Thermally-induced dielectric relaxation spectra in three aldohexose monosaccharides

Libby Yoerg · M. Ellen Matthews · Lakshmi Kaza · Naullage Indika Perera · David W. Ball · John Moran · Alan T. Riga

Abstract Three aldohexose monosaccharides, D-glucose, D-mannose, and D-galactose, were examined by scanning temperature dielectric analysis (DEA) from ambient temperatures through their melts. Phase transitions, including glass transition (T_g) and melting temperature (T_m), were evaluated by differential scanning calorimetry (DSC). The monosaccharides were found to exhibit thermally-induced dielectric loss spectra in their amorphous-solid phase before melting. Activation energies for electrical charging of each of the monosaccharides were calculated from an Arrhenius plot of the tan delta (e''/e', dielectric loss factor/relative permittivity) peak frequency versus reciprocal temperature in Kelvin. The DEA profiles were also correlated with the DSC phase diagrams, showing the changes in electrical behavior associated with solid–solid and solid–liquid transitions.

Keywords DEA · Dielectric analysis DSC · Differential scanning calorimetry · Monosaccharides · Activation energy · Transition temperatures

L. Yoerg · L. Kaza · N. I. Perera · D. W. Ball · A. T. Riga (✉)
Department of Chemistry, College of Science and Health Professions, Cleveland State University, Cleveland, OH 44115, USA
e-mail: alanriga@hotmail.com

M. E. Matthews
Buckeye Pharmaceuticals, 23715 Mercantile Road, Beachwood, OH 44122, USA

J. Moran · A. T. Riga
Department of Chemistry, Notre Dame College, South Euclid, OH 44121, USA

Introduction

Monosaccharides are the most basic units of biologically important carbohydrates. They are usually the simplest structures of sugar and are typically colorless, water-soluble, and crystalline solids. Some monosaccharides have a sweet taste, including glucose, fructose, levulose, galactose, ribose, and xylose. Monosaccharides are the building blocks of disaccharides such as sucrose and polysaccharides such as cellulose and starch. Further, each monosaccharide contains carbon atoms that support hydroxyl groups and are chiral, giving rise to a number of isomeric forms with the same chemical formula. For instance, galactose and glucose are both aldohexoses, but have different chemical and physical properties.

Monosaccharides have the chemical formula $C_x(H_2O)_y$ with the chemical structure $H(CHOH)_nC=O(CHOH)_mH$. If n or m is zero, the monosaccharide is an aldehyde and is termed an aldose; otherwise, it is a ketone and is termed a ketose. Monosaccharides contain either a ketone or aldehyde functional group, as well as hydroxyl groups on most or all of the non-carbonyl carbon atoms [1].

A hexose is a monosaccharide with six carbon atoms, having the chemical formula $C_6H_{12}O_6$. The aldehyde functional group in these carbohydrates reacts with neighboring hydroxyl functional groups to form intramolecular hemiacetals. Hexose sugars can form dihexose sugars with a condensation reaction to form a 1,6-glycosidic bond.

The focus of this study is to differentiate the amorphous and crystalline content of three monosaccharides using thermal analytical methods. Amorphous materials are of increasing interest in pharmaceutical development because they have more bioavailability and increased dissolution properties, which can increase clinical efficacy of existing

and developing drugs. There are two forms of solids: amorphous (glassy, with no apparent ordered structure) and crystalline (an ordered structure). With reference to a crystalline solid, an amorphous solid can be defined as a substance with short-range molecular order and no well-defined molecular conformation. This relatively disorganized molecular structure creates the enhanced bioavailability in pharmaceutical materials; however, amorphous materials are also less stable due to their lack of molecular order. In contrast, a crystalline solid has a long-range translational orientation symmetry and molecular packing order. Many crystalline solids in pharmaceutical development are found to be inadequately soluble for clinical application; however, crystalline solids are typically more stable than their amorphous counterparts.

The significance of amorphous solids to formulation scientists is presently ever-increasing due to their advantages in solubility, bioavailability, and ease of processing, and in carbohydrate research specifically, the amorphous form of a hexose solid has been an important aspect of sugar characterization, including in the following studies. Thermal analytical methods have been applied to starches and their derivatives to investigate thermal stability and decomposition [2]; the organic content of rice husks [3]; and the relationships between glass transition, water plasticization, and relaxation times as related to food quality [4–6]. Sugars in the crystalline form tend to melt and decompose [7], while sugars in the amorphous form have glass transitions and no defined melt. Differential scanning calorimetry (DSC) reveals phase transitions, including melting point (for crystalline materials) and glass transition (for amorphous materials). Dielectric analysis (DEA) reveals increasing amorphicity and molecular rearrangement depicted by the increased organization of the dielectric relaxation spectra during subsequent heating–cooling cycles (runs).

