

## Review

# Novel applications of ultrasonic atomization in the manufacturing of fine chemicals, pharmaceuticals, and medical devices

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## ABSTRACT

Liquid atomization as a fluid disintegration method has been used in many industrial applications such as spray drying, coating, incineration, preparation of emulsions, medical devices, etc. The usage of ultrasonic energy for atomizing liquid is gaining interest as a green and energy-efficient alternative to traditional mechanical atomizers. In the past two decades, efforts have been made to explore new applications of ultrasonic misting for downstream separation of chemicals, e.g., bioethanol, from their aqueous solutions. Downstream separation of a chemical from its aqueous solutions is known to be an energy-intensive process. Conventional distillation is featured by low energy efficiency and inability to separate azeotropic mixtures, and thus novel alternatives, such as ultrasonic separation have been explored to advance the separation technology. Ultrasonic misting has been reported to generate mist and vapor mixture in a gaseous phase that is enriched in solute (e.g., ethanol), under non-thermal, non-equilibrium, and phase change free conditions. This review article takes an in-depth look into the recent advancements in ultrasound-mediated separation of organic molecules, especially bioethanol, from their aqueous solutions. An effort was made to analyze and compare the experimental setups used, mist collection methods, droplet size distribution, and separation mechanism. In addition, the applications of ultrasonic atomization in the production of pharmaceuticals and medical devices are discussed.

## 1. Introduction

The chemical and processing industries (CPI) play a key role in converting available resources into desired products, such as chemicals, pharmaceuticals, energy, food, and fuels. In addition, the CPI are among the largest consumers of energy resources. During the past decade, this industrial sector has witnessed many critical developments enabled by process intensification (PI). PI involves the integration of multiple processing steps such as distillation, absorption, and drying, as well as the application of alternative energy sources such as ultrasound (US), microwaves, centrifugal fields, and electric fields to obtain more efficient, cleaner, and economical manufacturing processes (*Quadrennial Technology* [57]). In recent years, there has been an increased interest in the application of US processing in industries such as chemical, environment, food, and pharmaceutical industries as a “green and energy-efficient” alternative [81].

Sound waves with frequencies above those typically heard by humans are referred to as US waves. This frequency range is between 20

kHz and 5 MHz [60,81]. Unlike the sound waves with lower frequency, US waves propagate directionally in a narrow beam due to their high frequency and short wavelength. The wavelength of US is still significantly longer than the bond length between atoms in a molecule. Hence, when propagating through a liquid, US waves neither affect the vibrational energy of the bonds in molecules nor increase their internal energy [35]. Instead, the US waves cause physical and chemical effects such as mechanical effects and acoustic cavitation in the liquids [31,81].

The application of ultrasonic waves in unit operations, such as extraction, crystallization, distillation, and reactive distillation has been demonstrated to improve the process. The improvements include operational flexibility, increased energy efficiency, improved response time to inlet variations, improved reaction rates such as in synthesis and catalysis reactions, and decreased operational costs [60]. However, less effort has been made to scale up the ultrasound-assisted processes due to several reasons, mainly due to a lack of ultrasonic hardware manufacturing capacity.

In addition to the traditional chemical engineering processes, US

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waves are used in several applications in the field of atomization. Atomization is defined as the transformation of bulk liquid into sprays and other physical dispersions of mist droplets in a gaseous atmosphere (Lefebvre and McDonell, 2017 [41]). Several industrial processes such as film coating, spray cooling, spray drying, humidification, aroma diffusion, nanoparticle synthesis, incineration, liquid combustion, emulsion preparation, etc. use atomization to generate droplets of a fixed size distribution [58,85]. In order to produce a spray from liquid, a high relative velocity between the liquid and surrounding air or gas must be obtained. The traditional atomizers include pressure nozzle atomizers, two-fluid nozzle atomizers, rotary atomizers, etc. In these atomizers, mechanical energy is used to pressurize the liquid sheet and increase its kinetic energy for disintegration in the form of droplets. These atomizers have no control over the generated droplet sizes and their velocity. In addition, the energy demand of these atomizers exceeds the theoretical energy requirement for the generation of additional surfaces in the process of droplet formation. Therefore, it is required to develop processes that have control over the size of droplets and require low energy.

