular weight (within a certain range), but are found to be dependent on the temperature and nature of the solvent [20]. For fractions of hydrolysed B512 dextran, the exponent (a) was found to vary from 0.43 [21] to 0.5 [22], and up to 0.6 [23] for molecular weight in the range of 2000–10^5. In our studies, values of constants (K) and (a) were elucidated applying a system of equations based on Eq. (9) at 37 °C in water solutions and experimental values obtained for η_{int} for fractions 170 000 (**F1**) and 71 327 (**F2**). Molecular weights of fraction **F3** (M_w 43 000, according to manufacturer's data) and native dextran B110-1-2 and B512-F were estimated as Table 3 shows. All measurements take into account the TGA carried out before weighting samples. In this analysis, values of around 10% humidity for all dextran samples were found.

The intrinsic viscosity $[\eta_{int}]$ of the dextran samples was determined by plotting the reduced viscosities (at 37 °C) of the low concentration solutions, using the capillary



Legend: Axis Y-heat flow endo up (mW), DT- native dextran B110-1-2, ASA- acetyl salicylic acid, DNI-isosorbide dinitrate in lactose (40%, w/w), NIFED-nifedipine, PPL-propranolol hydrochloride.

——Drugs, ___ mixture DT:Drugs , ----- DT

Fig. 3. DSC analysis for native dextran B110-1-2, drugs and binary mixtures of dextran:drugs (1:1, w/w).

viscometer, as a function of polymer concentration, C, and extrapolated to infinite dilution, according to Huggins equation Eq. (10) generally followed by all polymers.

$$\eta_{red} = \frac{\eta_{sp}}{C} = \frac{\eta - \eta_s}{\eta_s C} = [\eta_{int}] + k_h[\eta_{int}]^2 C \qquad (10)$$

where η_{sp} is the specific viscosity, η and η_s are the solution and solvent viscosity (Pa s), respectively, and k_h is the Huggins constant. η_{red} is the reduced viscosity of the solution (L/g). The plot of reduced viscosity as a function of concentration for the dextran samples (natives and fractions **F1**, **F2** and **F3**) is shown in Fig. 4.

The intrinsic viscosity values obtained are plotted as a function of molecular weight in Fig. 5. As shown in this figure and in Table 3, the dependence of the intrinsic viscosity of polymer was found to increase with increasing molecular weight. Dependence was linear with a slope $a \approx 0.3$ up to M_w 2×10^6. This value and dependence agree well with those obtained in the same range by other authors for commercial dextran fractions B512-F from different companies (Sigma Co., and Pharmacia Co.) [24,25]. The inclusion of B110-1-2 and high correlation coefficient ($r^2 = 0.9956$) obtained for regression curve indicates a similarity of α-1,6 linkages of two series of dextran. It can be assumed especially because the slope has been found to decrease dramatically for other series of dextran containing only approximately 70% and 57%, respectively, of the α-1,6 linkages [21,22].

Morris et al. [26] and Tirtaatmadja et al. [25] studied the specific viscosity of B512-F commercial dextran (Pharma-

Table 3
Experimental values of M_w obtained for dextrans using intrinsic viscosity values

Dextran	K_h (37 °C)	η_{int} (L/g)	R^2	M_w[a]	M_w (GPC) manufacturer's data
DT B110-1-2	1.65	0.0765	98.98	1988000	2000000
DT B512F	1.49	0.1241	98.57	22000000	5000000–40000000
F1	1.20	0.0258	99.26	–	170000
F2	0.99	0.0201	98.84	–	71327
F3	0.63	0.0178	98.14	42973	43000

M_w, weight–average molecular weight. K_h at 37 °C, Huggins constant obtained for dextrans at 37 °C. η_{int}, intrinsic viscosity (L/g). R^2, coefficient of correlation obtained at 37 °C. **F1**, sigma dextran fraction M_w 170000. **F2**, sigma dextran fraction M_w 71327. **F3**, sigma dextran fraction M_w 43000.
[a] Experimental values obtained using intrinsic viscosity method, M_w of **F1** and **F2** (according to manufacturer's data), were used as references.