The molecular structures of mannose, glucose, and galactose, the three monosaccharides evaluated in this study, are shown in Fig. 1 below. Epimers differ in the configuration around a single carbon in their structure. D-mannose and D-galactose are epimers of D-glucose. Monosaccharides have been shown to undergo dielectric relaxation, and Kaminski et al. [8] have suggested the characteristics of the relaxation spectra is related to the biological roles of monosaccharides, particularly in building DNA and RNA chains. The relative strength of primary (α) and secondary (β) relaxations distinguished 2-deoxy-D-ribose and D-ribose from other monosaccharides, and the secondary reactions distinguished the two closely related monosaccharides from each other. These differences were related to the chemical and biological functions of 2-deoxy-D-ribose and D-ribose as building blocks of DNA and RNA chains.
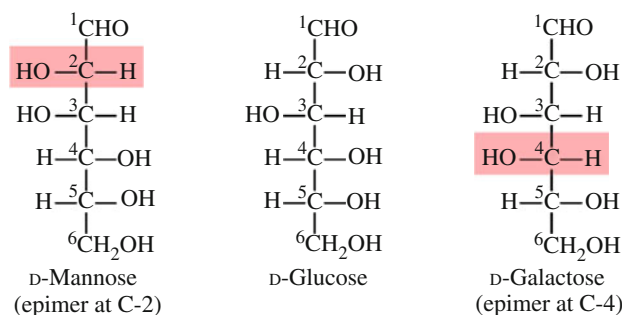

Fig. 1 Molecular structures of D-mannose and D-galactose are epimers of D-glucose

Methods

A TAI 2970 DEA was used to determine the electrical conductivity and tan delta curve (log tan delta vs. log frequency) for each carbohydrate studied. For each solid powdered carbohydrate, a sample of approximately 20 mg was placed on a single surface gold ceramic interdigitated sensor. The samples were linearly heated at a rate of 10 °C min^{-1} in a purged nitrogen flow at 60 mL min^{-1} from room temperature to 30 °C above the melting temperature of the hexoses. The samples were heated, using the above heating procedure, and air cooled for three sequential runs, labeled the First Run, Second Run, and Third Run. The gold ceramic interdigitated sensors were calibrated by the instrument and were used to evaluate the electrical properties of the hexoses. The conductivity measurements were recorded at controlled interval frequencies ranging from 0.10 to 10,000 Hz in logarithmic intervals for all the temperatures.

A TAI 2920 DSC was used to profile the carbohydrate phase transitions, melting, and glass transition temperature (T_g) of the sugars. A heating rate of 10 °C min^{-1} was applied to all the samples. A purge gas of nitrogen was flowed at the rate of 60 mL min^{-1} during heating and cooling cycles. The empty DSC aluminum pan weighed 13–14 mg. Samples in the range of 8–10 mg were weighed using the Mettler AT261 Delta Range® microbalance and loaded into a closed aluminum crimped pan. The temperature range was typically from room temperature to 30 °C above the peak melting temperature (T_m) for the sugars under study; glass transition (T_g) was also evaluated. Heat flow (W g^{-1}) values versus temperature and time were generated using the Universal Analysis 2000 (TA Thermal Advantage) software. Heat flow (heat of fusion) and temperature were calibrated by comparison to the Indium melt endotherm.

Results and discussion

Tan delta curves for D-glucose revealed no dielectric loss spectrum in the first run of the crystalline solid (Fig. 2).

Tan delta peaks are related to charge mobility and represents relaxation of the material as a function of frequency and the strength of the applied electric field (10 V mm^{-1}). The second and third runs revealed dielectric loss spectra, onset ca. 90 °C, with sharp, uneven peaks in the second run and diffuse evenly spaced peaks in the third run (Figs. 3 and 4).

Tan delta curves for D-galactose revealed a weak spectrum in the first run of the crystalline solid, onset ca. 145 °C (Fig. 5). The second and third runs revealed strong spectra, onset ca. 80 °C (Figs. 6 and 7).