The application of US waves in atomization is one such approach for obtaining droplets with diameters  $<10\ \mu\text{m}$ , a narrow size distribution, and with reduced energy consumption. In addition, the advantage of this process is that the droplet generation is governed by frequency, the intensity of the US, and the physical properties of the liquid [68]. Ultrasonic transducer consumes only about 10% of the energy required for vaporization by heating [36]. In a US atomization process, bulk liquid in the form of a liquid sheet or ligament is disintegrated into fine droplets in a gas phase [5]. In this process, a liquid sheet is maintained over a piezoelectric disk. Electric energy is transmitted to the piezoelectric disk to generate mechanical vibrations leading to the formation of fine droplets [33]. Under lower frequency, i.e., in the range of kHz, acoustic cavitation occurs in a liquid subjected to the US. Atomization is induced when the US of high frequency, in the order of MHz, is applied to a gas-liquid interface. At this frequency, there is high directivity and the atomization starts instantaneously along with a liquid jet or fountain [70]. Ultrasonic atomization has been used in devices such as humidifiers, aroma diffusers, medical nebulizers, fuel injectors for engines or burners, liquid sample atomizers for analytical instruments, and other devices [52,63]. In the past two decades, several studies have been conducted on the application of ultrasonic misting for the separation of ethanol from aqueous solutions. However, these studies were limited to lab-scale and the experimental setups used were quite different, often yielding inconsistent results. This article compiles studies on the application of ultrasonic energy for the separation of chemicals, with a focus on the separation of ethanol from dilute aqueous solutions. The application of ultrasonic atomization in the production of pharmaceuticals and its use in medical devices is also presented.

## 2. Application of ultrasonic atomization in the production of fine chemicals

In traditional ultrasonic atomizers, the entire bulk liquid is atomized to produce mist droplets. In applications such as atomization of chemicals, a special type of ultrasonic transducer was used [43,61]. These transducers are installed at the bottom of the misting unit and focused acoustic energy is transmitted to the bulk solution either directly or via a coupling liquid [2]. The volume of bulk solution is maintained such that it forms a layer of few centimeters deep above the ultrasonic transducer. A part of this bulk solution is transformed to mist. In addition, the use of a dry carrier gas such as air or nitrogen gas generates vapor from mist droplets [45]. The bulk solution remains in the ultrasonic mister and the mixture of mist droplets and vapor is brought to the exterior of the unit using a carrier gas [52]. The momentum of the mist droplets and vapor mixture is controlled by adjusting the flowrate of carrier gas in the mister. The amount of liquid suspended in the carrier gas in the form of mist and vapor is limited by the rate at which it falls back into the liquid

and by the flowrate of the carrier gas.

### 2.1. Ultrasonic misting for the separation of ethanol-water solutions

In the separation of ethanol-water mixtures in the traditional distillation method, an azeotrope is formed at a concentration of 95.63% by mass of ethanol. At this azeotropic point, the equilibrium concentration of ethanol in liquid and vapor phases becomes identical. This proportion of components in the bulk solution cannot be altered any further using the conventional distillation technique. Several researchers have reported that this azeotropic point can be avoided by using ultrasonic misting. This means that a high concentration of ethanol in the mist can be obtained using ultrasonic misting compared to the traditional distillation method. When compared with distillation, ultrasonic misting is not accompanied by a phase change and the solutes such as ethanol are preferentially enriched in the mist phase. A single ultrasonic transducer transforms  $50\text{--}100 \times 10^{-6}\ \text{kg/s}$  of the bulk solution to mist at a power input of 16 J/s [45]. This rate of misting is higher than that achieved by heating the solution at the vaporization energy of ethanol or water. The ultrasonic operation can be carried out at low temperatures and the energy input is also reported to be small. In addition, this method does not require tedious treatments such as desorption or the addition of chemicals [8]. Since the separation is carried out at low temperatures, heat-sensitive compounds could also be separated with minimal degradation.

