

Automated Liquid Fill Verification System Using High Frequency Non-Contact Ultrasonic Sensor

The pharmaceutical industry has a unique problem of adopting new sensor technology to meet government regulations as well as very special processing demands. These dual forces are at work in the pharmaceutical industry, thus increasing the requirements for accurate and reliable sensors and associated instrumentation. Increasingly complex pharmaceutical processes require sophisticated instrumentation to create new or improved products and improve operational efficiencies.

This article examines the novel uses of ultrasonic technology in the sensors and instruments used in pharmaceutical processing. Included is an overview of the installation and application guidelines that can help manufacturers not only achieve the desired measurement accuracy, but also meet new requirements for government regulation.

The automated handling of large numbers of liquid samples is necessary in many pharmaceutical and chemical applications such as drug packaging and testing of various types of liquids such as blood reagents and laboratory assays. In such applications, the volume of the liquid in a large number of containers must be measured accurately on a high-speed basis. The samples are often in the micro-liter size in test tubes or vials having restricted size openings.

In a manual, or semi-automated filling process, the liquid is aspirated into the containers using a pipetting technique and a measurement is made of the liquid level by inserting a probe into the container until it contacts the liquid. This is highly undesirable, particularly when the samples are contaminated, contain toxic liquids, or the sterility of the newly packaged product is to be preserved. Also, the step of making the measurement is relatively slow and sometimes produces inaccuracies.

A non-contact ultrasonic liquid level measuring system for products that are dispensed into small tubes, vials, micro plates and miniature vessels is more desirable. The system can operate on a single channel basis sequentially or on a multi-channel basis to measure sequentially, or in parallel, the amount of fill of a plurality of such tubes or micro plates. A narrow beam of ultrasonic energy is transmitted from a sensor to the open top of an opposing tube to be reflected from the air-liquid interface of the tube back to the sensor. The round trip transit time of the energy is calculated. The height and inner diameter parameters of the tubes being measured are previously stored and a microprocessor uses this data and the measured round trip time to calculate the volume of liquid in the tube. All of this is done without contact of any type with the liquid.

The system can measure any tube or micro plate on an individual basis and there can be a single sensor below which a series of tubes held in a tray are passed one at a time. The measured volume data of all of the tubes is stored to produce a data map of the measurements. For micro plates, the plurality of sensors of the bank are operated sequentially or in parallel and the calculated volume results are stored. In this manner, the volume data for the tubes in each row is mapped and has its own signature.

FIG. 1 shows a typical ultrasonic sensor. The sensor has a cylindrical body diameter approximately 1/4" to 3/8" of suitable material such as epoxy, plastic, Teflon®, or 316 SS compatible with the environment under which the measuring process is being carried out.



