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Nucleation phenomena in amorphous sucrose systems

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Summary

This study investigated the phase transformation of amorphous to crystalline sucrose. Particular attention was paid to the nucleation phenomenon, and a method was developed to isolate nucleation kinetics from crystallization kinetics. Using this method and a simple mathematical model, various nucleation parameters could be determined. Additionally, the effects that additives, temperature, and relative humidity have on the inhibition or acceleration of nucleation were examined and are reported.

Introduction

Some manufacturing techniques used in the production of certain pharmaceuticals and foods may produce organic compounds which are in the amorphous solid state (White and Cakebread, 1966; Pikal et al., 1978). Many organic substances, including alcohols, fats, protein solutions, carbohydrates, and simple sugars can be prepared in the amorphous state (White and Cakebread, 1966). Because the amorphous state is metastable with respect to the crystalline state, phase transformations are likely to occur. These transformations may produce quality defects or loss of potency in the product. A system at a specified temperature is in a metastable state if all small isothermal changes of its independent thermodynamic variables bring about an increase in free energy, while large isothermal changes in these variables can result in a state with lower free energy. An amorphous material, in crystallizing, must go through intermediate states which may be thought of as free energy barriers which can impede or prevent the transformation of the metastable state into the stable state (Kauzmann, 1948).

The crystallization of an amorphous material (or glass) depends on two steps (Tamman, 1926): First, nucleation must occur, and then the nuclei must grow. If nucleation can be inhibited by the addition of small amounts of additives, then the stability of the amorphous material may be increased. Amorphous sucrose has been studied by both the pharmaceutical and food sciences (Makower and Dye, 1956; Iglesias and Chirife, 1978; Herrington and Branfield, 1984a,b; Ritchie and Winfield, 1984). The emphasis in these studies has been on crystallization rather than nucleation. Since the nucleation event must occur before a phase transformation can happen, preventing or

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retarding nucleation is the logical place to start in attempting to stabilize an amorphous system. Due to the economic importance of sucrose, a great deal is known about its physical chemistry in the solid crystalline state and in solution. Little is known about the non-crystalline solid state. Therefore, it is an ideal model compound for the study of nucleation from the amorphous or glassy state.

The present study is an investigation of nucleation behavior of amorphous sucrose systems, in pure form and in the presence of small amounts ($\leq 5\%$) of various additives. Sucrose may be difficult to prepare reproducibly in an amorphous state by either melting or spray drying. A new method of preparing lyophilized amorphous sucrose in the form of macroscopic spheres was devised, which allowed nucleation to be studied over a wide range of conditions. The effects of additives, temperature, and relative humidity on nucleation and nucleation rates were determined. A model was developed to explain the experimental results.

Materials and Methods

Reagents

All solutions were prepared in triple distilled water. Sucrose, glucose, fructose (analytical grade), raffinose and dextrin were obtained from the Aldrich (Milwaukee, WI). Corn starch and lactose monohydrate were obtained from Mallinckrodt (Paris, KY). Gelatin (USP grade) was obtained from J.T. Baker (Phillipsburg, NJ). Acacia (USP grade), corn syrup (42 D.E.), and titanium dioxide suspension were gifts from M&M Mars (Hackettstown, NJ). Microcrystalline cellulose-carboxymethylcellulose (Avicel® RC-581) was a gift from FMC Corp. (Philadelphia, PA).

Apparatus

Lyophilization was carried out in a laboratory scale freeze dryer with a programmable controlled temperature shelf (Virtis, Gardiner, NY) The shelf temperature could be controlled from -46 to $+60\,^{\circ}C$ ($\pm 1\,^{\circ}C$). The freeze dryer was modifed by the addition of a liquid nitrogen trap to prevent contamination by vacuum pump oil and to improve the vacuum. A tank of nitrogen gas was equipped with a calcium sulfate drying cylinder (Drierite®, Hammond, IN) and connected to the freeze drying chamber. This allowed the freeze dryer to be filled with dry nitrogen when the vacuum was broken.

Electron micrographs were taken with a JSM-35C scanning electron microscope (Jeol, Tokyo). X-ray analysis was performed on a scanning X-ray powder diffractometer with a copper Kα filter at a wavelength of 1.5418 Å (Phillips Analytical, Eindhoven, The Netherlands). The polarized light microscope used was by Nikon (Tokyo). Differential scanning calorimetry was carried out on a DSC-4 differential scanning calorimetry system (Perkin-Elmer, Norwalk, CT). Surface area analysis was performed on a Quantasorb® sorption system (Quantachrome, Syosset, NY).

Procedures

Lyophilization specimens were prepared by dissolving sucrose alone or with the desired additive(s) in water to produce a 10% (w/v) solution or suspension. The additive content of the solutions and suspensions was 0, 0.5, 1, 2, 3, or 5% per g of total solid, with sucrose being used to give 100% total. The solutions which did not contain insoluble material were filtered through a 0.2 μm membrane filter to remove contaminating solid particles. The filters were weighed to ensure that a significant amount of material was not being adsorbed or trapped in the pores. The sucrose solutions or suspensions were placed in a buret and slowly added dropwise to a large container of liquid nitrogen. The drops assumed a spherical shape, quickly froze, and sank to the bottom of the container. After adding 10.00 ml of liquid dropwise to the liquid nitrogen, the frozen spheres were removed and placed in 10.0 cm diameter plastic dishes which had previously been weighed. The dishes and spheres were placed on the shelf in the freeze dryer ($-46\,^{\circ}C$) and were lyophilized at $-46\,^{\circ}C$ for 48 h, at $-34\,^{\circ}C$ for 24 h, at $0\,^{\circ}C$ for 12 h, and at $25\,^{\circ}C$ for 24 h.