Several researchers have examined the separation of ethanol-water solutions using various types of ultrasonic misting systems as shown in Fig. 1. These ultrasonic misting systems are classified based on the types of setups such as batch feed, continuous feed, open system, and close systems, and usage of components such as condensers, and inlet and outlet for carrier gas. These systems are only a schematic representation and are not a replica of the experimental setups used in the referenced research work. The experimental conditions used in these studies are listed in Table 1.

Among the various misting unit types, batch systems of open (Fig. 1 (a)) and closed types (Fig. 1(b)) were widely used. The early work of Sato et al., [61] reported ultrasonic misting experiments using a batch system of open type. This is one of the first studies reported in the field of separation of ethanol and water solutions using ultrasonic misting. Misting experiments were conducted at 10, 30, and 50 °C, and low temperature was found to be favorable for the separation of ethanol and water. The concentration of ethanol in the mist and vapor mixture generated by ultrasound increased with increasing ethanol concentration in the bulk solution. At 10 °C and for bulk solutions with concentrations of ethanol  $> 10\ \text{mol}\ \%$ , mist/vapor with a concentration of 100 mol %, i.e., pure ethanol, was collected in the mist. Nii et al., [52] reported similar results on ultrasonic misting of ethanol-water solutions. However, a batch system of a closed-type, instead of the open-type, was used. At 10 °C and for bulk solutions with ethanol concentrations from 10 to 100 mol %, ultrasonic misting resulted in a mist and vapor mixture comprising of 100 mol % ethanol. On the other hand, when experiments were conducted in a closed-type batch system and without using carrier gas, the concentration in mist and vapor mixture decreased. This is because the generated mist and vapor mixture had insufficient momentum and was not effectively removed from the mister. In addition, in an open-type system with a carrier gas, a vapor is generated along with the mist droplets which leads to enhanced removal of generated mist from the misting unit. In these studies, the mist was not collected and analyzed directly. Instead, the concentration and weight of bulk solution before and after ultrasonic misting was measured and the concentration in the mist was estimated using a mass balance.

At an electrical power input of 20 W to the ultrasonic transducer, the energy input was found to be equal to the vaporization energy of ethanol, i.e., 38.6 kJ/mol [61]. Nii et al., [52] have compared the energy required for misting and distillation. The latent heat of evaporation for bulk solution removed during misting was estimated. This value was

