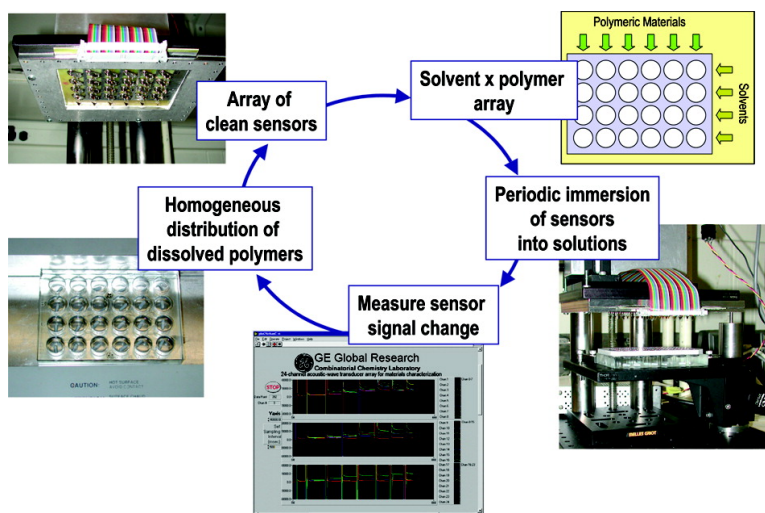


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Resonant Multisensor System for High-Throughput Determinations of Solvent/Polymer Interactions

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Solvent-resistant polymers are important in numerous research, engineering, and consumer applications. To address the limitations of existing methods of evaluation of polymer solubility and solvent resistance, we developed and built a 6×4 array of resonant acoustic-wave sensors operating in the thickness shear mode (TSM). The application of this system makes possible analysis of nanogram quantities of polymers in small amounts of solvent and permits the simultaneous analysis of multiple samples, such as those produced in combinatorial polymerization reactions. These parallel determinations of polymer/solvent interactions eliminate errors associated with serial determinations. During the periodic exposure of the TSM crystals to polymer/solvent combinations, the mass increase of the crystal is determined, which is proportional to the amount of polymer dissolved and deposited onto the sensor from a polymer solution. We demonstrate our sensor system for reliable quantification of solubility of several types of polymers in various solvents. The high mass sensitivity of our resonant TSM sensors (10 ng), use of only a minute volume of a solvent (<2 mL), and parallel operation (matching a layout of available 24 well plates) make this system a good fit with available polymer combinatorial synthesis equipment.

Introduction

Solvent-resistant polymers are desired for numerous research, engineering, and consumer applications ranging from advanced microfluidic components for sensing and combinatorial screening of materials formulations, to inert sensor substrates, and to plastic components of handheld electronic devices.^{1–6} For these and many other reasons, new types of polymers, their blends, and copolymers are under active development.^{7,8} A variety of recently reported parallel combinatorial polymerization reactors^{9–12} can be applied to accelerate polymer synthesis. However, analytical tools for rapid evaluation of combinatorially produced polymers are much less advanced and are highly desired.¹¹ For example, conventional polymer/solvent evaluations require exposure of a relatively large amount of sample to a solvent for extended periods of time. In addition, these determinations are manually performed and cannot handle multiple samples to match the throughput of combinatorial polymerization reactor arrays.

Meanwhile, sensors are well-accepted for the measurement of a diverse range of chemical and physical parameters.^{13–18} For combinatorial and high-throughput (HT) screening, sensors are almost an ideal screening tool for a variety of materials applications. Indeed, sensors are already miniaturized and do detect quantitatively small amounts of materials. In addition, sensors are often multiplexed into arrays for improvement of selectivity and overall performance. In

addition, data analysis from sensor arrays is well-understood. Finally, different types of sensor transduction mechanisms are known and available to fit a particular HT application.¹⁹

Thus, to address the limitations of existing methods for evaluation of solubility of numerous small-scale polymer samples produced in combinatorial reactors, we introduce here a sensor-based HT screening approach. We developed and built an array of 24 resonant acoustic-wave sensors²⁰ that we apply here for rapid determinations of solubility of polymers in different solvents. For measurements, sensor crystals are exposed to polymer/solvent combinations, and residual dissolved material is quantified after solvent evaporation from the crystals. The mass increase of the crystal is proportional to the amount of polymer film deposited onto the sensor from a polymer solution. Application of this system makes possible analysis of nanogram quantities of deposited materials due to the dissolution process and permits analysis of multiple samples simultaneously.