After the lyophilization cycle was completed, the dishes and spheres were immediately weighed. The spheres were then placed in tightly sealed

desiccators over saturated salt solutions to provide a constant relative humidity. Since it is known that the time required to reach an equilibrium relative humidity (R.H.) inside a desiccator may be on the order of hours to days, the following procedure was used to ensure that the proper relative humidities were quickly reached inside the desiccators. Dry air was bubbled through a jar containing a saturated salt solution of the same composition as that of the solution in the desiccator. This humidified air was blown into a small plastic glovebag (Aldrich) which contained the desiccator and a small hygrometer (Abbe, F.R.G.). First, the bag would be flattened to remove as much of the ambient atmosphere as possible. Then the bag would be inflated with the humidified air with the desiccators' tops removed. When the hygrometer showed that the R.H. inside the glove bag was within 2% of the desired value, the desiccators would be sealed. The desiccators were stored in a constant temperature incubator which could be adjusted from -10 to $60\,^{\circ}C$ ($\pm 0.5\,^{\circ}C$). The dishes and spheres were periodically removed and weighed to determine their moisture uptake kinetics. In addition, samples were routinely subjected to X-ray diffraction, polarized light microscopy, and moisture content studies to determine the relative degree of crystallinity. Makower and Dye (1956) and Palmer et al. (1956) showed that moisture uptake kinetics were a valid means of studying the crystallization of amorphous sucrose. The present study demonstrates the utility of these kinds of techniques in isolating and investigating nucleation rates and the effects that temperature and relative humidity have on nucleation phenomena.

Results and Discussion

The lyophilized spheres had a diameter of 4.6 mm after freeze-drying. Surface area analysis by nitrogen adsorption showed that the surface area of the highly porous spheres was approx. 3.9 m^2/g. Fig. 1 shows a photomicrograph of a freshly lyophilized sphere prior to exposure to moisture.

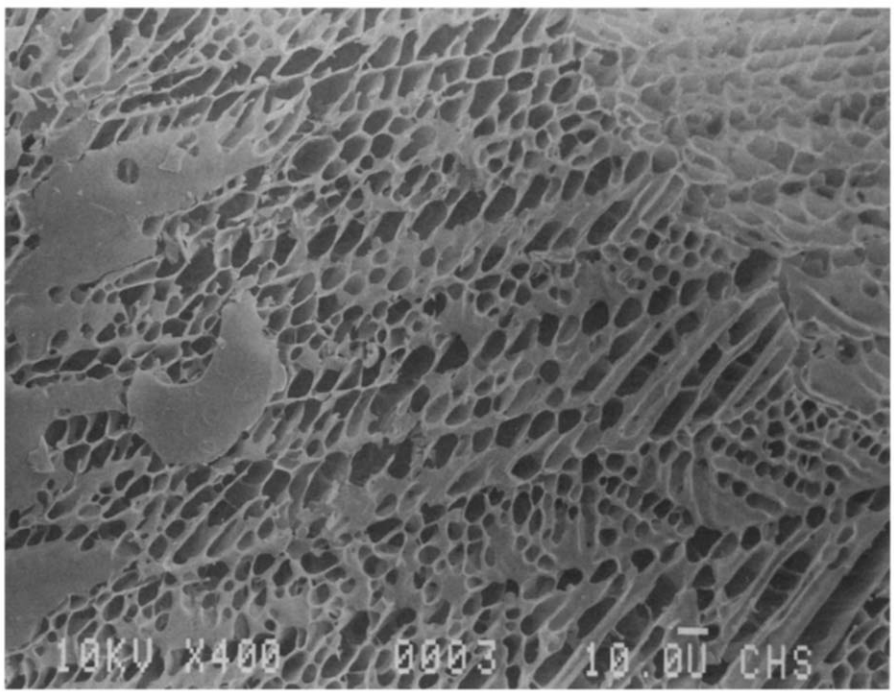

Fig. 1. Electron micrograph (400 × magnification) of lyophilized amorphous sucrose sphere prior to exposure to moisture.

