Fig.i Signals used in ultrasonic analysis
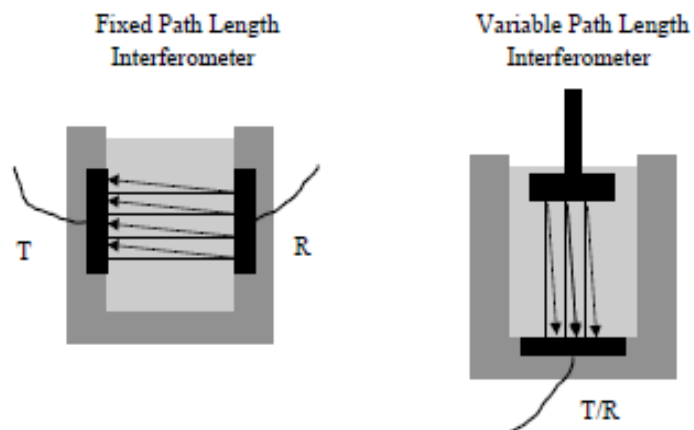

Fig. ii Fixed path length and variable path length interferometers

B. VARIABLE PATH LENGTH DEVICES: In a variable path length device the sample to be analyzed is placed in a thermo stated measurement cell which usually contains an ultrasonic transducer and a moveable reflector plate. A signal generator produces a sinusoidal electrical wave of the appropriate frequency and amplitude which is applied to the ultrasonic transducer where it is converted into a sinusoidal ultrasonic wave. The ultrasonic wave propagates into the sample and undergoes multiple reflections between the transducer and reflector plate which results in the formation of a standing wave. When the distance between the transducer and reflector plate is varied the amplitude of the signal received by the transducer goes through a series of maxima and minima because of constructive and destructive interference. The distance between successive maxima (Δd) is equal to half the

ultrasonic wavelength of the sample, and so the ultrasonic velocity can be calculated: $c = f\lambda = 2fd$. The attenuation coefficient is determined from by measuring the amplitude of the maxima as a function of the separation between the reflector plate and transducer.

PULSE TECHNIQUES: Ultrasonic spectrometers that utilize pulse techniques may be operated in a pulse-echo or through-transmission mode [8, 9]. In the pulse-echo mode a single transducer is used to both transmit and receive the ultrasonic signal, whereas in the through-transmission mode separate transducers are used to transmit and receive the signal.

a. THROUGH-TRANSMISSION TECHNIQUES: The sample to be analyzed is placed in a thermo stated measurement cell between two ultrasonic transducers: a transmitter and a receiver. The transmitting transducer produces a pulse of ultrasound which travels across the sample and is detected by the receiving transducer. The ultrasonic velocity and attenuation coefficient of the sample are determined by measuring the time-of-flight (Δt) and amplitude (A) of the ultrasonic pulse which has traveled across the sample. The ultrasonic velocity is equal to $c = d/\Delta t$ where, d is the length of the sample and Δt is the time required to travel this distance. The attenuation coefficient is calculated by comparing the reduction in the amplitude of the pulse that has traveled through the sample with that of a pulse which has traveled through a calibration material

b. PULSE-ECHO TECHNIQUES: The frequency-dependent ultrasonic properties of a sample are measured in a very similar fashion as in the through-transmission technique, except that a single transducer is used to both transmit and receive the ultrasonic pulses. The velocity and attenuation coefficient are calculated in exactly the same manner as described for

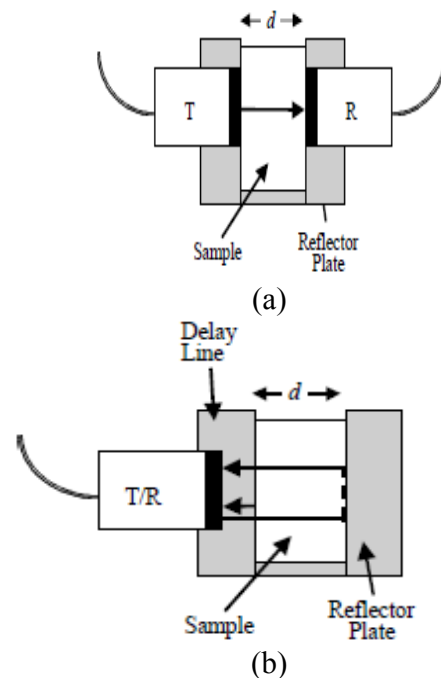the through-transmission technique, except that the pulse has now traveled a distance 2d rather than d (8).