Experimental Section

Sensor Array Design. For our materials screening applications, we implemented acoustic-wave sensors, such as thickness shear mode (TSM) resonators, also known as quartz crystal microbalances (QCMs).^{21–23} Our sensor system was arranged on two printed circuit boards as described earlier.²⁰ For the polymer solubility studies, one of the printed circuit boards accommodated a 6×4 array of sensor crystals (International Crystal Manufacturers, Oklahoma City, OK) operating at ~ 20 MHz. These sensors were 8-mm-diameter AT-cut quartz crystals polished with an optical finish of

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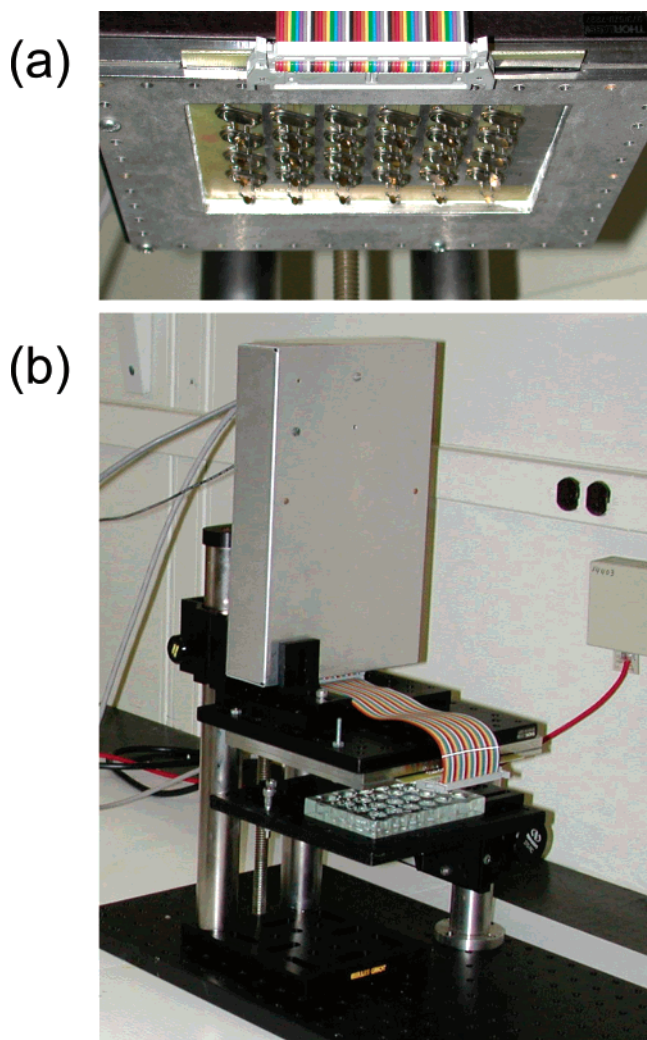


Figure 1. Sensor-based system for parallel evaluation of polymer solubility. (a) Layout of the 24-channel, 6×4 TSM sensor array positioned for evaluation of polymer solubility. (b) General view of the screening system.

$< 1 \mu\text{m}$. The crystals had 3-mm-diameter electrodes (1000-Å-thick gold, 99.99% purity) plated in the center of each face of the crystal. The spacing between the centers of sensor crystals was 20 mm. This layout was compatible with available 24-well plates that have a 16-mm well diameter. A general view of the sensor array is presented in Figure 1A. Connections were made from this printed circuit board to a second printed circuit board which contained 24 integrated circuit oscillators giving TTL level outputs. The oscillators were able to support oscillation frequencies of different TSM crystals in the range from ~ 4 to ~ 22 MHz and were purchased from Gewell International, Inc. (El Monte, CA). The 24 oscillator signals were selected one at a time using a TTL multiplexer integrated circuit and were connected to a time interval analyzer circuit card (Guide Technology, model GT650) installed in a desktop personal computer. The generation of analogue and TTL signals for the control of auxiliary equipment was achieved using a second installed digital I/O card (National Instruments, model PCI-6503).

High-Throughput Screening System and Operation.