Tan delta curves for D-mannose resembled those of D-galactose, revealing a weak spectrum in the first run of the crystalline solid onset ca. 145 °C (Fig. 8) and strong spectra onset ca. 90 °C in the second and third runs (Figs. 9 and 10).

Activation energies for electrical charging of each of the monosaccharides undergoing molecular rearrangement indicated by the dielectric loss spectra were calculated from an Arrhenius plot of peak frequency versus reciprocal temperature.

The Arrhenius plot for D-galactose (Fig. 11) shows that the slope decreases with each run. The slope of the first run curve differs significantly when compared to the curves of the second and third runs. D-glucose and D-mannose share these characteristics.

Table 1 contains the calculated activation energies (E_a) for each sample at each run.

The DEA profiles were also correlated with the DSC phase diagrams (a first run and second run), showing the changes in electrical behavior associated with solid–solid and solid–liquid transitions. Figure 12 shows D-glucose with first run peak T_m at 163 °C and second run T_g (I) at 48 °C. The absence of the melting peak in the second run indicates an amorphous material undergoing a glass

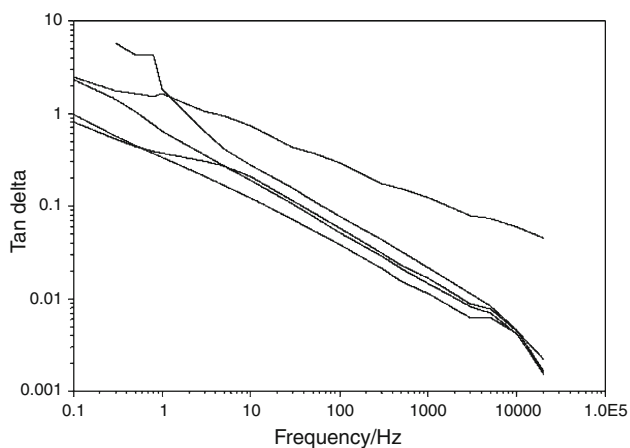**Fig. 3** D-Glucose: 2nd run tan delta curve
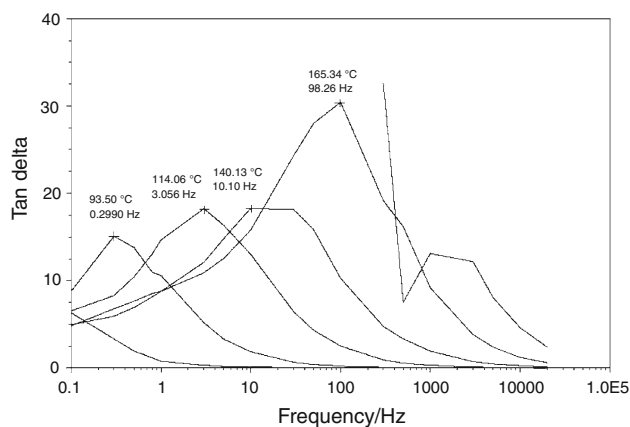

Fig. 4 D-Glucose: 3rd run tan delta curve
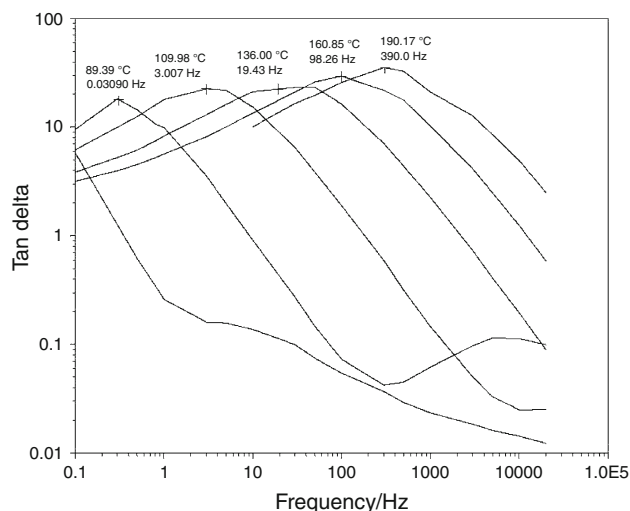