(a)

(b)

Fig.iii Through transmission and Pulse echo techniques

STEP2: INTERPRETATION OF ULTRASONIC SPECTRA:

After measuring the ultrasonic velocity and/or attenuation coefficient as a function of frequency the particle size distribution is then determined by finding the droplet size distribution that gives the best fit between the predictions of the ultrasonic scattering theory and the experimental ultrasonic spectra. There are two approaches to solving this inverse scattering problem: *model-independent* inversion and *model-dependent* inversion.

In the model-dependent inversion method it is assumed that the particle size distribution follows some common forms which can simply model mathematically,

$$P(r) = \frac{1}{x_g \ln \sigma_g \sqrt{2\pi}} \exp - \left(\frac{\ln^2 \sigma_g}{2} \right) \exp \left(\frac{[\ln r - \ln x_g]^2}{2 \ln^2 \sigma_g} \right)$$

Where, P (r) is the probability of having a particle of radius r, x_g is the geometric mean of the radius and σ_g is the standard deviation of the geometric mean. The droplet size distribution can then be characterized by only two parameters: x_g and σ_g

Commercial ultrasonic particle-sizing instruments typically make measurements over the range 1 to 200 MHz, which enables them to analyze particles between about 10nm and 1000 mm in radius [4-7]

INSTRUMENTATION

A typical ultrasonic spectrometer consists of a signal transmitter, a signal analyzer and a measurement cell.

HIGH RESOLUTION ULTRASONIC SPECTROSCOPY:

High-resolution ultrasonic spectroscopy (HR-US) is an analytical technique based upon precision measurements of parameters (velocity and attenuation) of ultrasonic compression wave propagating through the analyzed sample. The general principle of the high-resolution ultrasonic measurements includes transferring the generated ultrasonic signal by the piezotransducer into the ultrasonic wave. Another piezotransducer transfers the received ultrasonic wave into an electronic signal subsequent analysis.

Most widely used approach for the measurements of ultrasonic characteristics in the past was based on the pulse technique. In this technique the ultrasonic pulse generated at a certain frequency is sent through a sample and received either at the opposite side or, after the reflection from the wall of the container, back to the source of ultrasound. Measurements of the amplitude of the wave in the pulse allow the determination of the ultrasonic attenuation and the propagation time (or

related parameters), which characterize the ultrasonic velocity. The resolution of this technique is limited by the length of the pulse or by the size of the sample. Hence the HR-US Spectrometer involves a novel principle where the path length of the ultrasonic wave in the sample exceeds the size of the sample. The use of modern advances in ultrasonic design, electronics and digital processing allow the attainment of ultrasonic measurements with much greater resolution (down to 10^{-5}% for ultrasonic velocity) in abroad range of the sample volumes, down to a single droplet.

BENEFITS OF THE ULTRASONIC ANALYSIS:

➤ Most materials are ultrasonically transparent allowing the analysis of a broad variety of sample types, chemical reactions and processes. Hence, Ultrasonic analysis can now be easily performed in chemistry, physics, biotechnology, pharmaceuticals, agriculture, environmental control, medicine

➤ Modern ultrasonic cells do not have sharp corners and can accommodate even aggressive liquids such as strong acids or organic solvents without evaporation in the course of measurements sizes range from 4ml down to 30µl.