For parallel determinations of polymer solubility, the sensor array was incorporated into a screening system as shown in

Figure 1B. Minute amounts (three pellets, ~ 15 to 30 mg total mass) of different polymers were arranged in individual wells of a 24-well plate. One or more solvents of interest (~ 1 to 1.5 mL per well) were added. In the studies described here, several copolymers of the same chemical family were tested for solubility in chloroform, tetrahydrofuran (THF), and methyl ethyl ketone (MEK). Solvents were purchased from Mallinckrodt Baker Inc., Phillipsburg, NJ (J. T. Baker brand, reagent grade). The array of initially clean sensors was periodically immersed into the wells of the 24-well plate with these polymer/solvent systems. The 24-well plate was also periodically placed into a heating/stirring module (model Reacti-Therm III, Pierce, Rockford, IL) to stir solvents in each well after withdrawal of the sensors from the solutions. Upon dissolution of polymers, a certain amount of dissolved polymer was deposited onto the sensors. Frequency changes were measured when the sensors were slowly withdrawn from the solvents and the solvents were evaporated. The measured signal change was proportional to the amount of the deposited material from the solution. For sensor cleaning, we removed polymer deposits by washing the sensors with a pure solvent. Monitoring the frequency of the sensors ensured the quality of the cleaning procedure. Upon complete cleaning, the frequency reached the initial frequency as recorded before polymer dissolution experiment to within several hertz.

Results and Discussion

Combinatorial Screening Process Map. A layout of our combinatorial screening process map involving the designed sensor array is presented in Figure 2. The 6×4 array configuration is a derivative from a 96-well microtiter plate format and permits the use of standard robotic equipment for deposition of materials onto the oscillating crystals. Such deposition is achieved by first dispensing the materials into the wells of a 24-well plate, followed by dip-coating of the sensor array. Alternatively, we recently demonstrated^{12,24} that polymers can be synthesized in individual wells of glass or quartz well plates.

According to the process map depicted in Figure 2, an array of initially clean sensors is periodically immersed into polymer/solvent systems. The measurements of frequency changes are done when the sensors are periodically withdrawn from the solvents and the solvents are evaporated. In this way, the measured signal change is indicative of the amount of the deposited material from the solution. To ensure the homogeneous distribution of dissolved polymer in each well, the wells are stirred.

In a typical experiment, 2–4 replicates of the same materials are used for an adequate statistical interpretation of collected data. In the process map configuration described here, measurements of the changes in fundamental frequency are related to gravimetric changes upon polymer deposition onto the crystals. Additional steps of the process can involve exposure of polymers to different vapors, temperatures, radiation, etc.²⁵ Decision making is typically based on the predetermined threshold parameters selected on the basis of historical data of materials performance. The whole process can be further coupled to a database.