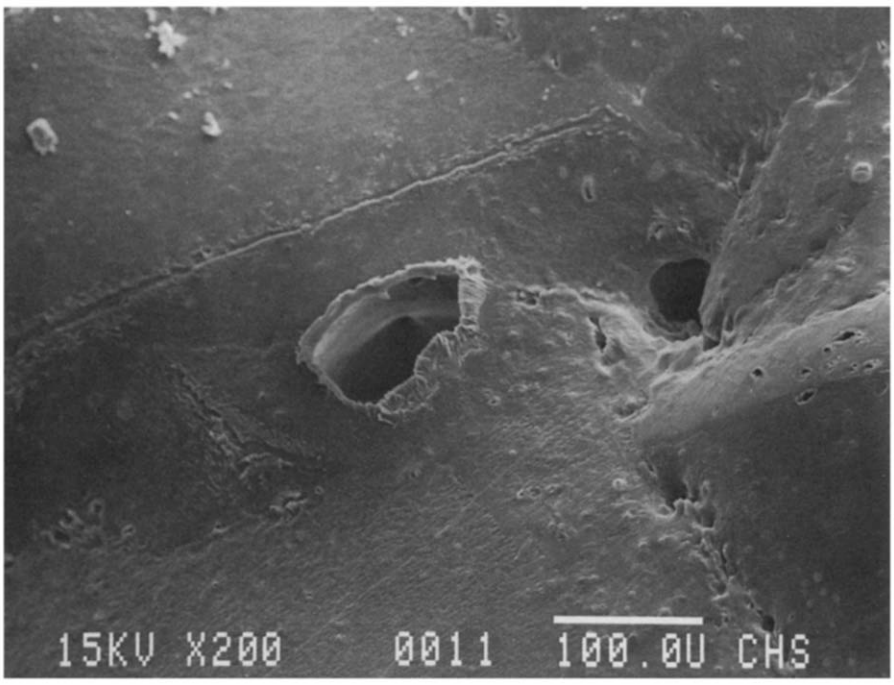

Fig. 2. Electron micrograph (200 × magnification) of crystallized sucrose sphere after exposure to 33% R.H. at 25 ° C.

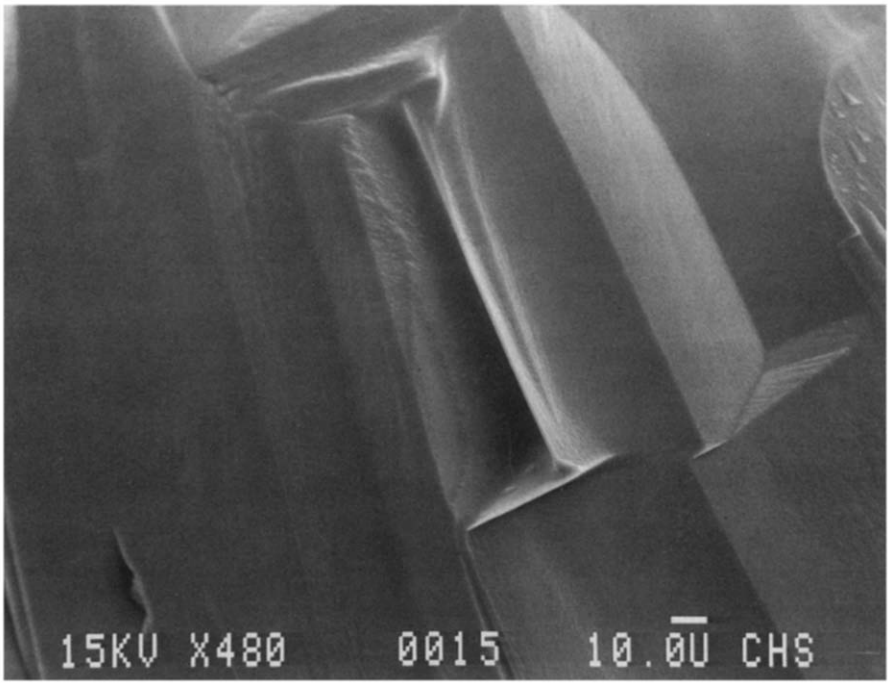

Fig. 3. Electron micrograph (480 × magnification) of crystallized sucrose sphere after exposure to 54% R.H. at 25 ° C.

The high degree of porosity and lack of crystalline morphology are apparent. The absence of crystallinity was confirmed by X-ray diffraction experiments. Freshly lyophilized material exhibited no sharp peaks,only a very slight, diffuse broad hump. As little as 5% of crystalline material added to the lyophilized powder with mixing showed sharp, albeit small, peaks. Similarly, the lyophilized material did not demonstrate detectable birefringence under the polarized light microscope, but after spiking with 5% crystalline material birefringence could be seen.

After the spheres were exposed to 33% R.H. at 25°C, they shrank rapidly and coalesced into hard, glassy sphere-shaped particles which had an average diameter of 2.0 mm. At this point in time there were still no crystalline peaks visible from the X-ray diffraction experiments. The weight gain observed in these particles due to adsorbed moisture depended on the temperature and relative humidity to which the spheres were exposed.

Fig. 2 is a micrograph of a sphere after exposure to 33% R.H. at 25°C for 10 days. At the time this micrograph was taken, the sphere had completely crystallized, as shown by X-ray diffraction. Although the material was crystalline (as confirmed by X-ray diffraction and moisture content studies), there was a lack of obvious crystal morphology, such as planar faces and sharp, well-defined edges. Additionally, disturbances in the surface which appeared to be 'eruptions' were present. These eruptions were probably caused by the release of water from the interior of the rapidly crystallizing sucrose sphere, and once formed did not disappear.