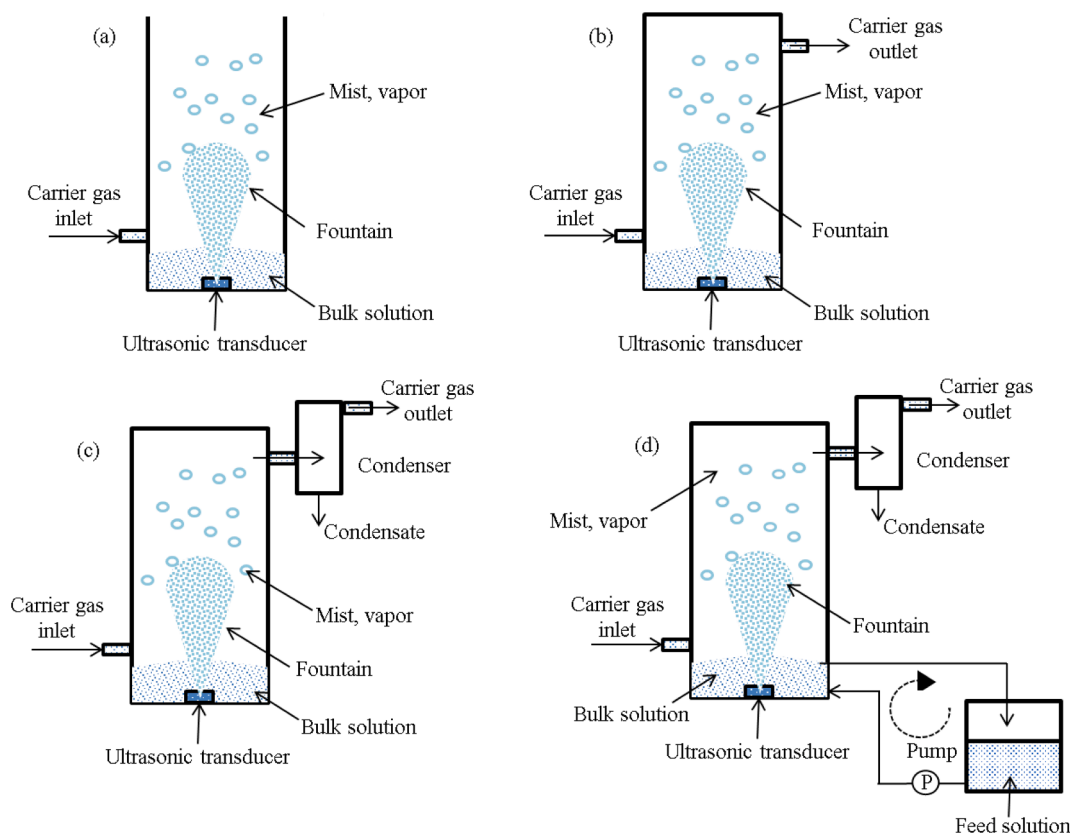


Fig. 1. Schematic of mister types used in the study of ultrasonic misting for ethanol-water separation (a) batch system, open-type, (b) batch system, closed-type, (c) batch system, with condenser, and (d) continuous feed system, with condenser.

found to be three to four times higher than the energy input to the ultrasound transducer, showing that the energy required in this type of separation is lower compared to distillation. This also shows that the generated mist droplets are enriched in ethanol to provide the reported degree of separation with lower energy requirements.

Although extensive experimental data was provided by Sato et al., [61] and Nii et al., [52], there was not much focus on the mechanism of separation for ethanol-water mixtures in ultrasonic misting. Kirpalani and Toll, [34] used a closed-type batch system with a condenser (Fig. 1 (c)) to investigate the physicochemical mechanism in the separation of ethanol-water solutions. During the ultrasonic misting process, liquid samples were collected from the liquid ligaments falling from the fountain jet and the bulk solution. The concentration of ethanol in the liquid ligaments was found to decrease while the concentration in bulk solution remained unchanged. At bulk solution concentrations of 10, 20, and 30 vol%, the corresponding concentrations in fountain jet were obtained as 10, 12, and 18 vol%. A marked decrease in the concentration of the bulk solution was observed after 15 min of misting process. This indicated that the separation occurred in the fountain jet and not the entire bulk liquid surface.

In batch systems, experimental parameters such as volume, concentration, and physical properties of the bulk solution change during the misting process. In order to scale-up the separation unit, a continuous feed system that maintains constant properties of bulk solution needs to be developed. Kirpalani and Suzuki, [33]; K. Suzuki et al., [67]; and Suzuki et al., [68] conducted experiments in continuous feed systems for the separation of ethanol-water solutions. The volume of bulk solution in the mister was kept constant by continuously supplying bulk solution using a feed tank and pump. This compensates for the loss of bulk solution in the form of mist and vapor during ultrasonic misting.

The mist/vapor was collected using a condenser and its concentration was directly analyzed. Nii et al., [52] and Sato et al., [61] used an

indirect method of analysis of ethanol concentration in the mist/vapor mixture. This method neglects the stoichiometric losses due to condensation along the walls of misting and collection systems and may lead to incorrect determination of the concentration in the mist. The direct collection method overcomes this problem by allowing the analysis of the condensed mist and vapor.

K. Suzuki et al., [67] compared the performance of batch (Fig. 1 (c)) and continuous ultrasonic misting systems (Fig. 1 (d)) for the separation of ethanol-water solutions. In the batch system and at 30 °C, the degree of separation of the ethanol-water solution was lower compared to that of Sato et al., [61]. When the misting time was increased from 20 mins to 1 h, the concentration of ethanol in the mist/vapor mixture decreased. On the other hand, the collection rate of mist/vapor increased by 3 times with the increase in misting time. Experiments were also conducted by varying the depth of bulk solution above the transducer in the range of 0.02–0.06 m and using a bulk solution of 20 mol % concentration. The increase in bulk solution level resulted in an increase in the concentration of ethanol in condensate by 2.5 times and decreased the mist and vapor collection rate by 3 times. This occurs due to the increase in the supply of ultrasound energy to the decreasing volume of bulk solution in batch systems. Overall, these studies show that in batch systems, the quality of the condensate is dependent on process time, conditions, and properties of the bulk solution.