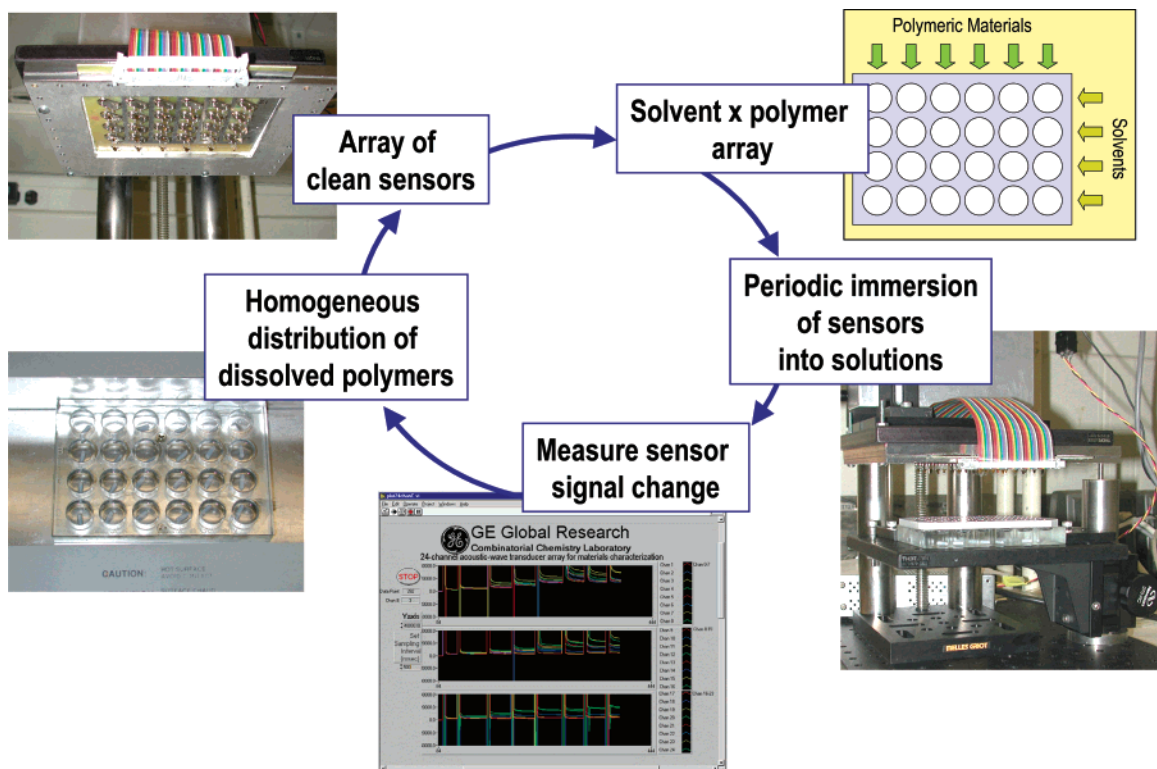


Figure 2. Combinatorial screening process map for evaluation of polymer solubility.

Mass Resolution of HT Solubility Determinations. The application of our acoustic-wave sensor system makes possible analysis of nanogram quantities of deposited polymers upon exposure to the polymer-containing solvent and solvent evaporation. If a polymer film is deposited onto the crystal surface, such film induces a change in resonant frequency of the crystal f_F described by a classical relation²²

$$\Delta f_F = -2f_0^2(m_F/A)(\mu_Q\rho_Q)^{-1/2} \quad (1)$$

where f_0 is the fundamental resonant frequency of an unloaded device, μ_Q is the shear modulus of the piezoelectric substrate, ρ_Q is the substrate density, m_F is the total mass of the coating deposited to both faces of the crystal, and A is the active surface area of one face of the crystal. Parameters of a given piezoelectric substrate can be combined into a constant C , $C = 2f_0^2(\mu_Q\rho_Q)^{-1/2}$. For an AT-cut quartz crystal, $\mu_Q = 2.947 \times 10^{11} \text{ g cm}^{-1} \text{ s}^{-2}$, $\rho_Q = 2.648 \text{ g cm}^{-3}$, and $C = 2.264 \times 10^{-6} f_0^2 \text{ Hz cm}^2 \text{ g}^{-1}$. The noise level of our sensor array (measured as root-mean-square noise) was ~ 2 Hz; thus, the mass resolution calculated for a 20-MHz crystal was 10 ng. Typical data collected from the parallel solubility experiments is presented in Figure 3, where several types of copolymers were exposed to chloroform. In this experiment, the 6×4 array was periodically immersed into the wells containing ~ 20 to 30 mg of six copolymers. The frequency change was measured upon sensor removal from the solvent and solvent evaporation. The stable horizontal regions in the sensor responses are their signals in air upon deposition of six different types of polymer films. The sensor readings just before the next immersion into the solvents were further used for data analysis.

Variability of System Performance. Because of the 6×4 configuration of the array, we can test a variety of solvents

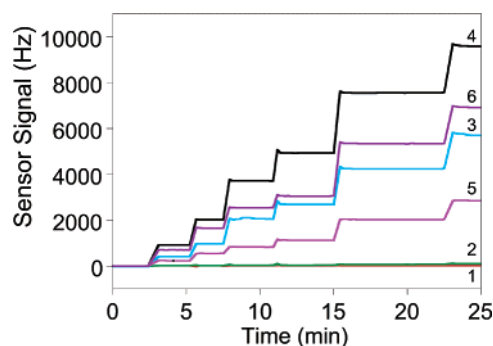


Figure 3. Typical results of the HT solubility experiments. Signals of sensors from the periodic immersion of sensors into the solvent with six (1–6) polymers are recorded as frequency change upon solvent evaporation during the run.

and polymers or other materials in a single experiment. Such studies are advantageous not only because they are done in parallel but also because they reduce the variability between the measurements by reducing possible uncontrolled environmental variations that may affect individual kinetic experiments (lab temperature, atmospheric pressure, etc.). To study the solubility of the polymers, measurements can be performed of the dissolved amount and dissolution rate.

