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In Situ Determination of Metastable Zone Width Using Dielectric Constant Measurement

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Abstract:

This study demonstrates the first use of a dielectric constant meter, coupled with an automated data logging module, for in situ monitoring of solution crystallization processes. The results show that this in situ measurement could detect not only the cloud point that corresponds to the onset of nucleation but also the clear point that closely represents the solubility limit. The metastable zone width (MZW) can subsequently be estimated as the gap between the loci of the cloud and clear points. In addition, the general phenomena of the crystallization process could be observed from several different regions of the dielectric constant profile. Direct comparison with turbidity measurement and focused beam reflectance measurement (FBRM) confirms that the cloud and clear points determined by the present dielectric constant measurement are reliable. This study opens new opportunities for the use of the dielectric constant meter as a simple, inexpensive, and convenient alternative tool in the field of crystallization process monitoring.

Introduction

Crystallization is one of the most widely used and important unit operations in many industries such as fine chemical, pharmaceutical, and agrochemical.[1,2] It has been mainly used for the formation, separation, and purification of synthetic intermediates, final solid products, etc. The metastable zone width (MZW), which denotes the region between the solubility curve and the onset of nucleation,[1] marks an operating boundary during solution crystallization processes to avoid excessive secondary nucleation thus ensuring the required size and size distribution of the final crystalline particles.

In the past decade, many techniques of process analytical technology (PAT) have been developed for in situ determination of the MZW during solution crystallization processes.[3−15] These techniques include, but are not limited to, direct visual observation using hot stage microscopy (HSM)[3] and bulk video imaging;[15] detection of the presence of solid particles using focused beam reflectance measurement (FBRM)[4−6] and a turbidity meter;[13] and monitoring of the solute concentration change via bulk solution property measurements using attenuated reflection-Fourier transform infrared (ATR-FTIR),[4−9] a densitometer,[10] an ultrasonic velocity meter,[10,11] a quartz crystal sensor,[12] conductivity, and a refractive index meter;[14] etc.

The dielectric constant is known to be a sensitive physical property and has been widely used for characterizing pharmaceuticals,[16] investigating solutions and molecular structures,[17] detecting phase separation,[18] determining solubility,[19] etc. However, to the best of our knowledge, its potential application for monitoring solution crystallization processes has not been explored. There are a few reasons indicating that a dielectric constant meter can be a convenient alternative PAT tool for monitoring solution crystallization. In addition to its sensitivity, dielectric constant measurement can be carried out in situ and the instrument is relatively inexpensive as compared to some other methods of measurement as mentioned above (i.e., HSM, FBRM, ATR-FTIR, densitometer, etc). In this contribution, we demonstrate the first use of a dielectric constant meter, coupled with an automated data logging module, for in situ monitoring of a solution crystallization process. In order to validate the present technique, a direct comparison study with more established techniques, namely a turbidity meter and FBRM, was performed. The results show that this in situ measurement could reliably detect both cloud and clear point temperatures.

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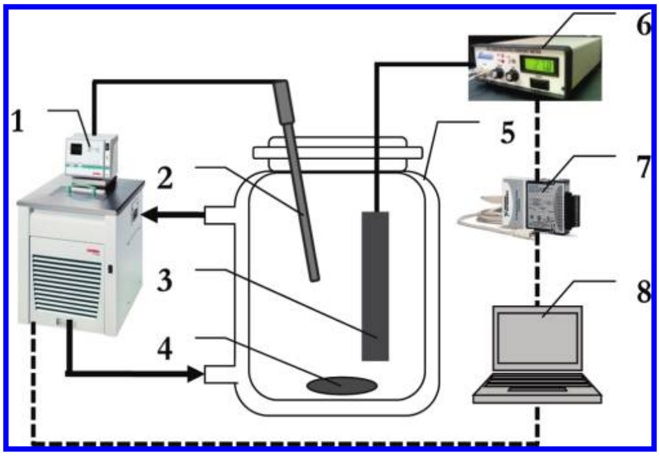

Figure 1. **Schematic of experimental setup. (1) Water circulator; (2) Thermocouple; (3) Dielectric constant probe; (4) Magnetic stirrer bar; (5) Jacketed crystallizer; (6) Dielectric constant meter; (7) Data logging module; (8) Computer.**

Subsequently, this information was used to estimate the MZW of the solution system.

Experimental Section

Materials. Paracetamol (Sigma, 98.0−101.0%) and ethanol (VWR International, ≥99.8%) were used as received.