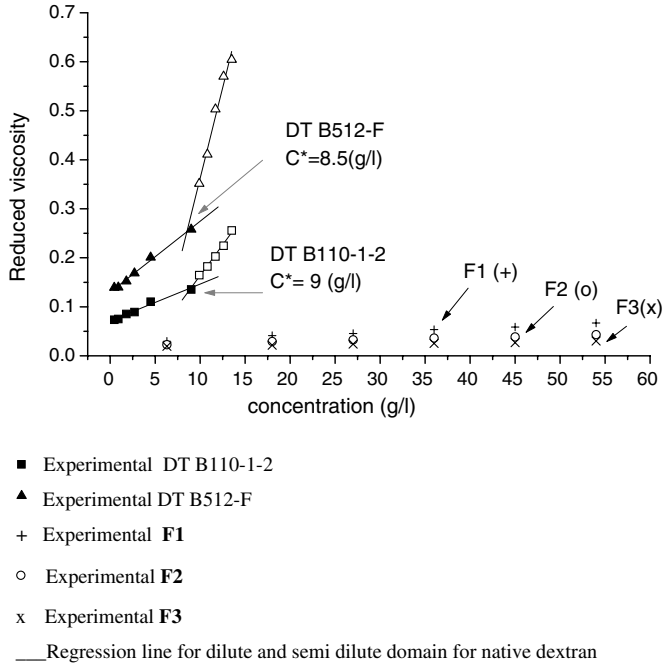


Fig. 4. Reduced viscosity as a function of concentration for the dextran samples.

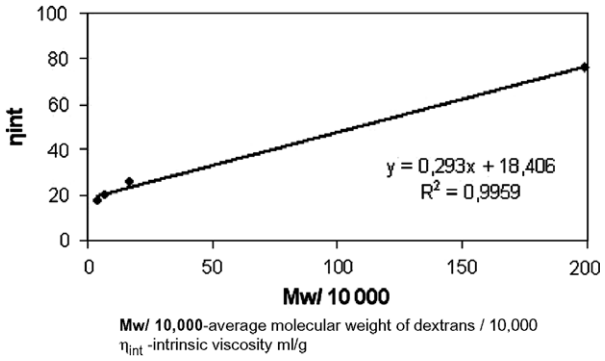


Fig. 5. Plot of intrinsic viscosity of the dextran samples as a function of nominal molecular weight.

cia T2000) of nominal molecular weight 2×10^6, as a function of concentration, and found the critical concentration, c^*, for the transition from dilute to semi-dilute region. In our studies c^* for native dextran B110-1-2 and B512-F were also found as shown in Fig. 4. The results indicate two distinct regions with a critical overlap concentration, c^*, of approximately 8.5 g/L (B512-F) and 9 g/L (B110-1-2), which are lower than the values obtained by others authors [25,26]. Our results, and the results obtained by Morris and Tirtaatmadja, demonstrate that dextran has an exceptionally large c^* compared to the other polysaccharides, and hence, considerably lower $[\eta_{int}]$. This exceptional behaviour is probably due to the branched nature of the dextran molecules with a number of very long side-chains in these branches which causes a more compact molecular configuration and a reduction in the molecular volume in solution [25].

3.5. Dextran tablets

The influence of applied force on the hardness of dextran tablets is shown in Fig. 6. According to this result applying a force of 14 kN is sufficient to obtain the highest

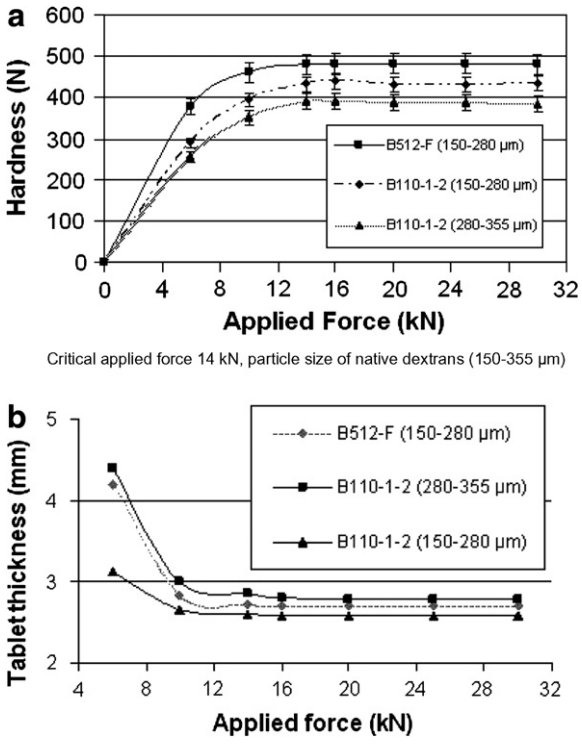


Fig. 6. Typical dependence hardness and tablet thickness/applied force for native dextrans B512-F and B110-1-2 tablets.

hardness. In the figure, the mean values of hardness for twelve samples are plotted. Relative standard deviations were less than 4% (all points) for two series of native dextran. The friability was less than 1% (0.30% for DT B110-1-2 and 0.25% for DT B512-F, respectively) (see Fig. 7).