With the goal to use this sensor system for detailed evaluation of polymer solubility, we determined the variation sources in the response of the sensors. Some of these sources included the initial condition of the sensor crystals, position of polymer samples in each well, and differences in the initial mass of polymer samples. To reduce the variability in analysis as much as possible, we attempted to minimize identified variation sources in sensor response. First, a good initial condition of the sensor crystals was ensured by checking for mechanical integrity of crystals and their cleanness before the measurements. The cleanness of crystals

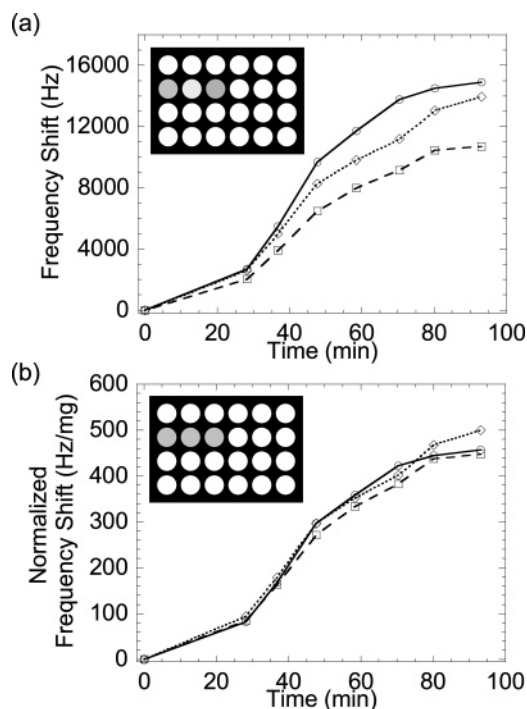


Figure 4. Significant reduction of variability in sensor response due to differences in initial polymer amounts in each well of the 24-well plate. Response of three representative sensors (a) before and (b) after the normalization by the initial mass of the polymer in each well. Gray levels of three replicate wells in insets in (a) and (b) illustrate the normalization approach.

was ensured by observing no changes in measured frequency upon crystal washing with a solvent. Second, to minimize the variation in dissolving rate of polymers in each well and to ensure the homogeneous distribution of dissolved polymer in each well, solutions in the wells were stirred after withdrawal of sensors from solutions. Third, to compensate for the differences in the initial mass of polymer samples in each replicate well, the frequency response of each sensor was normalized by the initial total mass of polymer pellets in individual wells of the 24-well plate. This total mass of polymer in each well was available from measurements before the solubility experiment. Typical achieved improve-

ments are illustrated in Figure 4. When measured at 60 min after the beginning of the experiment, the relative standard deviation of frequency measurements was improved from $\sim 20\%$ to $<4\%$.

In addition, other potential sources of variability were considered. For example, the sensor surface may potentially differently adsorb deposited polymers. However, the inert nature of the quartz crystal and the gold sensor electrode²⁶ with respect to the employed solvents and polymers resulted in no detectable irreversible adsorption of polymers to the sensor surface as measured by the recovery of the sensor baseline after washing off the deposited polymers. Thus, the sensors were completely reusable because the solvents and dissolved polymers did not chemically interact with the quartz crystal and gold electrodes of the sensor.

Another potential problem may be in differences of the wetting and spreading behavior of different solvents and dissolved polymers on the gold sensor surface.²⁷ In our situation, this was not an issue because the employed solvents had very similar surface tension values (24.6, 26.4, and 27.5 mN/m for MEK, THF, and chloroform, respectively, compared to 72.8 mN/m for water,^{28,29} all at 20 °C). In our experiments, the employed pure solvents showed similar spreading behavior on gold electrodes of the sensors. Similar spreading behavior on gold electrodes was also observed for dissolved copolymers that were from the same chemical family. For more diverse solvents and polymers, one possible solution to reduce the differences in spreading of dissolved polymers may be to employ unpolished sensor crystals.^{22,30,31}

Representative Example of HT Screening of Polymers.

