Perfect crystallization processes with inline control

LiquiSonic® Application Report

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Directory

1. LiquiSonic® Method

LiquiSonic® is a highly sophisticated inline/in-situ liquid analyzer well-suited to biotechnological, pharmaceutical, supersaturation, concentration and crystallization processes. Using sonic velocity and temperature measurement technology combined with a unique sensor design, the system allows control and monitoring of concentrations and general process trends at different points.

LiquiSonic® supplies the operator with real-time knowledge needed to optimise the process. A **LiquiSonic®** system consists of one or more intelligent sensors and a controller connected to each other by a digital line.

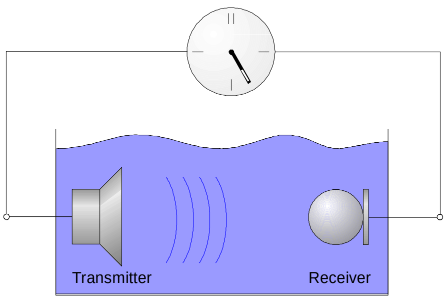
In addition, modern manufacturing technologies guarantee precise measuring results and convenient device operation. This includes the simultaneous presentation of mass-concentration or crystal content, product temperature, and product or recipe identifiers.

The data memory and event tracking capabilities (according to FDA 21 CFR Part 11) in conjunction with user-defined passwords ensure a maximum degree of process and application safety and security.

A multi-channel, real-time chart and the non-volatile configuration and process data RAM card allow easy system adaptation for lab, pilot, or production scale applications.

LiquiSonic® sensors are available in different designs and process fittings to suit tubes or vessels. For installations in hazardous areas, an explosion proof sensor is available. All sensors can be equipped with an electro-polished finish, and all sensors may have an ultra-sanitary design without gaskets to handle the toughest process environments and typical CIP / SIP procedures.

All systems include inline validation capability, which guarantees precise, traceable, and reproducible results under every circumstance.



2. Fundamentals of crystallization

Crystallization processes are of great importance in both the chemical and pharmaceutical industry. No wonder that manufacturers in these sectors are interested in having effective tools available for determining parameters and controlling the processes involved. Ultrasonic measuring methods play an ever greater part in this connection.

Ultrasonic measuring systems not only offer a convenient possibility for determining the crystallization and saturation temperatures and, thus, the metastable range, but are also well suited for determining kinetic variables such as the crystal growth kinetics.

Ultrasonic equipment allows to measure the degree of supersaturation during the crystallization process and to use the result obtained for deriving a control variable for directly influencing crystallization.

When solid substance is dissolved in a liquid, the liquid is absorptive up to a certain concentration. If further substance is then added to the liquid, it will no longer be dissolved, the solution is saturated, and the substance remains in its solid form.

This „maximum“ concentration is designated as *solubility* or as *saturation concentration*. The saturation concentration is dependent on temperature. The temperature at which the solution becomes saturated is designated as saturation temperature. If the temperature is increased, more substance can be dissolved (except in the case of negative solubility), and the saturation concentration increases as a result. The saturation concentration is also dependent on temperature.

If the concentration is lower than the saturation concentration, the solution concerned is designated as an unsaturated solution.

If the temperature of an unsaturated solution is decreased, it may be cooled down for many solutions to a temperature which is lower than the saturation temperature without causing the solid substance to become crystallized. The solution is supersaturated in such a case. If it is cooled down further, spontaneous nucleus or crystal formation will take place at a certain temperature, designated as nucleation temperature.

If the solution is then reheated, the crystals become dissolved again. On reaching the saturation temperature, all crystals are dissolved. The saturation temperature usually is higher than the nucleation temperature.