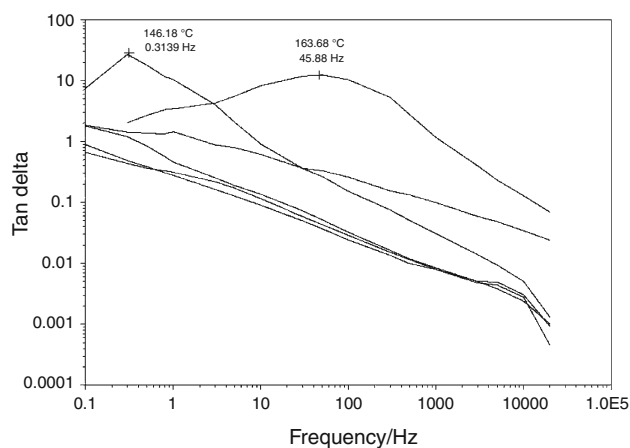**Fig. 2** D-Glucose: 1st run tan delta curve

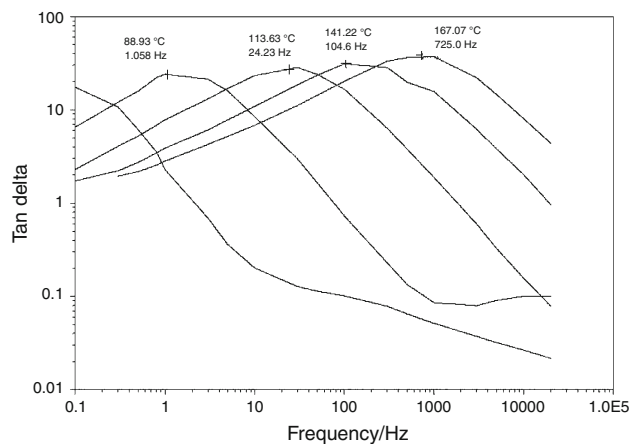**Fig. 5** D-Galactose: 1st run tan delta curve

Fig. 6 D-Galactose: 2nd run tan delta curve
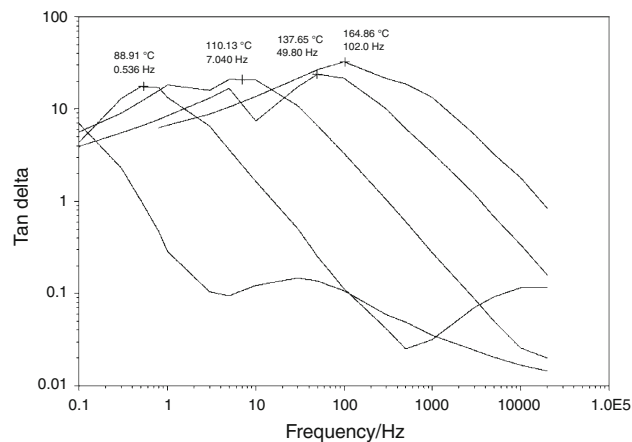

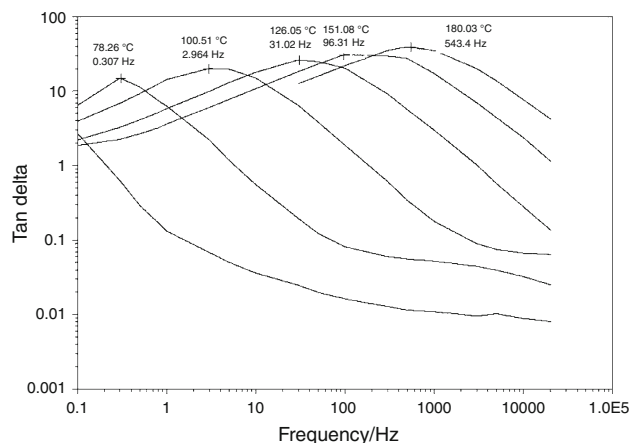**Fig. 9** D-Mannose: 2nd run tan delta curve