In experiments using solutions of different ethanol concentrations, a high concentration of ethanol was obtained in the mist and vapor in continuous systems compared to batch systems. For bulk solutions of concentration >40 mol %, the condensate concentration was found to be greater than the concentration at vapour-liquid equilibrium (VLE) at 0.1 MPa. In addition, the condensate concentration and collection rate were found to be constant for a misting time of over 7 h [68]. In addition, at different flowrates of carrier gas, higher gas flowrates increased the volume of condensate collected without affecting the concentration

**Table 1**  
Experimental conditions used in the ultrasonic misting experiments for the separation of ethanol-water in various studies.

Reference	Ultrasonic misting system	Frequency of ultrasound transducer (MHz)	Carrier gas	Flow rate of carrier gas (l/min)	Volume of bulk solution in the mister (mL)	Height of liquid above the transducer (m)	Concentration range of bulk solution	Temperature of bulk solution (°C)	Misting time (min)	Method of obtaining the concentration in mist	Detection method
Sato et al [61]	Fig. 1(a)	2.3	air*	25	n/a	n/a	0–100 mol %	10, 30, and 50	n/a	mass balance	gas chromatography
Kirpalani and Toll [34]	Fig. 1(c)	2.4	air*	20	150	n/a	10, 20, and 30 vol %	25	15	analysis of condensed mist	abbe refractometer
Yasuda et al [87]	Fig. 1(b)	2.4	air*	56.5	235	0.03	26.5 vol%	20	30	mass balance	n/a
Nii et al [52]	Fig. 1(b)	2.4	air*	25	250	0.03	0–100 mol %	10, 30, and 50	n/a	mass balance	gas chromatography
Suzuki et al [67]	Fig. 1(c)	1.6	air*	0.174	50–130	0.025–0.067	10–80 mol %	24 ± 1	60	analysis of condensed mist	gas chromatography
Bando et al [8]	Fig. 1(d)	2.4	nitrogen	7.96–51.8	450	0.035	15 wt%	n/a	420	mass balance	gas chromatography
Matsuura et al [45]	Fig. 1(b) with PSA <sup>#</sup>	2.4	dry air	12	n/a	n/a	20 mol %	30	n/a	analysis of condensed mist	gas chromatography
Suzuki et al [68]	Fig. 1(d)	1.6	air*	0.172	68.75	0.035	10–80 mol%	10–40	420	analysis of condensed mist	gas chromatography
Hamai et al [25]	Fig. 1(d) <sup>†</sup>	2.4	air*	4	120	0.1	0–4 mol/L	10	30	mass balance	gas chromatography
Jung et al [29]	Fig. 1(b)	1.64 and 2.4	nitrogen	2	47.54	0.036	0.05–0.95 mol fraction	22	n/a	mass balance	refractometer and NMR
Kirpalani and Suzuki [33]	Fig. 1(d)	2.4	air*	0.086–0.271	58.92	0.03	0–90 mol%	10 and 24	60	analysis of condensed mist	gas chromatography
Tanaka et al [70]	Fig. 1(d) <sup>§</sup>	2.4	nitrogen	3 and 6	509	0.045	39 wt% (20 mol %)	25	90	analysis of condensed mist	gas chromatography
Yasuda et al [85]	Fig. 1(c)	2.4	nitrogen	19.8	235.7	0.03	0–1 mol fraction	20	5	mass balance	gas chromatography
Spotar et al [66]	Fig. 1(c) <sup>&amp;</sup>	n/a	air <sup>^</sup>	4–7.5	n/a	n/a	0–1 mol fraction	10	60–240	analysis of condensed mist	Refractometer and Anton Par Densimeter
Yasuda et al [86]	Fig. 1(c)	2.4	nitrogen	0.25–2	200	0.04	5–9 wt%	n/a	60	analysis of condensed mist	gas chromatography
Naidu et al [51]	Fig. 2	2.4	nitrogen	1	100	0.0153	0.1–1 mol fraction	22	35	analysis of condensed mist	high-performance liquid chromatography

\*Humidity value is not reported, <sup>#</sup>Pressure swing adsorption unit, <sup>†</sup>condenser was not used, <sup>§</sup>two condensers in series, <sup>&</sup>cotton was used to collect the mist, <sup>^</sup>air with relative humidity of 80–95% was used.