The behaviour of powders during compression is often very complicated. In compactation of powders, materials are subjected to compressive forces which lead to a volume reduction of the powder column. A volume is reduced by decreases in the inter- and intra-particulate pore space. Several equations for describing the relationship between the porosity, and/or change in relative density of a powder column and the applied pressure, have been proposed. Equations of Heckel, Kawakita and Cooper-Eaton are some examples of them [27a].

Three types of volume reduction mechanisms of pharmaceutical powders have been distinguished by using the Heckel equation. Materials were categorized by compressing different particle size fractions of various powders. In one of them namely case A, size fractions had different initial packing fraction and the plots remained parallel as the compression pressure was increased. Generally, type **A** behaviour was related to the densification by plastic flow, preceded by particle rearrangement [27a]. As Fig. 6b shows dextran has a similar behaviour as case A. An increased volume reduction (expressed as reduction of tablet thickness) was observed from 6 to 14 kN compression force (compression time >10 s) corresponding to the rearrangement of the relative regular particles that occurs at relative low pressure and porosity reduction occurs exponentially. The volume reduction process of dextran powder column is continuous and the proportion of air between and inside the solid particles is decreased. At relative higher pressures (>14 kN) the volume reduction becomes more difficult. From this pressure, porosity of the system becomes minimal and low porosity reduction is observed (14–30 kN).

Dextrans exhibit high tablet strength. Primary (the dominating bond mechanism) and secondary factors (the surface area over which these bonds are active) affecting compact strength of this polymer are: a very plastic deformation and a pronounced surface roughness. Dextran material exhibits extensive plastic deformability, such as many amorphous binder materials, in which the number of weak distance forces would probably be much higher and thereby contribute significantly to the compact strength [27b]. Also materials as dextran having a rough surface texture ought to be capable of forming a relative large number of weak distance forces, in spite of the fact that such a material does not fragment extensively. If the powder being compressed consists of particles with both a rough surface texture and a pronounced plastic deformability, compacts of extremely high mechanical strength ought to be obtained, due to a large number of weak distance attractive forces developed. The initially high surface roughness is reduced with a subsequent reduction in intermolecular forces after compression.

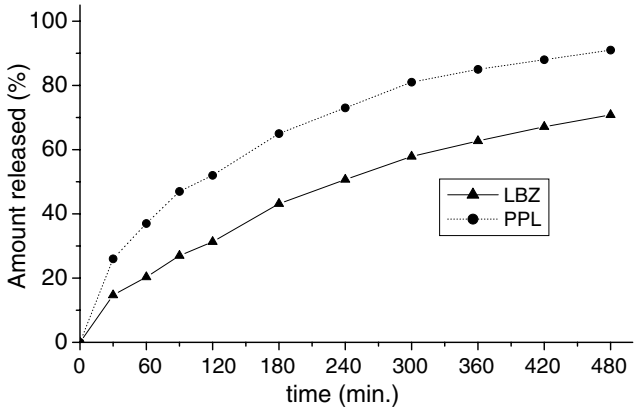


Fig. 7. Dissolution profile for lobenzarit disodium (LBZ) and propranolol hydrochloride (PPL) from dextran tablets.

Many of the common uses of amorphous tablet binders with pronounced plastic deformation may provide an effective means of creating large interparticulate attraction surface areas. It seems that a high external specific surface area is a prerequisite for high compactibility. This is best achieved by using fine particle size (see Fig. 6a) or qualities with high surface roughness, as reported earlier for Sta-Rx 1500 and sodium carbonate [27b].

3.6. Swelling and erosion

The change in wet weight, reflecting swelling, with time for compacts of the five polymer types is shown in Table 4. The higher molecular weight polymers show the higher maximum average relative swelling, which occurred since the initial time with little erosion. In contrast, the lower molecular weight polymers (Fractions **F1**, **F2** and **F3**) exhibited minimal swelling properties and erosion mechanism is predominating. Consequently, tablets were dissolved very fast (100% before 45 min). These polymers and fractions show a wide range of viscosities as indicated in Fig. 4, reflecting molecular weight which causes differences in their swelling and erosion behaviours. These results agree with some results obtained by Sakar and Walker for HPMC polymer [28].