Fig. 3 shows the surface of a sphere which had been exposed to 53% R.H. at 25°C for 3 days. These spheres had shown a much higher amount of moisture uptake (with a subsequent proportional moisture loss) than the spheres subjected to the lower relative humidity. Typical crystalline features may now be seen. These two micrographs show the differences in appearance which occur at different relative humidities and different degrees of moisture uptake. At a higher moisture content, the decreased viscosity of the supersaturated sucrose solution or glass allows the growth of crystal faces which are not seen at the lower relative humidity, even though the material is fully crystalline on a molecular level. In contrast with the spheres exposed to 33% R.H., there were no eruptions or other defects seen in the surface of these particles. It may be assumed that since these spheres adsorbed sufficient moisture to form supersaturated liquid droplets, the moisture released from the crystallizing sucrose was able to diffuse into the atmosphere without the hindrance of any solid material in its path.

Moisture uptake studies

Each dish contained approx. 200 spheres of amorphous material. Each concentration of additive was studied in triplicate. In each additive study, three dishes of pure amorphous sucrose spheres were used as controls, or internal standards, to provide a measure of the effect of the additive on inhibition of nucleation, and to serve as a general check of the reproducibility of the experiments. X-ray diffraction was performed to demonstrate the absence or presence of crystalline material.

Fig. 4 shows a representative moisture uptake curve, in this case of amorphous sucrose containing 0, 1, 3, or 5% gelatin at 25°C and 33% R.H. It can be seen that a significant difference exists in the amount of time it takes for moisture loss to begin depending on the gelatin content of the sample. This moisture loss is due to the crystallization of the amorphous sucrose following nuclea-

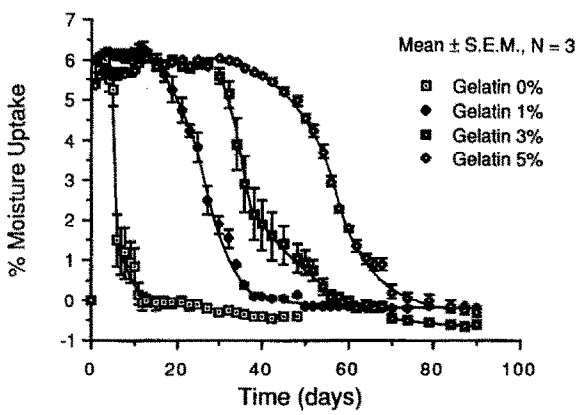

Fig. 4. Moisture uptake curves of amorphous sucrose with 0, 1, 3, or 5% gelatin.

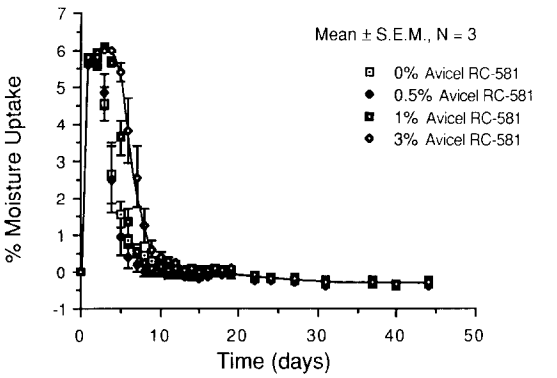

Fig. 5. Moisture uptake curves of amorphous sucrose with 0, 0.5, 1, or 3% Avicel RC-581.

tion, since crystalline sucrose is anhydrous at room temperature, below 80% R.H. (Karel, 1973). Additives which were shown to have a significant (i.e., they more than doubled the time necessary for the first nucleation event to occur) retarding effect on nucleation included gelatin, raffinose, corn syrup, dextrin, lactose, invert sugar, fructose, and various combinations of these compounds.

Fig. 5 shows the moisture uptake curves of sucrose containing 0, 0.5, 1.0, and 3% Avicel RC-581 at 25°C and 33% R.H. It can be seen that there is no significant difference in moisture uptake kinetics in this case, which means that microcrystalline cellulose was not an effective inhibitor of nucleation. Other additives which had little or no effect on delaying nucleation included acacia, acacia + corn syrup, and glucose.

The mechanisms responsible for inhibition of nucleation are thought to be either a mass transport step or an orientation and incorporation step (Van Hook and Frulla, 1952). The mass transport step (diffusion) will be influenced by materials which alter the ability of water to act as a solvent for sucrose. This would have an impact on the activity of the dissolved sucrose (its solubility) and on the diffusion of sucrose molecules through the medium. All of the substances shown to inhibit sucrose nucleation are hydrophilic molecules which would have a strong tendency to hydrogen bond with any available water, thus impeding the movement and collisions of sucrose molecules necessary to build up the critical nucleus. It is also known that some substances inhibit nucleation and crystallization by preventing the molecules of the crystallizing substance from approaching the growing nucleus or crystal lattice in the proper orientation (Smythe, 1967). Smythe showed that raffinose had a significant inhibitory effect on the growth rate of certain crystal faces of sucrose. Raffinose exerted this effect by taking the place of a sucrose molecules in the growing crystal lattice. The extra glucose group present in the raffinose interfered with the approach and incorporation of subsequent sucrose molecules. In the present study, it was found that 3% raffinose increased by a factor of 3.5 the length of time required for nucleation to occur in the amorphous sucrose spheres, and had a greater effect on inhibiting nucleation than glucose, fructose, gelatin, dextrin, corn syrup, or lactose. Since any one of these substances may increase the viscosity of the glassy sucrose systems by bonding interactions with water, it is interesting to note that raffinose is the only compound in the group which has been previously shown to interefere with nucleation and crystallization of sucrose by a surface incorporation effect.