Figure 1

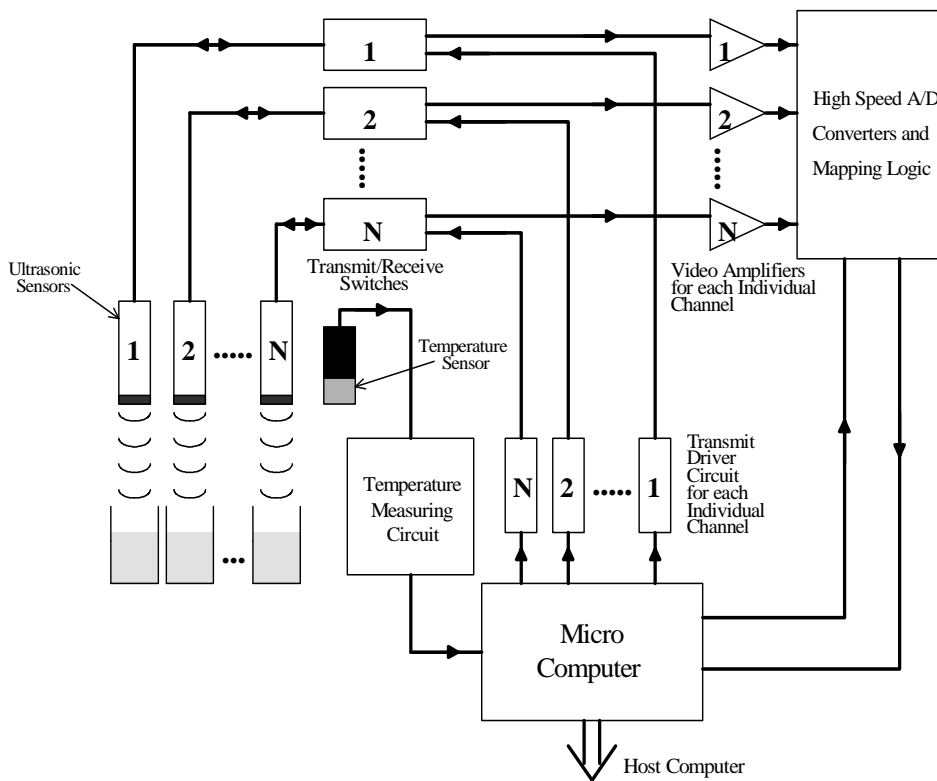
Typical Ultrasonic Sensor

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An ultrasonic sensor is configured to be able to transmit a narrow beam of ultrasonic energy from the piezoelectric element through the air, reflected from the surface of the air-liquid interface of a tube that has previously been filled, back to the element. Transmitting ultrasonic energy through air has the advantage of range resolution. The system achieves this advantage using high frequency transmission through air. That is, the sensor element is supplied signals for transmission in the range of 1 to 2 MHz. The velocity of sound in air at room temperature is 343.2 meters per second. Using a 1 MHz ultrasonic frequency, a system resolution of 0.0003 inches can be achieved. An ultrasonic sensor has a 1 to 2 MHz piezoelectric element with a multi-layer matching impedance structure to match with air. Each layer of the matching impedance is designed to match a quarter wavelength to an adjacent layer until the final layer, which matches closely to air. This provides a complex impedance match with the impedance of the air. This 1 to 2 MHz energy burst has a very narrow beam angle (less than 2 degrees), a measurement resolution of ± 0.0005 " and a dead zone of [0.5".

FIG. 2 is a block diagram for a single / multi-channel system. The plurality of the sensors are designated 1,2,...N. A microprocessor is programmed to control operation of the system. The microprocessor sequentially produces a drive signal of the desired frequency, such as 1 MHz, for each of the sensors which is applied to a respective driver circuit 1,2,...N. The drive signal produced by the microprocessor is a series, or burst of pulses that are amplified by the respective driver circuit. For sequential actuation of the sensors, a time interval is provided between the drive signal to each sensor to allow for reception of the signal reflected from the interface and processing of the acquired data.

Figure 2



Single / Multi-Channel System

A transmit / receive switch is connected to each sensor. Each switch has a connection to its respectively connected sensor and also a connection to a respective amplifier, which is

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preferably of the wide band video type. The operation of each switch is controlled by the microprocessor so as to be open to convey the signal for transmission from its connected driver circuit to its connected sensor.

FIG. 2 diagrammatically shows the plurality of sensors arrayed in a row opposing the open (top) end of a respective tube that holds an amount of a liquid. The tube has been filled prior to reaching the measuring station containing the sensors. The internal dimensions of the containers are stored in a memory which is either separate from or a part of the microprocessor. Each sensor is at a fixed and known distance from the top end of its opposing tube and the beam of ultrasonic energy it produces is aimed into the open top of the opposing tube.

In one mode of operation of the system in FIG. 2, each sensor of the row is operated in sequence. The actuated sensor is supplied a burst of the drive signal for transmission to its opposing container from the microprocessor. The activated sensor transmits a beam of energy into the open top of the opposing container to impinge on the top surface of the liquid, i.e., the air-liquid interface, and be reflected back to the sensor. The received reflected signal is applied from the output of the amplifier to the input of a high speed A/D converter and mapping logic circuit. Receipt of the signal by the circuit stops the time measurement and this is converted into digital data that is supplied to the microprocessor. The entire row of sensors 1,2,...N is operated in sequence and the digital data produced by the A/D converter is processed by the microprocessor. The round trip transit time of the energy from a sensor to the air-liquid interface and back to the sensor is used as a factor in the measurement of the volume of liquid in a tube. Knowing the dimension and the inner diameter of the tube, the volume can be calculated. The microprocessor is programmed, for example, from a personal computer, to store the various factors, such as tube height and inner diameter and distance from the top of the container, to the sensor.