For native dextran, linear relationship was seen between mass polymer loss and initial dissolution time (i.e. mass polymer loss $= 0.3441t + 5.6634$, $r^2 = 0.9902$ for DTB110-1-2 and $= 0.1456t + 3.0507$, $r^2 = 0.9998$ for DT B512-F). Native dextrans also show the highest maximum dissolution medium uptake. Here, increment of molecular weight of dextran becomes in increment of water uptake (native polymer with 10 times more than fractions **F1**, 13 times more than **F2** and 15 times more than **F3** for the first 30 min) and less erosion. Anywhere the rate of water uptake per unit weight of polymer started to decline with last initial time and in consequence for longer periods of time non-linear dependence could be expected. Applying Davidson and Peppas model Eq. (3) values of $n = 0.356$ ($r^2 = 0.998$) for native dextran B512-F and $n = 0.353$ for B110-1-2 were obtained ($r^2 = 0.984$). They indicate that

Table 4
Water uptake and mass polymer loss from dextran tablets (applied force: 14 kN)

	Hardness	Mass polymer loss (%)			
		15 min	30 min	60 min	90 min
DT B110-1-2	431 N	11.48 ± 2	14.59 ± 4	27.47 ± 3	36.22 ± 7
DT B512-F	482 N	5.29 ± 3	7.33 ± 4	11.83 ± 6	16.15 ± 2
F1	431 N	52.89 ± 3	87.38 ± 2	–	–
F2	420 N	62.79 ± 5	89.21 ± 1	–	–
F3	460 N	66.30 ± 5	95.85 ± 6	–	–
	% Water uptake				
	15 min		30 min	60 min	90 min
DT B110-1-2	59.80 ± 2		84.68 ± 4	103.73 ± 2	117.15 ± 4
DT B512-F	110.03 ± 4		142.94 ± 5	178.50 ± 4	210.02 ± 3
F1	31.61 ± 5		33.14 ± 3	–	–
F2	17.61 ± 6		26.89 ± 6	–	–
F3	16.82 ± 5		17.65 ± 7	–	–

water penetration mechanism is the same for two polymers, but water penetration for B512-F is two times faster ($K_s = 42.15$ and $K_s = 24.25$, respectively). An inverse relationship between erosion rate constant and molecular weight was reported by Reynolds et al. [29]. Tahara et al. [8] reported that the lower viscosity HPMC (50 cps) polymer eroded faster than the 4000 cps polymer, consistent with the current work. Thus, the higher molecular weight of native dextran polymers has higher intrinsic water holding capacity and the matrices formed from such polymers are less prone to erosion than fewer molecular weight fractions.

Wan et al. [30] showed that the normalized increase in matrix thickness after 30 min of swelling for HPMC matrix tablets was higher for higher molecular weight HPMC grades. They attributed this to the larger hydrodynamic volume occupied by higher molecular weight chains when hydrated. As the polymer chains become more hydrated and the gel becomes more diluted, the 'disentanglement concentration' may be reached, that is, the critical polymer concentration below which the polymer chains disentangle and detach from a gelled matrix. The polymer will then undergo simultaneous swelling, dissolution and diffuse into the bulk medium resulting in erosion of the polymer [31]. However, in our case more experimental data and longer period of time are necessary, particularly to evaluate the effect of hydrodynamics on the native dextran erosion process and to determine the polymer concentrations at the wet weight peak, called the 'experimental disentanglement concentrations' [31]. Since at the point a drop in the water uptake per unit weight of polymer decline from the start and in consequence for longer periods of time non-linear dependence could be expected.

3.7. Studies of mechanism of LBZ and PPL release from dextran tablets

Soluble drugs are considered to be released by diffusion through the matrix and poorly soluble drugs released by erosion of the matrix [9]. Moreover, it is considered that factors affecting swelling and erosion of these polymers may account for differences between in vitro dissolution results and subsequent in vivo performance, when hydrophilic matrix tablets are compared [32].

Lobenzarit disodium (LBZ) is a drug conceived for the treatment of rheumatoid arthritis. This drug produces an improvement of immunologic abnormalities and has a regulatory effect upon the antibody producing system. Propranolol hydrochloride (PPL) is a β-adrenergic blocking agent, i.e. a competitive inhibitor of the effects of catecholamines at β-adrenergic receptor sites. It is widely used in therapeutics for its antihypertensive, antiangorous and antiarrhythmic properties. These two drugs are suitable candidates for the design of controlled release delivery systems [5,33]. According to their solubility in water they can be considered as soluble (PPL) and sparingly soluble (LBZ) drugs.

Fig. 5 shows dissolution profiles for tablets of PPL or LBZ with DTB110-1-2, respectively (1:1, w/w). The value for relative standard deviation (CV) was lower 5% for all points measured ($n = 12$).