Insoluble additives have been used as 'seeds' to promote nucleation in various crystallization operations. The solid surface is thought to act as a heterogeneity which decreases the free energy necessary for formation of critical nuclei. In this study, particulate additives did not have a significant effect in delaying nucleation, which is what one would expect. However, the insoluble additives did not accelerate nucleation either compared to the pure sucrose samples. This may be because the extremely high degree of supersaturation after moisture uptake at 33% R.H. results in such an unstable system that nucleation occurs regardless of the effects of a foreign solid surface.

Modeling of moisture uptake studies

The system used in this study consisted of approx. 200 spheres of amorphous sucrose, with or without additives. The spheres were of nearly identical size, which was insured by the fact that they were formed by slowly dropping from a buret tip. The spheres were placed in dishes which were large enough to allow the spheres to be separate

from one another after they had taken up moisture and shrunk. Even at high relative humidities (up to about 80%) when the spheres actually liquefy, they remain independent of one another. This is an important point, for it allows the spheres to be thought of as N independent entities. Upon taking up moisture, these identical spheres form highly supersaturated, homogeneous, solid (or liquid) metastable systems. At some point in time, nucleation will occur in each sphere or droplet.

In the present system, it was found that once nucleation occurred, crystallization was rapid. This was demonstrated by seeding the glassy sucrose solutions with small sucrose crystals. At 25 °C and 33% R.H., crystallization took place within 3–4 h after seeding. Since this represents only 13–17% of a typical observation period (24 h), crystallization was assumed to have occurred instantaneously for the purposes of this model. This seeding experiment was an independent way of showing that crystallization was rapid once the rate-limiting nucleation event (the seeding) had occurred. The loss of water from the 200 or so spheres in each plate is proportional to the number of spheres which have nucleated in a given time, since the spheres are independent of one another, crystallization is rapid, and crystalline sucrose is practically anhydrous. The weight loss measurements are of a cumulative nature, since each measurement reflects the previous moisture losses of the sample. For each different population of spheres (e.g., sucrose and raffinose), it is hypothesized that there is some time at which nucleation will occur, and that this time is normally distributed, with some unknown mean and standard deviation.

When dealing with data which are suspected to have a normal distribution, and are of a cumulative nature, the data may often be linearized by the use of probability paper (Waugh, 1952; Freund, 1960). Although the mean and standard deviation may be determined graphically from such a plot, the estimates are subject to error arising from the way in which the line is drawn through the points. Drawing the 'best' line by linear regression cannot be done. This problem may be circumvented by direct use of the cumulative normal distribution function, as demonstrated in the Appendix.

TABLE 1

Data demonstrating method of Z value determination

Time (days)	Moisture uptake (%)	Fraction of weight	Z value
8	5.42	1.00	–
9	5.30	0.978	2.0141
10	5.18	0.956	1.7060
11	5.10	0.941	1.5632
12	4.82	0.889	1.2212
13	4.41	0.814	0.8927
14	4.00	0.738	0.6372
15	3.39	0.625	0.3186
16	2.72	0.502	0.0050
17	1.48	0.273	−0.6038
18	0.55	0.101	−1.2759
19	0.42	0.077	−1.4255
20	0.24	0.046	−1.6849
22	0.00	0.000	–

The following example using data from Table 1 will show how the moisture uptake data are linearized. In the experiments, there is a *lag time* during which the amount of moisture taken up remains constant from a period of hours to weeks (Fig. 6A). If day 8 is the last day the spheres are at their constant moisture content, then the percent moisture uptake value on day 8 is denoted 100%, since it represents the moisture content of the system before the spheres have nucleated and crystallized. This corresponds to a fraction of spheres which have *not nucleated* of 1.00 (or 100%). After day 8, the sample loses weight with the passage of time. Each value of percent moisture uptake is divided by the value at 100%, and the resulting fractional number is denoted the fraction of weight or *fraction not nucleated*. This fraction is equated to the area under the standard normal distribution curve (obtained from the body of a normal error table) and the corresponding normal standard deviate Z (C in some books) is read from the column in the table. It is noted that there are no zero or 100% values in such tables. In the literature, these kinds of plots (done directly on probability paper) are sometimes called the 'cumulative less-than percentage' or the 'percent undersize' plot (Waugh, 1952; Freund, 1960).