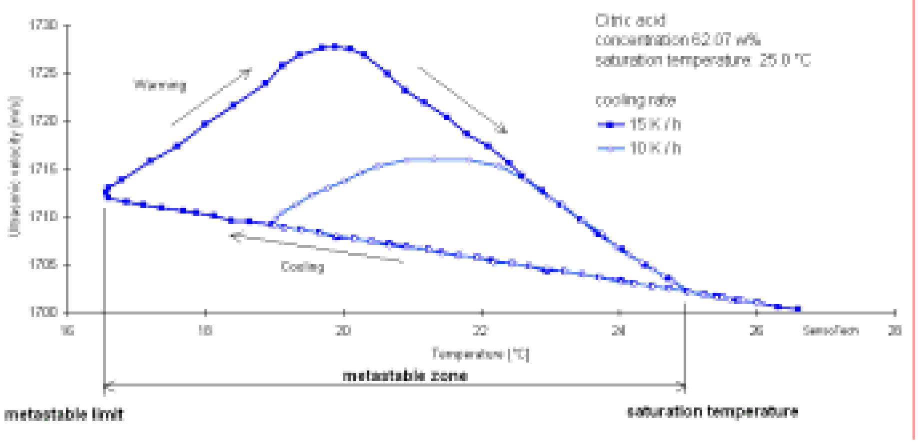
The range between the saturation temperature and nucleation temperature is designated as metastable range.

The relations described in this document were investigated by the application specialists of SensoTech GmbH in close cooperation with Prof. Ulrich of the Institute of Thermal Process Engineering at the University of Halle.

3. Sonic velocity and crystallization parameters

3.1. Crystallization parameters

Sound velocity and temperature are measured during cooling and heating the solution to establish the parameters of process relevance. The sound velocity presented as a function of the temperature, important crystallisation parameters, such as **saturation temperature**, **nucleation temperature**, and the position in the **metastable range** can be directly determined.



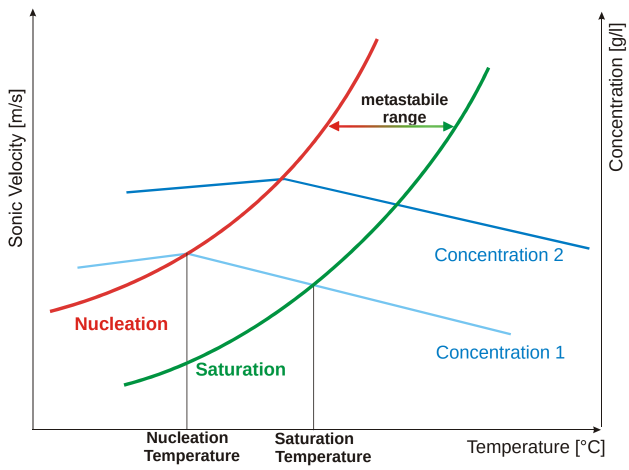
The figure provides an explanation of this effect: if the solution is slowly cooled down, the sound velocity changes at a specific temperature coefficient. From a certain temperature a marked change of the sound velocity can be observed. The relating temperature is the nucleation temperature. If the solution is reheated, its sound velocity curve differs from that obtained during cooling. Both curves meet again at saturation temperature.

Consequently, it is possible to determine the metastable range as well as the solubility curve via the sonic velocity. The metastable range is dependent on the chemical composition of the solution, on the cooling down rate and on contaminations.

Using the sonic velocity as a function of temperature, you can determine the metastable range for any desired solution. The sonic velocity can also be determined for dark, turbid or contaminated solution and is, thus, also suited for use with real solutions as are encountered in industrial applications.

3.2. Saturation difference

Online measurements of the degree of saturation are based on saturation concentrations varying at different temperatures:



The saturation behaviour depicted in the figure below as a function of concentration, temperature and sound velocity is stored in the **LiquiSonic®** Controller in form of calibration curves.