[33]. The studies by Kirpalani and Suzuki, [33]; K. Suzuki et al., [69]; and Suzuki et al., [68] proved that it is feasible to scale up ultrasonic misting units from batch to continuous units that are suitable for industrial-scale applications. These studies also showed the dependence of ethanol enrichment on the frequency of the transducer. The concentration of ethanol in mist collected was lower in the systems using a transducer of 1.6 MHz frequency when compared to other studies using 2.3 and 2.4 MHz transducers.

In order to design a continuous misting system, it is also important to study the effect of operating conditions such as flowrate of carrier gas, height, and location of inlet and outlet of carrier gas on solute enrichment in mist/vapor. Yasuda et al., [87] studied the separation of ethanol-water solutions in ultrasonic misting systems from the standpoint of reactor engineering. When the inlet and outlet of carrier gas are in level with each other and by increasing their heights to 0.2, 0.3, 0.4, and 0.5 m from the bottom of the mister, the concentration of ethanol in the mist and vapor increased to ~40, 50, 60, and 80 vol% from 26.5 vol % in the bulk solution. On the other hand, the rate of bulk solution removed by misting decreased from 15 to  $2.5 \times 10^{-9}$  m<sup>3</sup>/s with increasing heights of inlet and outlet from the bottom of the mister. The flowrate of carrier gas was varied from 18.9 to 132 L/min and the ethanol content in the mist and vapor decreased from 90 to 45 vol%. On the other hand, the amount of bulk solution removed from the mister increased with increasing the gas flowrate. The authors assumed that as the height of the outlet increased and carrier gas flowrate decreased, smaller droplets with higher ethanol content are carried to the exterior of the mister compared to larger droplets with lower ethanol content.

Experiments by several researchers have also shown that the collection of smaller liquid droplets from the mixture of mist/vapor was reported to enhance the concentration of condensate. Bando et al., [8] studied the effect of the flow behavior of carrier gas on mist and vapor generation, separation, and collection efficiencies using a computation fluid dynamics model and experiments using a batch system of closed-type. The trajectories of droplets showed that more liquid droplets reached the outlet when the inlet is at a lower height from the bottom of the vessel. The experimental results showed that the rate of mist/vapor removal increased with a decrease in the height of the inlet and outlet of carrier gas from the bottom of the mister. On the other hand, the concentration of ethanol in the collected liquid decreased with an increase in the rate of mist removal. This confirms that smaller liquid droplets with high ethanol concentrations are carried effectively when the carrier gas inlet and outlet are present at a higher level from the bottom of the mister. This study showed that the control of the rate of mist/vapor generated, and the flow behavior of carrier gas is important to enhance the concentration of ethanol in mist/vapor mixture.

In all the above-discussed studies, there has not been much attention paid to the mist collection or capture methods. Matsuura, [44] and Matsuura et al., [45] reported a mist collection method based on thermal swing and pressure swing adsorption (PSA), respectively. The main advantage of using ultrasound misting for the separation of ethanol-water solutions is its low energy requirement. The use of thermal swing adsorption will require thermal energy in the desorption step. Hence, Matsuura et al., [45] recommended the use of PSA as the collection method due to its low energy requirement. The mist and vapor generated by ultrasonic misting were first passed to an adsorption column containing a 3 Å molecular sieve for dehydration and are further purified using a hydrophobic adsorption column. The temperatures of bulk solution and condenser were controlled at 30 and -17 °C. When the concentration of bulk solution was 20 mol %, the concentration of ethanol collected at PSA reached 97 mol %. When the bulk solution concentration was >40 mol %, the concentration of ethanol in the condensate reached 98 mol % (99.5 v/v %) and a collection rate of  $5\text{--}6 \times 10^{-6}$  kg/s was obtained for one ultrasonic transducer.