If the data in Table 1 are plotted with time as the abscissa and Z value as the ordinate, then the

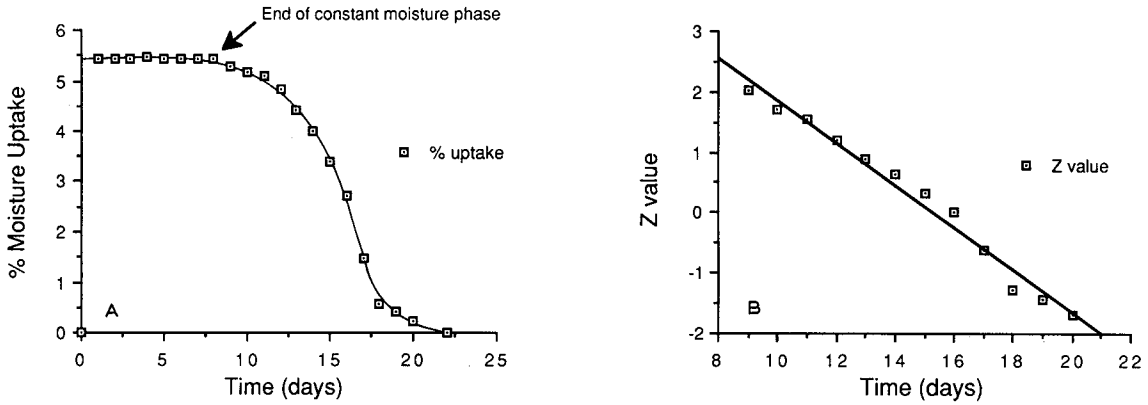

Fig. 6. (A) Moisture uptake vs. time data from Table 1. (B) Z transformation of data from Table 1, panel A.

resulting plot is linear with a correlation coefficient close to unity (Fig. 6B). In addition, linear regression may now be performed on the data to provide the equation for the best fitting line, and to provide a correlation coefficient. In this manner best values are obtained for the average time required for nucleation (where the regression curve cuts $Z = 0$), denoted the mean nucleation time in the following text, and for the standard deviation, s. A large standard deviation implies longer times between nucleation events in the individual spheres, while a small standard deviation implies shorter times between nucleation events. The standard deviation hence serves as a kind of rate constant. The mean nucleation time is different from the lag time, which is the time which must elapse before the first nucleation event can be detected.

The lag time and the mean induction time are both quantities that can be used to evaluate the effect of additives, temperature, or other variables on the nucleation of an amorphous material. For example, Fig. 7 shows the relative effect of additives at a 5% concentration on the lag times of amorphous sucrose. The lag time ratio is calculated by dividing the lag time of sucrose + additive by the lag time of the pure sucrose control (or internal standard) in the same experiment. It can be seen that 5% gelatin and a 5% gelatin-corn syrup mixture (equal parts by weight gelatin and corn syrup) have a significant effect on the lag time ratios at 25 °C, 33% R.H.

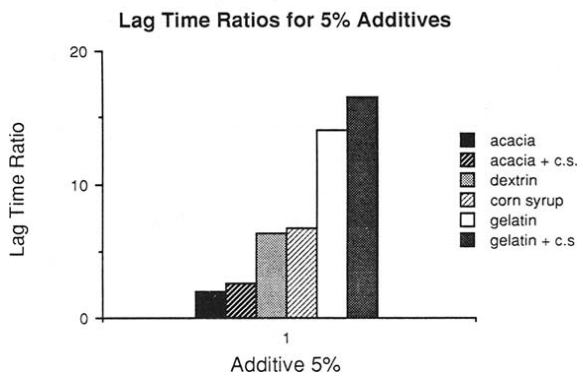

Fig. 7. Effect of additives at 5% concentration on lag time ratios.

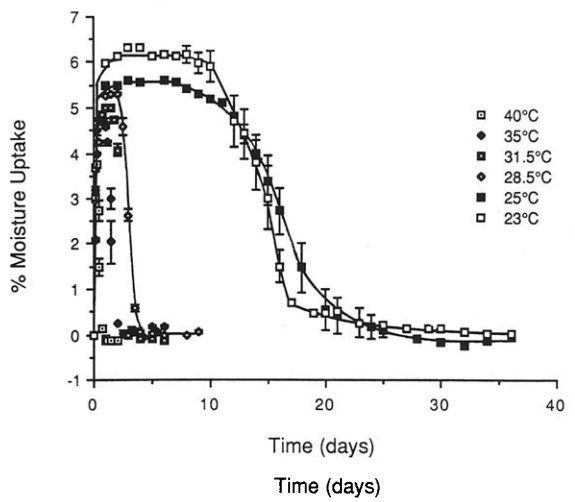

Fig. 8. Moisture uptake curves for amorphous sucrose at different temperatures.

Effect of temperature on nucleation in amorphous sucrose

An experiment was conducted to determine the effects of temperature on the nucleation of pure amorphous sucrose. The lyophilized amorphous sucrose spheres were stored in tightly sealed desiccators over saturated solutions of $MgCl_2$ with excess salt present. The relative humidity over these solutions only varied slightly within the temperature range used, and was approx. 32–33% (Nyqvist, 1983). The temperatures (40.0, 35.0, 31.5, 28.5, 25, and 23° C) were maintained by the use of a controlled temperature incubator. Figure 8 shows the moisture uptake data from the different temperature experiments, Fig. 9 illustrating the results of the 4 highest temperatures only. It is apparent that a large difference in lag times exists between 28.5 and 25° C. This difference is even more apparent when lag times are plotted vs. temperature (Fig. 10).