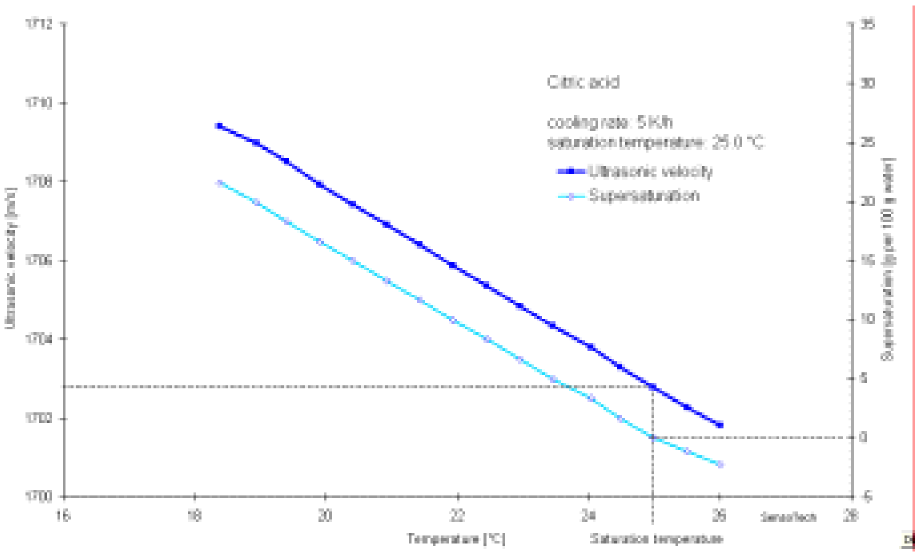
The current concentration is determined by sound velocity and temperature measurements, and is made available as the saturation difference (degree of saturation) for downstream process control.

This control variable serves to advance the process (temperature) quickly to the stage of saturation, saving time and energy. Concentration variations in the initial solution are determined to facilitate individual control of the process. Then, a secondary (spontaneous) nucleation occurs on the nucleation curve.

The range between saturation and nucleation is called the metastable (supersaturated) range. This range can be also stored as a calibration curve to be used for primary (controlled) nucleation.

3.3. Supersaturation

Sound velocity as a function of temperature also serves to determine the degree of supersaturation as shown in the figure below. The degree of supersaturation reflects a specific point within the metastable range (refer to 3.2). The closer this point is to the nucleation curve, the higher is the degree of supersaturation.



Superaturation of the solution varies during crystallisation due to crystal growth. Crystal growth reduces the degree of supersaturation. Supersaturation increases again when the temperature of the mother solution is increased or the solvent evaporates.

If crystallization takes place too close to the upper limit of the metastable range, the risk of nucleus formation (too fine end product) is too big. If, in turn, crystallization (growing of crystals) takes place too close to the saturation curve, perfect and large crystals will be obtained, on the one hand, but, on the other hand, the residence time and, thus, the costs of the process will increase.

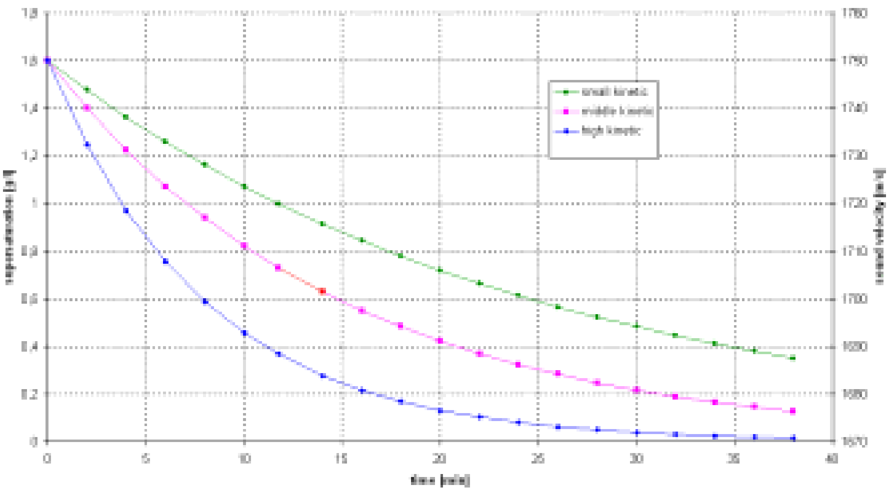
Optimum crystallization will take place exactly at a point where the parent solution is kept at an optimum level which is usually located in the middle of the metastable range.