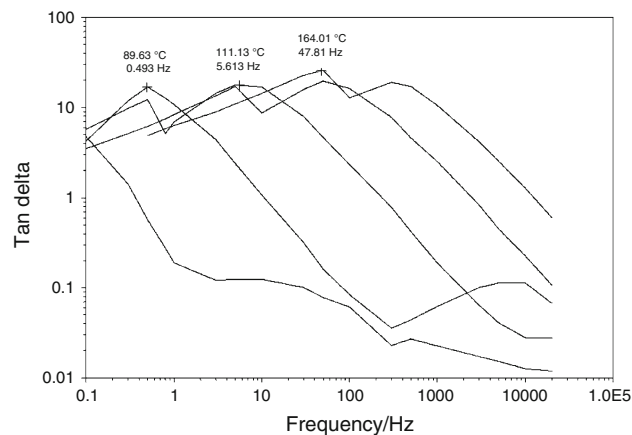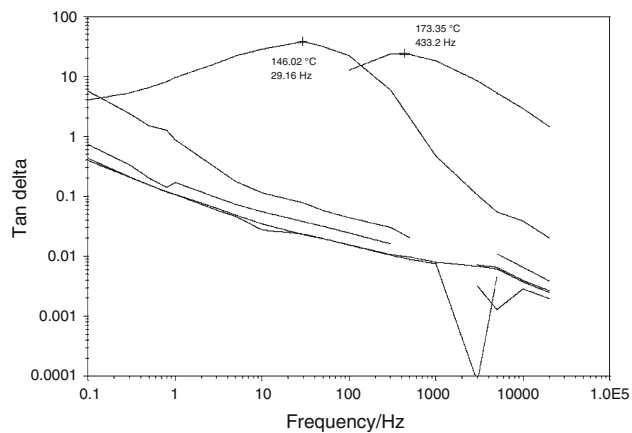**Fig. 7** D-Galactose: 3rd run tan delta curve

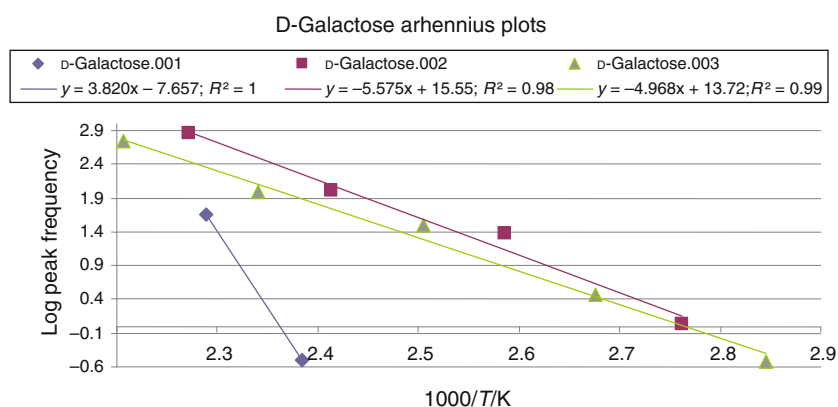**Fig. 10** D-Mannose: 3rd run tan delta curve

**Fig. 8** D-Mannose: 1st run tan delta curve

transition. The DEA curves show conductivity increasing with temperature in the second and third runs.

Figure 13 shows D-galactose with first run peak T_m at 171 °C and second run T_g (I) at 49 °C. Again, the absence of the melt in the second run indicates an amorphous material undergoing a glass transition. The DEA curves show a sharp increase in conductivity leading up to the melting peak in the first run and an increase in conductivity with temperature in the second and third runs.

Figure 14 shows D-mannose with first run peak T_m at 137 °C and second run T_g (I) at 63 °C. Again, the absence of the melting peak in the second run indicates an amorphous material undergoing a glass transition. The DEA curves show a sharp increase in conductivity leading up to

Fig. 11 D-Galactose: Arrhenius plots

D-Galactose arhennius plots

- ◆ D-Galactose.001
- ■ D-Galactose.002
- ▲ D-Galactose.003
- $y = 3.820x - 7.657; R^2 = 1$
- $y = -5.575x + 15.55; R^2 = 0.98$
- $y = -4.968x + 13.72; R^2 = 0.99$