The system also includes a temperature sensor that is applied to a temperature measuring circuit. The temperature data, in digital form, is also applied by the microprocessor, which modifies the output data with corrected velocity of sound at that temperature. Since the position of the sensor and its transducer is known as well as the internal diameter of the test tubes, these parameters being programmed in the microprocessor, the volume of the liquid can be calculated by the microprocessor.

A signature is produced for the row of containers measured by the row of sensors and is mapped in memory, which can be located in the microprocessor. The microprocessor analyzes the data in real time and outputs the corresponding liquid volume and /or simply the presence / absence of liquid in the containers. The liquid volume measurement of the plurality of tubes can be outputted to a suitable mechanism, such as one for handling containers that are not filled with the required volume, such as being empty, or can be stored in memory for further use.

The system can have the plurality of the sensors all transmitting and receiving data simultaneously. For this to take place, each sensor would be under the control of its own microprocessor and a common storage used to map the results of the plurality of volume measurement results. For a single tube or vial system, response time can be as fast as two milliseconds with a one millisecond repetition rate.

FIG. 3 shows a typical micro plate and sensor configuration used to measure a plurality of wells. In a typical application, there are 12 rows of 8 wells, making a total of 96 wells in the micro plate. A series of twelve or eight sensors (bank) are mounted on a common plate and

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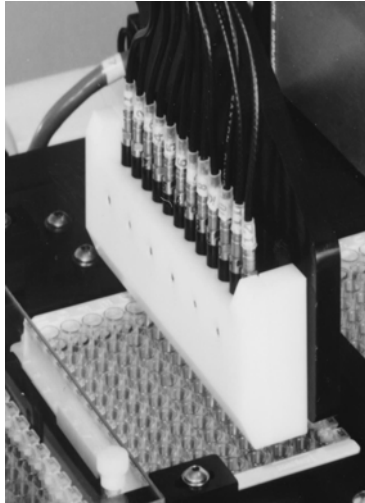


Figure 3

Typical Microplate and Ultrasonic Sensors

Picture courtesy of Oyster Bay Pump Works

positioned above the micro plate. The micro plate and sensor bank are moved relative to each other by a suitable stepping mechanism on a row by row basis. That is, after the measuring system of FIG. 2 has completed making the measurements of the liquid volume of each of the wells in one of the rows, either sequentially or simultaneously, a stepping signal is provided to position the next row of containers under the bank of sensors. The volumetric measurement results for all of the wells of the micro plate preferably are stored, or mapped, in memory. The wells in the tray can be of different shapes and volume so long as they are in an order and the dimensional data for the different wells has been previously and appropriately programmed into the microprocessor. The map of the filling volume of the wells in the micro plate can be displayed, by printing or displaying on a monitor, for use by an operator.

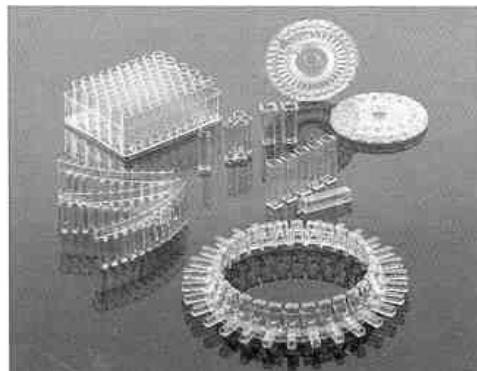


Figure 4

Other Microplates and Vials

FIG. 5 shows different shapes and sizes of test tubes placed in a tray that is mounted in a carousel. The carousel is on a shaft that is rotated by a stepper motor controlled by the microprocessor in FIG. 2. Here the volume of liquid in each of the test tubes on the tray is measured one at a time on a sequential basis. Only one of the sensors of the system shown in FIG. 2 need be used. As the carousel is stepped, for example, every millisecond, the microprocessor controls the system to transmit and receive ultrasonic energy through the electronic circuit as previously described. In a continuous operating mode for the system of FIG. 5, the carousel is stepped continuously and no external synchronizing signal is required and