The reduction in the supersaturation can be directly monitored by means of an ultrasonic measuring instrument.

By measuring the sonic velocity and the temperature of the parent solution during crystallization, you can optimize the control of the crystallization process in the metastable range.

3.4. Decreasing supersaturation and crystal growth kinetics

The degree to which supersaturation is decreasing during crystallization, the so-called supersaturation decline curve, can be represented as a function of time.



As can be seen, the time curve of sound velocity during crystallisation is identical with that of known supersaturation reduction. The supersaturation reduction curve in the figure below, which was calculated from sound velocity, is compared with the chemical analysis suggested by Tavare and Chivate [3].

From the supersaturation decline curve, the so-called crystal growth kinetics, R, an important variable in crystallization processes, may be calculated. This variable indicates how fast the crystals grow in the parent solution and must therefore be duly taken into consideration when designing and dimensioning crystallizers

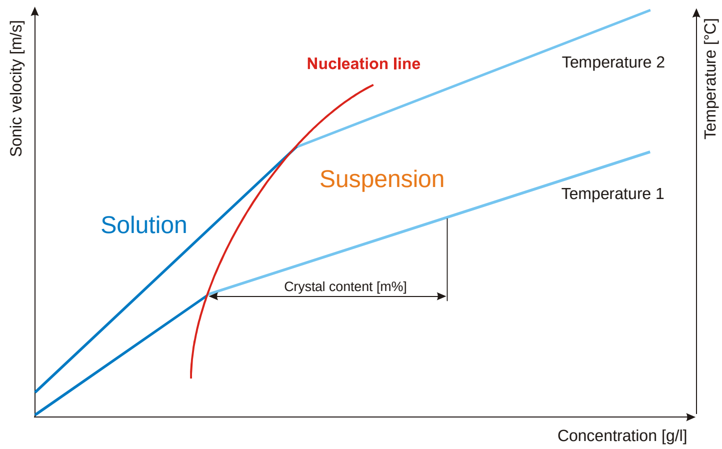
Using the appropriate scale, one can directly measure the supersaturation decline curve based on the correlation between supersaturation and the sonic velocity.

Crystal growth kinetics may be determined from the time dependent variation of the sonic velocity.

3.5. Determination of the crystal content

Each suspension is characterised by a specific sound velocity behaviour depending on temperature and concentration.

A typical curve is depicted in the figure. The corresponding family of characteristic curves is also stored in the **LiquiSonic® system**. This facilitates direct inline measurement of the solid concentration (crystal or dry matter contents):