Experimental Procedure. All experiments were conducted using a simple setup shown in Figure 1. Paracetamol−ethanol solutions with different concentrations (210, 225, 240, 255, and 270 g/kg solvent) were prepared. Crystallization experiments of these solutions by temperature ramping were conducted in a 250 mL jacketed glass reactor (Winzer). The reactor is airtight such that the evaporation of solvent can be avoided. The temperature and stirring rate were controlled by a water circulator (Julabo FP50) equipped with a thermocouple (Julabo Pt100) and a magnetic stirrer (IKAMAG RCT Basic), respectively. In situ dielectric constant measurement of the solutions was performed using a dielectric constant meter (Scientifica 870), coupled with a data logging module (National Instruments USB-9215A).

It should be noted that the dielectric constant of the solutions determined by the Scientifica dielectric constant meter is actually the relative dielectric constant, ε_r, which is defined as "*the ratio of the capacitance of the capacitor with the dielectric (C_x) to the capacitance without the dielectric (C_0) (i.e. with a vacuum between the plates of the capacitors)*".[20]

Two different temperature ramping cycles with the same heating and cooling rates have been applied on the solutions: (1) the solutions were preheated to 40 °C and kept at 40 °C for *ca.* 2 h (solutions remained homogeneous); they were then slowly cooled to 10 °C at 0.1 °C/min and kept at 10 °C for 1 h; finally they were heated back to 40 °C at 0.1 °C/min; (2) the solutions were precooled to 10 °C and kept at 10 for *ca.* 2 h (solutions were saturated and in equilibrium with paracetamol crystals); they were then slowly heated to 40 °C at 0.1 °C/min and kept at 40 °C for 1 h; finally they were cooled back to 10 °C at 0.1 °C/min. Simultaneous measurements of the dielectric constant and temperature of the solutions every 2 s were automatically conducted by LabVIEW SignalExpress 2009 (National Instruments) and the in-house Visual Basic program, respectively.

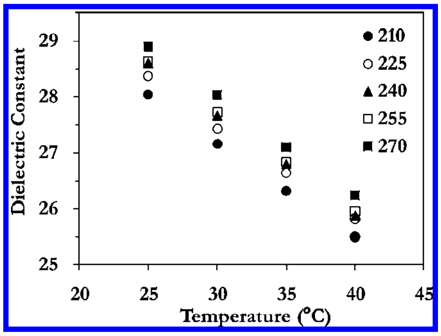

Figure 2. **Dielectric constants of paracetamol−ethanol solutions with different concentrations (210, 225, 240, 255, and 270 g/kg solvent) as a function of temperature.**

PAT Comparison. In order to validate the reliability of the dielectric constant measurement, simultaneous in situ monitoring of the crystallization process of the paracetamol−ethanol solution (240 g/kg solvent) was additionally carried out in a 1 L jacketed glass reactor using three different apparatus, namely a dielectric constant meter (Scientifica 870), a colorimeter (Brinkmann PC920), and a focused beam reflectance measurement (FBRM) system (Lasentec D600X). This experiment was performed using a similar experimental procedure as described above.

Results and Discussion

A small data set of the experimentally measured dielectric constants of paracetamol−ethanol solutions with different concentrations as a function of temperature is presented in Figure 2. Note that all solutions remained homogeneous at these conditions. For the given model system, the dielectric constant increases with the increase of concentration and decreases with the increase of temperature. The trends shown in Figure 2 are similar to those of many solution systems reported in the literature.[21−23] The correlations between both concentration and temperature with the dielectric constant obtained from this homogeneous condition help to interpret the more complex physical behavior of the paracetamol−ethanol solutions observed from the dielectric constant profiles during crystallization processes.

The dielectric constant and temperature profiles of a typical experimental run of solution crystallization are depicted in Figure 3. During the in situ monitoring, two phase transition points, namely the cloud and clear points, were observed. The cloud point, denoted as *N*, corresponds to the onset of nucleation during the cooling process. Theoretically, point *N* should indicate the appearance of the first crystal. However, in the present experiment, the occurrence of *N* can only be observed through a drastic drop of the dielectric constant of the solution resulting from a sudden decrease in the paracetamol concentration due to primary nucleation. It is expected that the appearance

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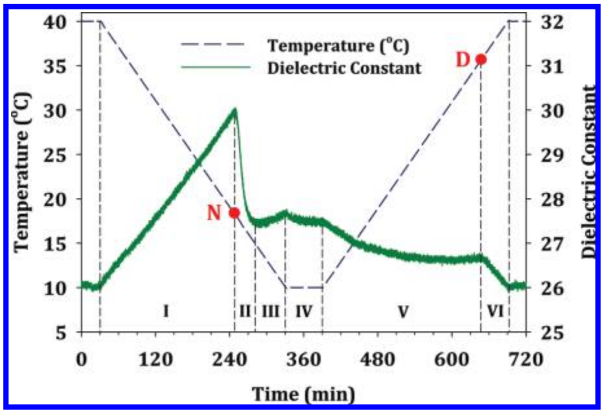