The plateau levels and lag times are shown as functions of temperature in Table 2. It is noteworthy that both parameters are plottable by Arrhenius equations with activation energies of 4.5 kcal/mol (% uptake at plateau level, correlation coefficient of 0.98) and 33.7 kcal/mol (lag time, correlation coefficient of 0.98%).

Relative humidity studies

The effect of relative humidity on the moisture uptake kinetics of amorphous sucrose was studied.

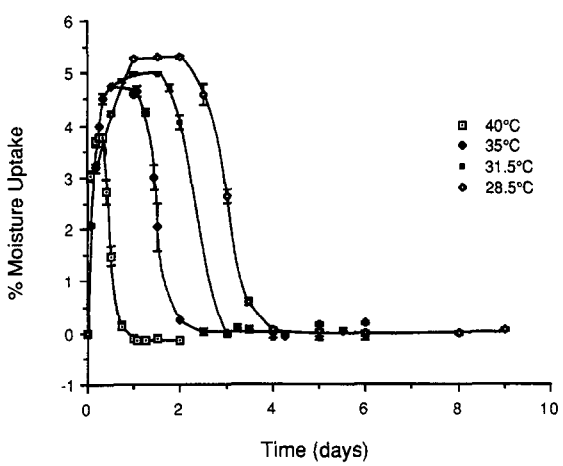

Fig. 9. Moisture uptake curves for amorphous sucrose: Four highest temperatures.

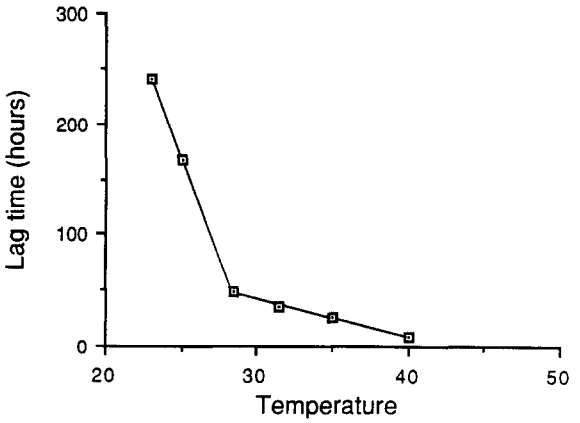

Fig. 10. Lag times vs. temperature for pure amorphous sucrose.

Amorphous sucrose spheres were stored in sealed desiccators over saturated salt solutions giving constant relative humidities of 32.8, 54.4, 40 and 68.9% (Nyqvist, 1983). The moisture uptake data are presented in Fig. 11.

The results of this experiment show that at higher relative humidities, the greater the percent moisture uptake and the faster the transition from amorphous to crystalline sucrose. This is in qualitative agreement with the findings of Makower and Dye (1956) whose experimental procedure did not allow relative humidities above about 34% to be studied. With the present experimental method, any relative humidity may be used in moisture uptake (nucleation and crystallization) experiments. Even at high relative humidities, where complete liquefaction occurs before nucleation and crystallization become apparent, the small drops of liquid are still separated from one another.

TABLE 2

Moisture uptakes and nucleation lag times at 33% RH as a function of temperature

Temperature (° C)	Lag time (h)	Plateau (% moisture uptake)
40.0	10	3.8
35.0	26	4.6
31.5	36	5.0
28.5	48	5.3
25	168	5.6
23	240	6.15

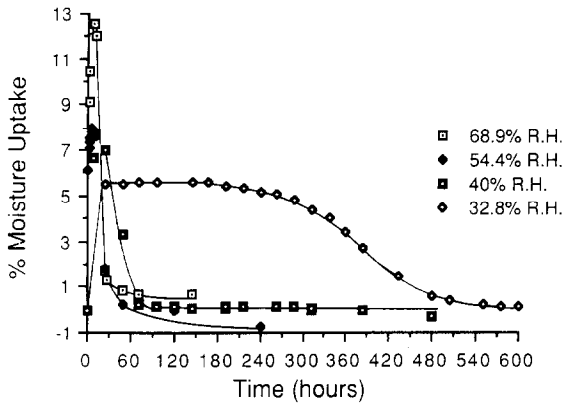

Fig. 11. Moisture uptake data for pure amorphous sucrose at different relative humidities.

Above approx. 80% R.H., the sucrose absorbs sufficient moisture for the formation of a saturated, or unsaturated solution and nucleation will not occur (Karel, 1973).

Conclusions

The present experimental method may be used in the evaluation of the amorphous to crystalline phase transition of any organic compound or formulation in which moisture sorption precedes the phase transition. The amount of moisture needed to effect the transition at any particular temperature, which will vary, can also be determined.

It has been shown that small amounts of various organic substances can have a significant effect on the nucleation rate of amorphous sucrose. This method and mathematical model allows the amorphous to crystalline transition to be studied over a wide range of relative humidities and temperatures by focusing on nucleation rather than crystallization. It is possible to determine the lag time, the mean induction time, and a relative nucleation rate *independent* of crystallization kinetics.

Summary:

(1) A convenient, reproducible method for making uniform amorphous spheres of sucrose has been described.