Log peak frequency vs 1000/T/K

Table 1 Activation energies

Sample name	Run		
Activation energies (J mol^{-1})			
	1st	2nd	3rd
D-Glucose	–	103	96
D-Galactose	435	107	95
D-Mannose	154	92	78
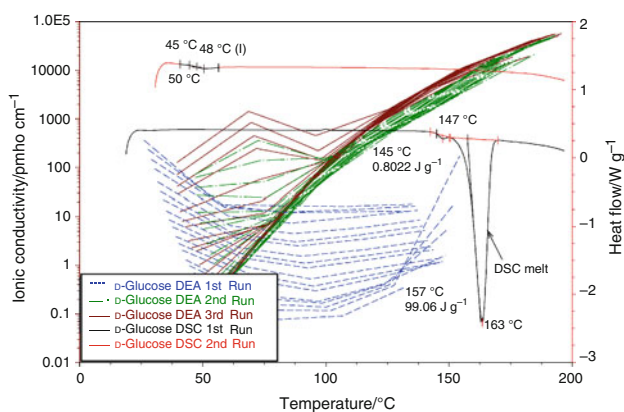
Fig. 12 Phase diagram and conductivity: D-glucose
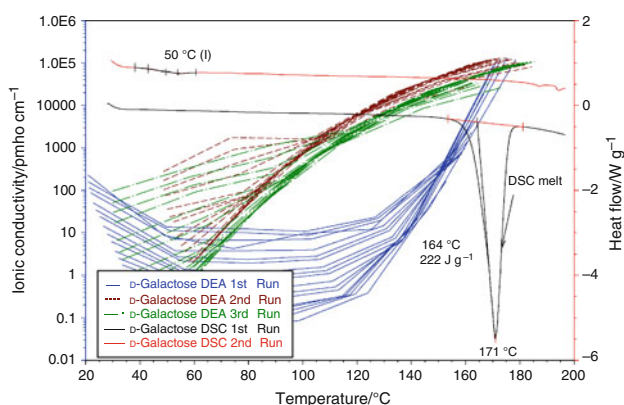
Fig. 13 Phase diagram and conductivity: D-galactose
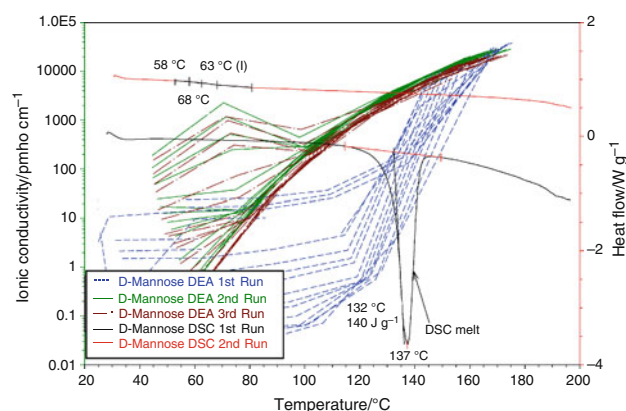
Fig. 14 Phase diagram and conductivity: D-mannose

the melting peak in the first run and an increase in conductivity with temperature in the second and third runs.

Conclusions

The monosaccharides were found to exhibit thermally-induced dielectric loss spectra in their amorphous-solid phase before melting. The samples become increasingly amorphous with each heating and cooling, indicated by the first and second run DSC curves; the first, second, and third run DEA curves; and the decreasing activation energies for each run. The weak spectra in the first runs of D-galactose and D-mannose may indicate a small amount of amorphous material in the crystalline solid forms of these sugars. Activation energies (E_a) show that the energy required to initiate charge mobility and molecular rearrangement, indicated by the dielectric loss spectra, appears within the amorphous state second and third runs.

References

1. Morrison RT, Boyd RN. Organic chemistry. 2nd ed. Boston: Allyn and Bacon; 1966. p. 167–9.
2. Capek P, Drabik M, Turjan J. Characterization of starch and its mono and hybrid derivatives by thermal analysis and FT-IR spectroscopy. J Therm Anal Calorim. 2010;99:667–73.
3. Genieva SD, Turmanova SCh, Dimitrova AS, Vlaev LT. Characterization of rice husks and the products of its thermal degradation in air or nitrogen atmosphere. J Therm Anal Calorim. 2008;93:387–96.
4. Roos YH. Thermal analysis, state transitions and food quality. J Therm Anal Calorim. 2003;71:197–203.
5. Roos YH. Glass transition temperature and its relevance in food processing. Annu Rev Food Sci Technol. 2010;1:469–96.
6. Seo J, Oh J, Kim HK, Hwang Y, Yang YS, Kim SJ. Study of glass transition temperatures in sugar mixtures. J Korean Phys Soc. 2005;46(3):606–9.
7. Hurtta M, Pitkänen I, Knuutinen J. Melting behavior of D-sucrose, D-glucose and D-fructose. Carbohydr Res. 2004;339:2267–73.
8. Kaminski K, Kaminska E, Wlodarczyk P, Paluch M, Ziolo J, Ngai KL. Dielectric relaxation study of the dynamics of monosaccharides: D-ribose and 2-deoxy-D-ribose. J Phys Condens Matter. 2008;20:355104–12.