➤ The measurements are completely computer controlled and results are presented in a graphical and digital format, which is compatible with Excel and most current data analysis software.
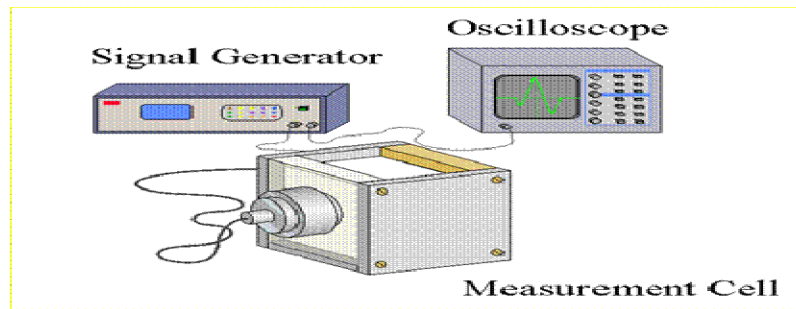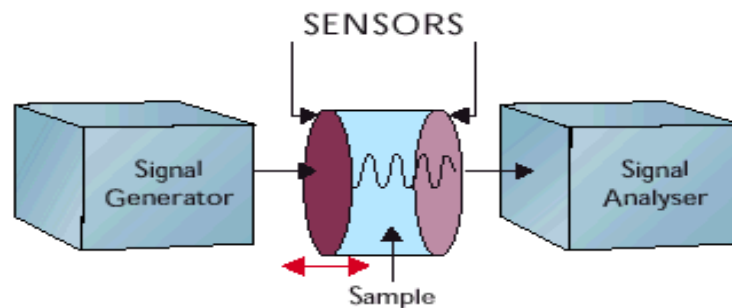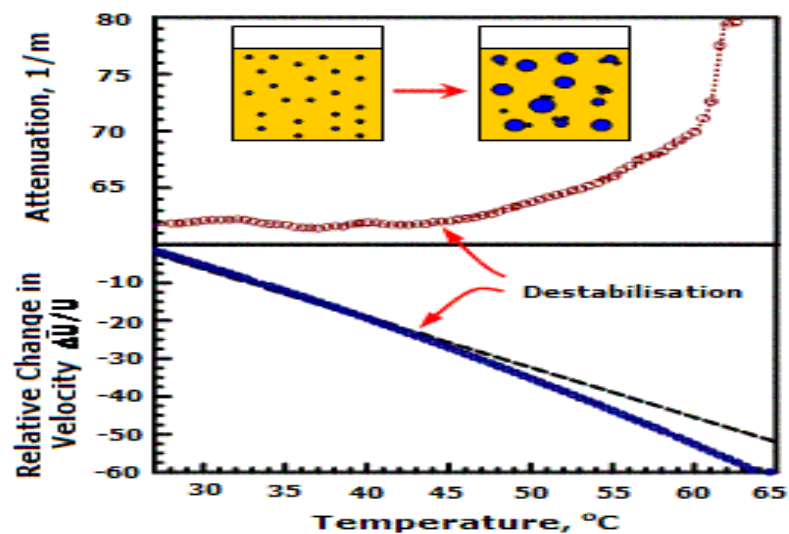
Fig.iv Ultrasonic spectrophotometer

Fig.v HR-US System

➢ The novel design of the Ultrasonic Scientific HR-US makes possible ultrasonic measurements in the temperature ramp regime for analysis of heat stability, phase transitions, conformational transitions in polymers and others

➢ There is the impressive dynamic range allows the analysis of solutions of small concentration, down to 0.3ppm (0.3μg/ml).

In short HR-US 102 allows high-resolution measurements of the velocity and attenuation of acoustical waves at high, ultrasonic frequencies propagating through materials. It provides fast, non-destructive analysis of a wide spectrum of properties of materials.
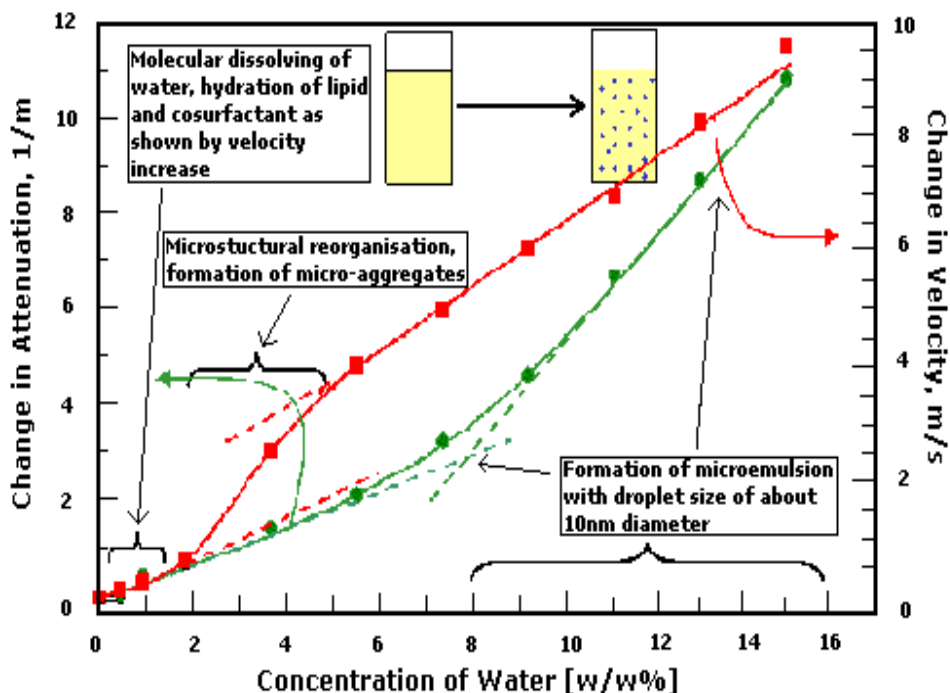
It combines simple sample handling with record precision, variety of measuring regimes, small sample volume, convenience and exceptional simplicity of use.