Our developed sensor system was applied for reliable quantification of solubility of several polymers in a variety of solvents of industrial importance. Results of these determinations are presented in Figure 5 for three representative polymers exposed to chloroform, THF, and MEK solvents. The error bars for each data point indicate one standard deviation from the mean of three measurements obtained from individual sensor crystals. The data also provides some initial insights on the dissolution kinetics of

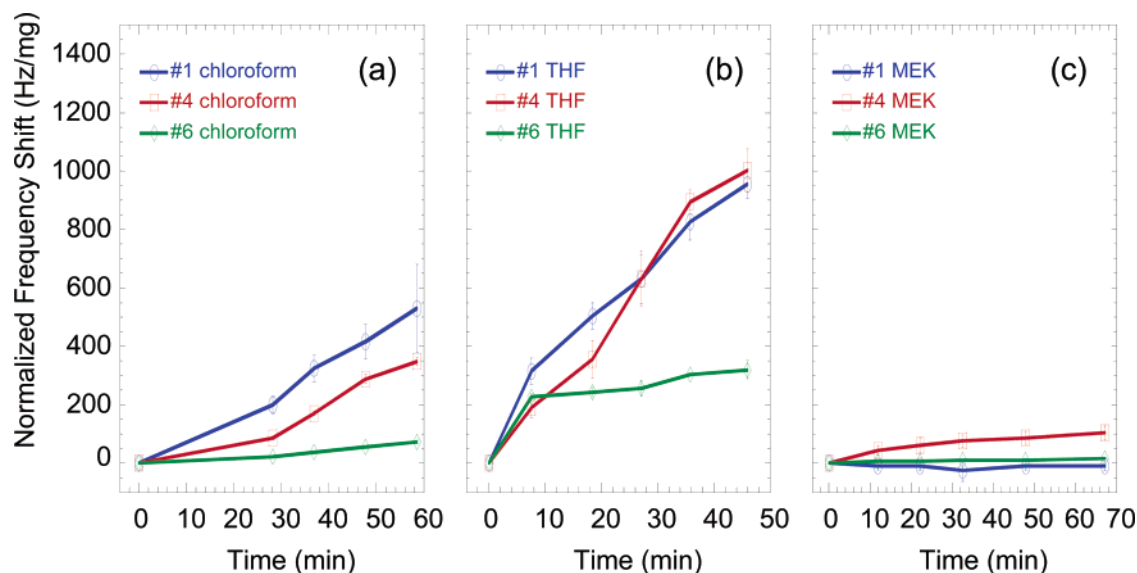


Figure 5. Dissolution of different copolymers in exemplary solvents: (a) chloroform, (b) THF, (c) MEK.

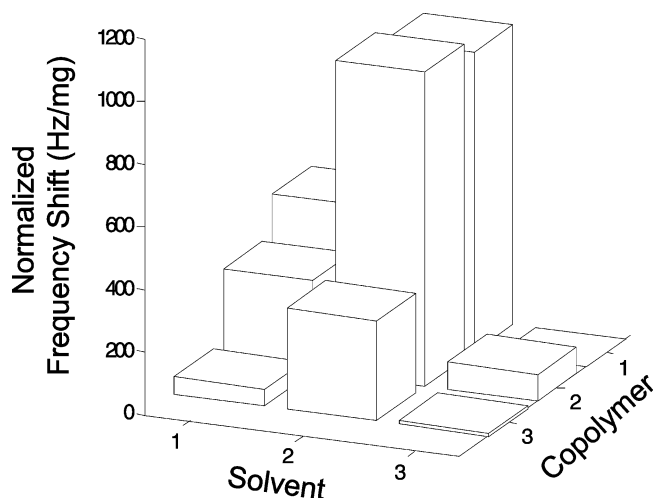


Figure 6. Results of ranking of solubility of three copolymers in exemplary solvents (chloroform, THF, and MEK).

polymers, which are currently under a more detailed study to be reported in the future.

Comparison of solubility of copolymers in solvents of different nature is presented in Figure 6, for which data were obtained from measurements of sensor signal change after 46–48 min after the beginning of the experiment. These data indicate the simplicity and effectiveness of such determination for both highly and sparingly soluble polymers.

Conclusions

In summary, the developed sensor system provides previously unavailable capabilities of parallel evaluation of polymer solubility. Importantly, the high mass sensitivity of the resonant sensors makes possible operation of sensors with very small amounts of polymers, which perfectly matches with the capabilities of available polymer synthesis equipment. This sensor system can be applicable not only for determinations of polymer solubility but also for evaluation of extractables in polymeric and other types of formulated materials.³²

Although this report details only a typical example of the operation of the sensor-based system for the HT screening of polymers, additional experiments have been performed, and their results were further coupled with simulation tools to extract desired quantitative structure–property relationships. The application of this sensor-based polymer-screening system, indeed, provided a lot of stimulating data, which would be difficult to obtain using a conventional one-sample-at-a-time approach. We will disclose results of these studies soon.

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