Figure 3. **Dielectric constant and temperature profiles of a typical run of cooling crystallization of paracetamol−ethanol solution (255 g/kg solvent).** ***N*** **and** ***D*** **indicate the cloud and clear points of the solution, respectively. Regions I−VI in the dielectric constant profile represent six different physical phenomena of the solution crystallization process in this study.**

of the first crystals should take place before this drastic drop of the dielectric constant; therefore, point *N* should be regarded as an approximation of the onset of nucleation. The clear point, denoted as *D*, is defined as the disappearance of the last crystal during the heating process, i.e. the end of dissolution. The locus of the clear points asymptotically approaches the solubility curve when the heating rate is very slow.

Regions **I**−**VI** in the dielectric constant profile represent different physical phenomena of the solution crystallization process during temperature ramping. (**I**) The solution remained homogeneous, and the paracetamol concentration was constant. The dielectric constant increased as a result of decreasing temperature. (**II**) After the onset of nucleation, simultaneous nucleation and crystal growth took place, leading to a rapid decrease in solute concentration. In this region, a decrease in concentration would cause a decrease in the dielectric constant while the decreasing temperature would cause the dielectric constant to increase. These two competitive effects gave rise to a net outcome of a decreasing dielectric constant, suggesting that the concentration effect was dominant. (**III**) The rates of nucleation and crystal growth have significantly slowed down due to the desupersaturation of the solution. Analogously, a net outcome of increasing dielectric constant shows that the temperature effect was dominant. (**IV**) The target temperature has been achieved and kept. A slight decrease in the dielectric constant followed by reaching a plateau implies that both nucleation and crystal growth were completed as determined by this technique. (**V**) The temperature was raised such that the dissolution of paracetamol crystals resulted in an increase in solution concentration. However, the temperature effect on the dielectric constant caused by heating is dominant, leading to an overall decrease in the dielectric constant. (**VI**) The dissolution of solute is complete. The solution has returned to a homogeneous state, and the solute concentration became constant. The dielectric constant of the solution decreased with increasing temperature.

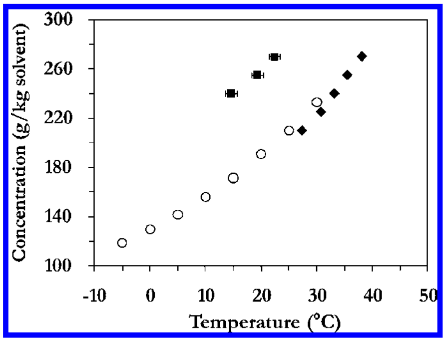

Figure 4. **Phase diagram of paracetamol−ethanol solution. Open circles are solubility data obtained from literature.[24] Solid diamonds and squares represent the clear and cloud point temperatures, respectively. Note that the error bars for the clear points are smaller than the size of the solid symbols.**

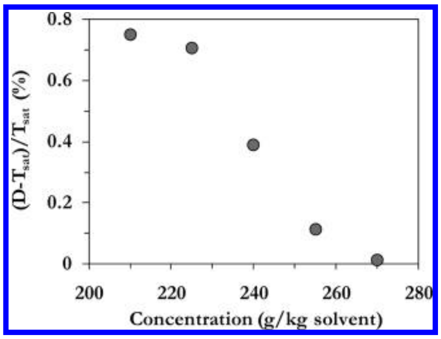

Figure 5. **Discrepancies between clear points (*D*) and saturated temperatures (T_{sat}) as a function of solution concentration.**

Figure 4 demonstrates the phase diagram of the paracetamol−ethanol solution system. Open circles are the solubility data obtained by Granberg and Rasmuson.[24] Solid squares and triangles represent the clear and cloud point temperatures determined in this study, respectively. Note that for solutions with relatively lower concentrations, 210 and 225 g/kg solvent, only the clear point temperatures are reported. For the solution of 210 g/kg solvent, no nucleation event was observed throughout the entire cooling and heating cycle. For the solution of 225 g/kg solvent, nucleation took place stochastically and it occurred in two out of the four experimental runs. Therefore, cloud point temperatures for these two solutions could not be accurately determined.