APPLICATIONS:

❖ **To evaluate stability of emulsions:** stability of emulsions (including the composition and microstructure) is a key element for evaluation of the lifetime and temperature conditions for the storage and use of emulsion based products. Ultrasonic measurements allow very simple procedures for the evaluation of the stability of emulsions.

In this experiment, ultrasonic analysis of the thermal stability of a pharmaceutical water/oil emulsion (0.5mm) was performed during gradual heating of the sample. The changes in the attenuation and relative ultrasonic velocity were measured. The arrows in the above figure indicate the temperature corresponding to the destabilisation of the sample. (Temperature measurements were taken at various frequencies in the range 2-15 MHz). The rise in the attenuation at 44°C provides clear evidence of restructuring in the emulsion. The increase in the attenuation can be attributed to the flocculation of dispersed aqueous droplets induced by heating. As seen above, the change in ultrasonic velocity deviates from the baseline at the same temperature that the ultrasonic attenuation begins to rise. This demonstrates the sensitivity of both ultrasonic parameters (attenuation and velocity) for accurate characterisation of the emulsion.

❖ **To determine particle size distribution of colloidal systems:** The attenuation spectra of a series of corn oil-in-water emulsion with different disperse phase volume fractions (1–50 vol. %) can be drawn. There will be excellent agreement between the measured and actual volume fractions of the emulsions up to the highest droplet concentration. In addition, the mean particle diameter is relatively insensitive to droplet

concentration, indicating that the ultrasonic technique is capable of analyzing this system over a wide range of concentrations without any sample preparation.

❖ **In the analysis of micro emulsions:** High-resolution ultrasonic spectroscopy is used for analysis of the formation of a micro emulsion in a system consisting of pharmaceutically accepted components, namely, isopropyl myristate, lecithin (Epikuron 200) and n-propanol as a co surfactant in a w/w ratio 6:1:1 and water. The measurements were performed at 20ºC using HR-US 102 spectrometer equipped with standard 1ml cell in the frequency range 2-20 MHz

The representation above shows a typical dependence of ultrasonic velocity (squares) and attenuation (circles) on concentration of water in the system (at 5 MHz). Molecular dissolving of water in the mixture at low concentrations (up to 2 wt %), which is accompanied by hydration of lipid and co surfactant as shown by the steady increase in ultrasonic velocity. Following this a micro structural reorganisation takes place, indicated by an additional increase in ultrasonic velocity in the range between 2% and 6% of concentration of water HR-US Spectroscopy provides a powerful tool for quality control and process control in PAT (process analytical technology).

❖ Used in the analysis of sedimentation and aggregation of drugs prepared using different polymer coatings.

❖ Used in measurement of concentration profile and sedimentation for suspensions in flow.

PERSPECTIVE AND FUTURE DEVELOPMENTS

The ability of ultrasonic spectroscopy to characterize colloidal suspensions which are concentrated and optically opaque without the need for any form of sample preparation is extremely important for many applications. One of the areas where the technique is most likely to be used is for the on-line determination of particle size distributions of colloidal suspensions during processing. The ultrasonic technique could be used to monitor the efficiency of a processing operation in real time that could lead to a major improvement in the manufacture of many colloidal-based materials, e.g. foods, pharmaceuticals, petrochemicals, agrochemicals and cosmetics.

Conclusion:

The arrival of new generation ultrasonic and HR-US analyzers provides real time information on chemical and micro structural characteristics across a broad range of materials. They act as a powerful tool for the development of new products and the optimization of existing products. Thus they have a profound impact on the efficiency and profitability of pharmaceutical processes.

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