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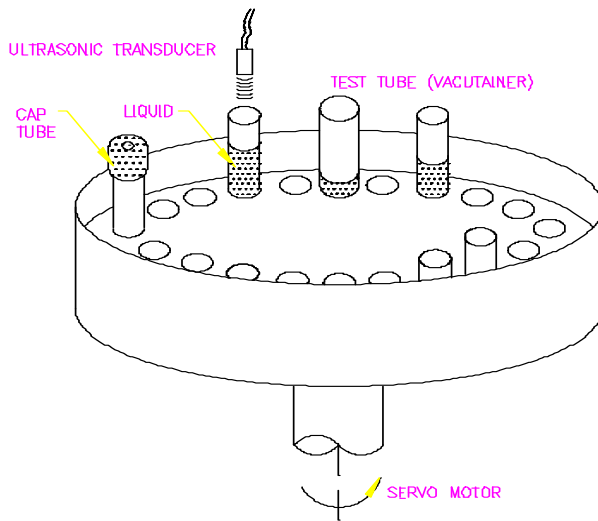


Figure 5

Sample Carousel

continuous data is gathered. In a strobe mode of operation, there is a wait for a valid "Sync" pulse to synchronize the measurement to outside events. The "Sync" informs the unit that a new tube to be processed is in place under the sensor and the measurement cycle to determine the volume is initiated. This process is repeated for each tube. A section of a typical two dimensional mapping of the FIG. 5 Liquid Fill Verification is shown in FIG. 6.

Sensor Face

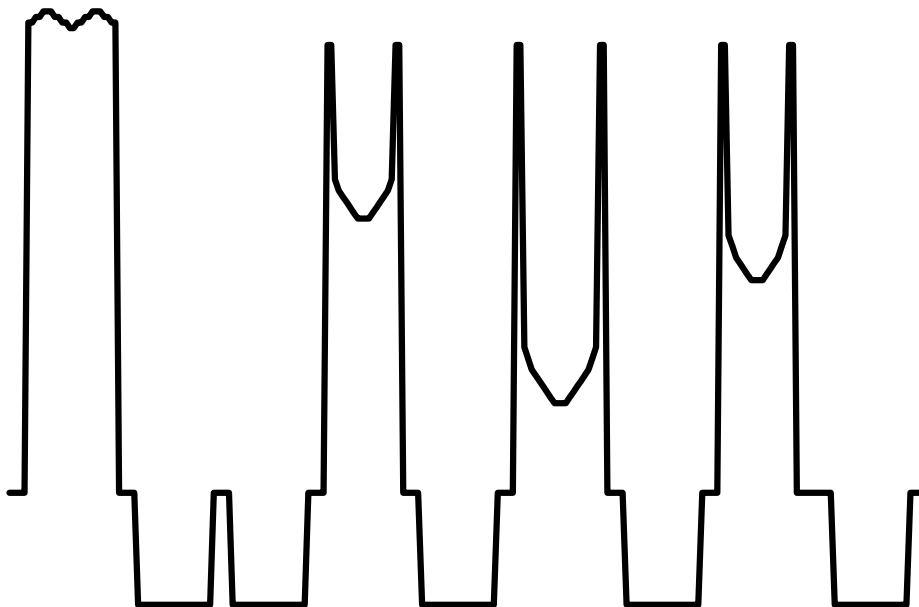


Figure 6
Typical Two
Dimensional
Mapping of
Sample
Carousel from
Figure 5

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The non-contact, noninvasive ultrasonic technology described in this article is a fast response, very high resolution and high-speed technique for measuring relatively small changes in volume for filling of micro plates, test tubes and vials. Also, the two dimensional mapping technique with pattern recognition logic eliminates a major problem of synchronizing the measurement with a driving mechanism, and eliminates all the common mode problems related to sync systems. A major advantage of the mapping and pattern recognition technique is that it eliminates a human interface. The system can work stand-alone. It can also be configured to be independent of micro plate movement, irregular shape and size, change in velocity of the carrying mechanism, and other characterizable and uncharacterizable variables.