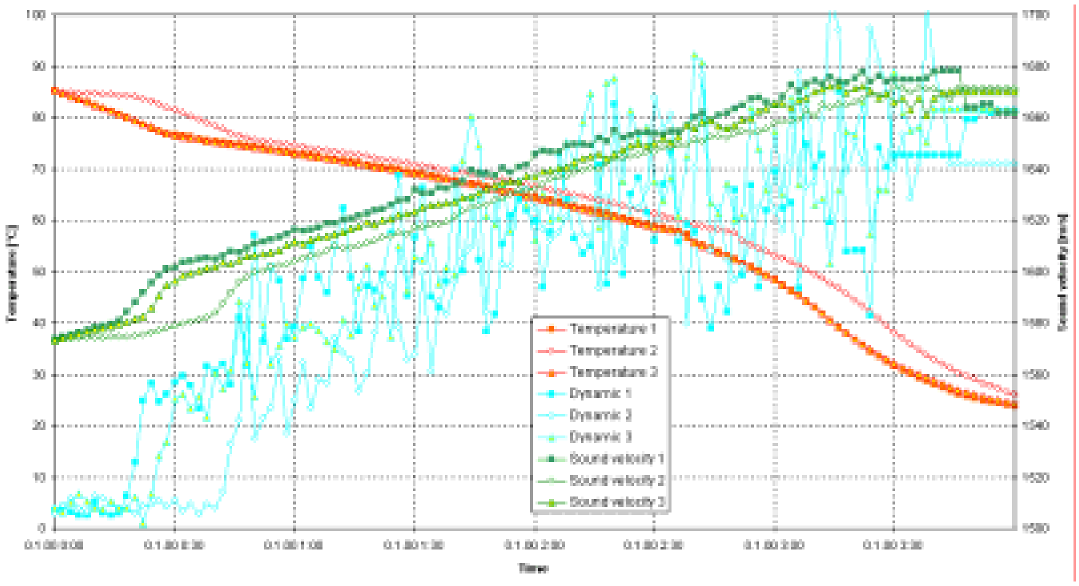


The crystal content established, it is possible to monitor and control separation in continuous crystallisation processes. In batch processes the end point of crystallisation and crystal growth can be determined and monitored.

4. Process Flow / Measuring Technology

4.1. Process control

Crystallisation processes can be monitored by continuous measurement of the sound velocity. This facilitates immediate intervention in case of malfunction or deviation from process specifications, ensuring an optimum process flow or the desired product quality.



LiquiSonic® also calculates the "dynamics" of the current process on the basis of statistical measurement information. The "Dynamic 3" trend shown in the figure signals a clear deviation of this process from the other two processes, and hence facilitates immediate intervention for correcting the process flow.

4.2. LiquiSonic® 50

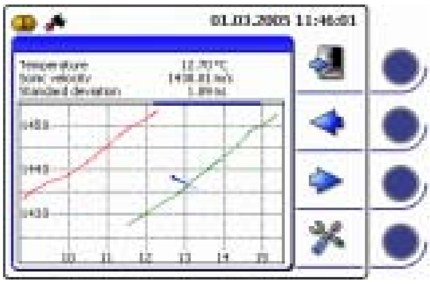
For monitoring and controlling crystallisation processes in the **LiquiSonic®** system the Controller 50 is needed.

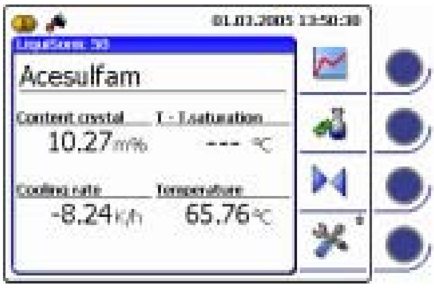
The Controller 50 comprises various additional functions:

- Digital PID controller (target concentration actual value (X1) and control input (Y1) as 4..20 mA)
- Setpoint generator for the temperature to generate cooling ramps for cooling crystallisation
- Setpoint generator for the sound velocity to facilitate reproducible process control with defined characteristics of the end point

Additional display functions facilitate the graphic presentation of supersaturation:

- Distance to solubility curve
- Cooling rate, crystal content and difference to saturation temperature





5. Further Readings

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SensoTech

For almost 20 years **SensoTech** has been primarily focused on the development, production, marketing. and support of high-performance in-line analyzers for concentration, density, or the monitoring of complex chemical reactions in liquid systems. During this time, **SensoTech** has an overall installation base of over 2000 devices worldwide. The unique products offer optimized and cost saving solutions for virtually every kind of application and process.

Providing solid solutions to complex problems has been both the challenge and the cornerstone of the **SensoTech** business. With the global installations and an extensive range of innovative products, **SensoTech** offers affordable, efficient solutions that meet our clients' exacting needs in food and beverage production and in chemical, pharmaceutical, biotechnical, semiconductor, iron and steel industries.

With **SensoTech**, cost-effective equality control, reduced developmental expenditures, optimized benchmark processes, and elevated standards are attainable.

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