The Higuchi's and Hixson Crowell model as well as the non-linear regression of Peppas and Peppas-Sahlin were employed to study the released data. The results obtained are shown in Table 5. As it can be observed in this table, the Higuchi's slope (3.179 and 4.500% $min^{-1/2}$ for LBZ and PPL, respectively), Korsmeyer's rate constant (1.195% $min^{-0.697}$ and 4.125% $min^{-0.540}$ for LBZ and PPL, respectively), the low relaxational constant $K_r = 0.101$ (% $min^{-0.898}$) for LBL and $K_r = -0.040$ (% $min^{-0.898}$) for PPL, compared with K_d values (2.941 (% $min^{-0.449}$) and 6.518 (% $min^{-0.449}$), respectively) of Peppas-Sahlin, indicated diffusional mechanism as predominant for soluble drugs from native dextran tablets. The influence of solubility of drug can be observed for hydrophilic matrix (release of PPL is faster than LBZ in correspondence with its solubility in water). Values of diffusional exponent 0.697 (Korsmeyer equation) for sparingly soluble drug correspond to increment of influence of erosion mechanism and this well agrees with other authors

Table 5
Parameters and correlation coefficient obtained from kinetic equations for the matrix tablets prepared with dextran B110-1-2/LBD and dextran B110-1-2/PPL

	Higuchi		Hixson Crowell		Korsmeyer			Peppas y Salhin		
	k_1	r^2	k_2	r^2	k_3	n	r^2	K_d	K_r	r^2
B110-1-2 /LBZ	3.179	0.981	0.012	0.615	1.195	0.697	0.999	2.941	0.101	0.999
B110-1-2 / PPL	4.500	0.986	0.013	0.545	4.125	0.540	0.999	6.518	−0.040*	0.999

r^2 coefficients of correlation for each model, k_1 (% $min^{-1/2}$), Higuchi's slope; k_2, Hixson Crowell constant; k_3, kinetics constant of the Korsmeyer model; n, diffusional exponent; K_d (% min^{-m}), diffusional constant of Peppas and Sahlin model; K_r (% min^{-2m}), relaxational constant of Peppas and Sahlin model; m is the diffusional exponent, that depends on geometric shape of the releasing device through its aspect ratio.

* The negative values obtained for K_r in lot 2 should be interpreted in terms of a relaxation mechanism insignificant compared to the diffusion process.

[8,34]. This can also be observed in Peppas y Salhin equation where the negative value obtained for K_r for dissolution profile of PPL from dextran tablets should be interpreted in terms of a relaxation mechanism insignificant compared to the diffusion process.

The results obtained from the mathematical methods described in this paper as with all empirical models should be viewed with caution. Models such as Higuchi, Hixson Crowell, Peppas, Korsmeyer, Langer, Heller and others have been used several times, but as ''Empiric methods'' have also some limitations and should be considered together with additional evidence based on direct measurements such as swelling, erosion and textural changes with time.

The dissolution profiles for LBZ:B110-1-2 and PPL:B110-1-2 tablets were also compared using similarity factor f_2. The value obtained $f_2 < 50$ (37.48) indicates the influence of solubility of drug in dissolution profile. Furthermore, other parameters, such as the dextran: drug ratio, particle size of polymer and drug, influence of pH, have to be studied to obtain an optimum and robust formulation.

The mechanisms of drug release from dextran matrix occur in the early stage by polymer swelling, and the tablet thickness increases. Soon, thereafter, the polymer (and drug) dissolution starts occurring. The polymer dissolves because of chain disentanglement. Thus, there is a slow diminution of the thickness because of erosion and eventually, the tablet disappears (time > 480 min).

4. Conclusions

Dextran B110-1-2 is similar to commercial grade Dextran B512-F. The molecular weight of dextrans and its fractions can be established by the analysis of intrinsic viscosity of different aqueous solutions of dextrans. The critical overlap concentration of approximately 9 g/L was obtained for native polymer. The molecular weight of dextran has a high influence on specific viscosity of aqueous solution. Therefore, the results obtained from the study of the release profiles of lobenzarit disodium and propranolol hydrochloride, as well as the release mechanism, indicated that dextran B110-1-2 is a good candidate as new functional excipient in future pharmaceutical developments, suitable for sustained release solid dosage form formulation because this polymer with a $M_w \geqslant 2000000$ (such as native dextran B512-F) swells considerably in contact with an aqueous liquid and forms a gel layer which spreads the whole tablet, controlling the drug release rate. At the same time, fractions of dextran with molecular weight between 43000 and 170000 (**F1**, **F2** and **F3)** seem to be suitable for immediate release.

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