Under the condition when the heating rate is slow (i.e., 0.1 °C/min in this study), the discrepancies between the solubility data (T_{sat}) measured by gravimetric method[24] and the clear points determined by dynamic dissolution are considerably small (Figure 4). Slight discrepancies between the solubility data and the clear points are observed for the solutions with lower concentrations, and they become negligible for the solutions with higher concentrations (Figure 5). A plausible explanation for this phenomenon is that the dissolution rate of paracetamol particles in ethanol is reduced at lower temperature and this more significantly affects the dissolution of the lower concentration solutions which have lower clear points.[25]

Since the clear points can be determined with reasonably good accuracy, the MZW can thus be approximated by the loci of the clear points and the cloud points obtained from this study. In Table 1, the estimated MZWs are compared to the actual

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Table 1. Cloud points, clear points, saturated temperatures, and metastable zone width (MZW) of cooling crystallization of paracetamol−ethanol solutions with different concentrations

Concentration (g/kg solvent)	Saturated temp T_{sat} (K)[a]	Cloud point N (K)[b]	Clear point D (K)[b]	Estimated MZW $D - N$ (K)	Actual MZW $T_{sat} - N$ (K)
210	298.21	N/A	300.45 (0.17)	N/A	N/A
225	301.79	N/A	303.92 (0.12)	N/A	N/A
240	305.13	287.72 (2.68)	306.32 (0.15)	18.60	17.81
255	308.27	292.38 (2.42)	308.62 (0.31)	16.23	15.89
270	311.23	295.52 (3.00)	311.27 (0.13)	15.75	15.71

[a] Saturated temperatures of paracetamol−ethanol solutions are obtained through interpolation or extrapolation of the literature data.[24] [b] All numerical values of the cloud and clear points are averages of three repeated experiments; the values in the brackets indicate the standard deviations (±1σ) of the three runs.

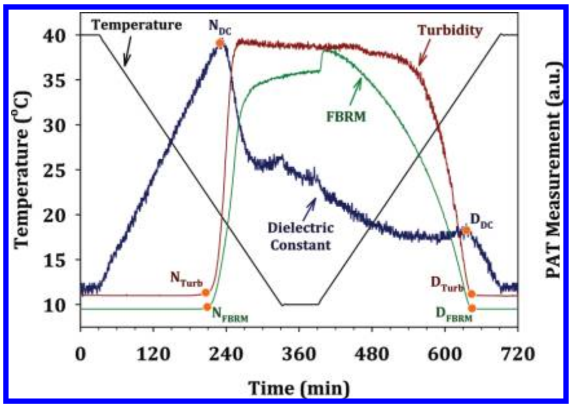

Figure 6. Temperature and PAT measurement (dielectric constant meter, turbidity meter, and FBRM) profiles of the cooling crystallization of paracetamol−ethanol solution (240 g/kg solvent). Points *N* and *D* represent the cloud and clear points determined by each technique, respectively.

MZWs, which are calculated based on the solubility curve (from literature) and the locus of the cloud points.

PAT Comparison. In order to examine the accuracy of the cloud and clear points determined by the dielectric constant measurement, a direct comparison of measurements with other more established PAT tools was performed. In this comparison study, the crystallization process of a paracetamol−ethanol solution (240 g/kg solvent) was monitored simultaneously by a dielectric constant meter, a turbidity meter, and FBRM.

As can be seen in Figure 6, all three measurements can clearly identify both the cloud and clear points. The clear point determined by the dielectric constant meter is nearly identical (vary within 0.1 °C) with those determined by the turbidity meter and FBRM. A slight delay of *ca.* 1 °C is observed between the cloud point determined by the dielectric constant meter and the other two measurements. The observation of this slight delay is expected due to the influence of temperature on the dielectric constant. Nevertheless, this comparison study confirms that the dielectric constant meter can be reliably used to monitor and detect the nucleation and dissolution events in the solutions.

Conclusion

In this contribution, dielectric constant measurement has been successfully applied for monitoring a solution crystallization process of a paracetamol−ethanol solution. A dielectric constant meter could detect not only the cloud point that corresponds to the onset of nucleation but also the clear point that closely represents the solubility limit when the heating rate during the dissolution of particles is slow. The detection of the cloud and clear points from the dielectric constant measurements is reliable as confirmed by turbidity measurement and FBRM. The MZW can therefore be estimated from the cloud and clear points determined from the dielectric constant measurements. In addition to the identification of cloud and clear points, the general phenomena of crystallization processes could be observed from several different regions of the dielectric constant profile. These observations provide a qualitative understanding concerning the nucleation and dissolution process of the crystals. This study opens new opportunities for the use of the dielectric constant meter as a simple, inexpensive, and convenient alternative tool in the field of crystallization process monitoring.

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