(2) This method is well suited for nucleation rate studies, because (a) the particles are independent of one another, and (b) the nucleation may be followed by monitoring the weight of the sample.

(3) The kinetics of the nucleation can be treated by assuming the nucleation time to be normally distributed about a mean nucleation time t^* with a standard deviation s.

(4) This statistical treatment allows calculation of the nucleation lag time as t^* minus 3 standard deviations.

Appendix

The nucleation curves (per cent moisture uptake vs. time plots) are such that they suggest three phases: (A) a water uptake phase with associated weight gain; (B) a lag phase at this particular weight; and (C) a weight loss phase corresponding to nucleation and crystallization. The profile of the latter suggests that nucleation is a stochastic process, and that the downward, S-shaped profile of weight (or % moisture uptake) versus time in this phase is distributed normally.

The process is handled in the following manner. Suppose at time t there are N of an original number N_0 amorphous spheres which have not nucleated. There is a certain probability, $P(t)$, that nucleation will occur in a given sphere at a given point in time t. The fraction of spheres which have nucleated or not nucleated should be a function of time that is normally distributed about a mean t^*, with a standard deviation of s.

The standardized normal distribution function (the one found tabulated in handbooks) is given by:

$$y = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{z} \exp\left(\frac{-x^2}{2}\right) \mathrm{d}x \qquad (1)$$

where y would be N/N_0 or its complement if they had a mean of zero and a standard deviation of 1 with Z and x representing time variables. If $y = N/N_0$ were plotted vs. x, than an S-shaped plot as shown in Fig. 12 (curve A) would result. If Z is

plotted vs. x, then a straight line with zero intercept and unit slope results. This is the inherent principle of a normal error function table.

If, more realistically, as in the case of N/N_0, a distribution is normal with a mean of t^* and standard deviation s, as shown in Fig. 12 (curve B), the equation for the distribution curve is

$$\frac{N}{N_0} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp \frac{-(t-t^*)^2}{2s^2} \, dt \qquad (2)$$

where N/N_0 is the fraction of spheres not nucleated (and is analogous to fraction or percent undersize values (Waugh, 1952; Freund, 1960). If t^* and s were known, then the t values could be expressed with t^* as the origin, i.e. as their distance from t^*, in units of s, and one could utilize the variable

$$u = (t - t^*)/s \qquad (3)$$

In such a case the Z value corresponding to N/N_0 can be obtained (from normal error tables) and plotted vs. u, and the distribution in Eqn. 2 will then reduce to the standard normalized distribution given in Eqn. 1. Denoting the words 'a function of' by '{ }', it is hence seen that plotting $Z\{N/N_0\}$ (the normalized standard deviate obtained from the fraction not nucleated) or $z\{1 - N/N_0\}$ (the fraction nucleated) vs. u would give a straight line with zero intercept and unit slope, as in Fig. 13.

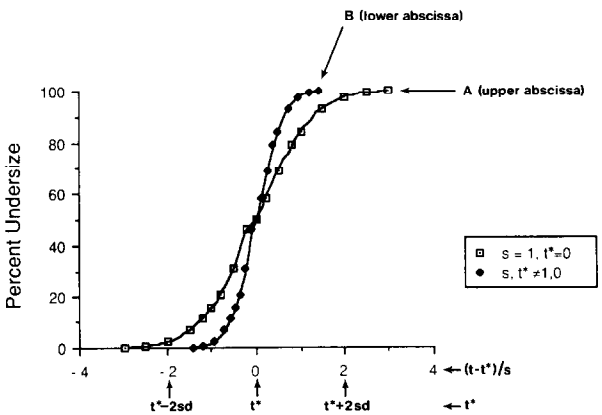

Fig. 12. (A) Curve according to Eqn. 1 in the Appendix. (B) Curve according to Eqn. 2 in the Appendix.

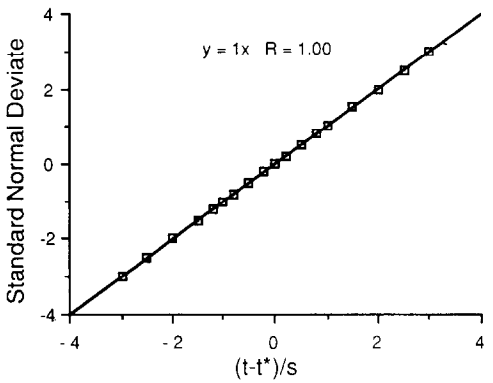

Fig. 13. Z transform of Eqn 2.

If, however, $Z\{N/N_0\}$ were plotted vs. Zs, then the graph would still have a zero intercept, but the slope would be $1/s$ (because the abscissa unit is now larger by a factor of s). If $Z\{N/N_0\}$ were plotted vs. $Zs + t^*$, the graph would no longer have a zero intercept, but $N/N_0 = 0.5$ ($Z = 0$) would occur when $t = t^*$.

The above method is identical to the use of probability paper, where the manufacturer of the paper has made the N/N_0 substitution by scaling the y-axis appropriately. This method then allows least-squares fit regression of Z on t, giving statistical estimates of both t^* and s. This then allows for estimation of the lag time as $t^* - 3s$ (assuming minimal nucleation probability beyond the 3 σ limit).

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