In the study conducted by Matsuura et al., [45], a single collection unit was used to collect the mist and vapor. Tanaka et al., [70] reported that the collection efficiency of mist/vapor and the concentration of

ethanol in the condensate can be improved using a staged-collection method. This collection method consisted of two units of temperature-controlled condensers, TC<sub>1</sub> and TC<sub>2</sub>, connected in series. The temperature of the first condenser was varied from -10 to 20 °C with 5 °C increments and the temperature of the second condenser was maintained at -20 °C. When comparing the concentration of ethanol collected in TC<sub>1</sub> at 5 °C and TC<sub>2</sub> at -20 °C, the amount of condensate collected and its concentration in TC<sub>2</sub> was higher than that in TC<sub>1</sub>. For a bulk solution with a concentration of 39 wt%, the concentration in the vapor phase at VLE at 0.1 MPa is ~75 wt%. The concentration of condensate collected in TC<sub>2</sub> was ~85 wt% and in TC<sub>1</sub> it was ~65 wt%. With an increase in temperature in TC<sub>1</sub>, the amount of condensate collected in TC<sub>1</sub> decreased and TC<sub>2</sub> increased.

These results show that by collecting the condensate with a staged collection method, higher concentrations of ethanol and a higher amount of mist/vapor could be collected in the second stage condenser. It also revealed that mist/vapor consisting of droplets of a broad range of ethanol concentrations are not collected in a single unit, even if the temperature in TC<sub>1</sub> is as low as -20 °C. This is because the droplets evaporate while being transported by the dry carrier gas to the condensers. In the droplets containing multi-components similar to that in the ethanol-water system, the more volatile compound would be preferentially released. This leads to preferential evaporation of ethanol. In TC<sub>1</sub> the carrier gas is not condensed immediately, smaller droplets are encouraged to evaporate or shrink to a greater extent than larger droplets with less ethanol content in TC<sub>1</sub>. Due to this reason, the concentration in TC<sub>1</sub> is hard to reach the value at VLE and larger droplets and gas saturated with a vapor of water and ethanol will be condensed in this stage. In TC<sub>2</sub>, the smaller droplets and remaining vapor-phase ethanol and water are recovered. Yasuda et al., [85] have also reported that with bulk solutions of concentration higher than a 0.3-mole fraction, the ethanol concentration in atomized droplets almost reached a molar fraction of 1, and is higher than that in the vapor. When a multi-staged collection system is used, each collection stage will collect different concentrations and amounts of ethanol. Thus, by using a collection system with different number of stages, ethanol with a desired concentration and amount can be recovered. Further, the optimization of gas-flow conditions and temperature will also contribute to the concentration and amount of product collected. The authors note that for practical use of such a design, recycling of the condensed mist/vapor with low ethanol concentration in first stage (TC<sub>1</sub>) needs to be considered.

Our research group has conducted extensive experimentation on the separation of ethanol-water solutions using a novel ultrasonic misting apparatus [51] (Fig. 2).

In this method of collection, the mist and vapor mixture were fractionated and collected based on droplet sizes. In the 3-stage mist collection (MC) stage setup, due to the low temperature (-10 °C) in the 1st collector, as soon as vapor is in contact with the cold collector surface, condensation takes place. Naturally, most of the vapor is collected in MC stage 1. Afterward, the remaining vapor and the larger mist droplets in micrometers can mostly be collected in MC stage 2. Finally, the fine droplets can be carried further into stage 3 and collected in MC stage 3. The concentration of ethanol in the collected mixture was greater than that at VLE in all the stages for a bulk solution with a concentration >0.1 mol fraction. A higher ethanol concentration in stage 3 indicates that finer droplets are with ethanol concentrations higher than the large droplets collected in MC stage 2. Accordingly, the vapor-rich liquid in MC stage 1 has the lowest ethanol concentration.

Several researchers tried to compare the efficiency of separation obtained by ultrasonic misting to that of sparging methods [29,66]. Jung et al., [29] reported that sparging produced a high concentration of ethanol in the mist compared to ultrasonic misting. However, the mist was not collected and analyzed directly. The weight and concentration of bulk solution before and after misting was measured and the concentration of ethanol in mist was measured using a mass balance and

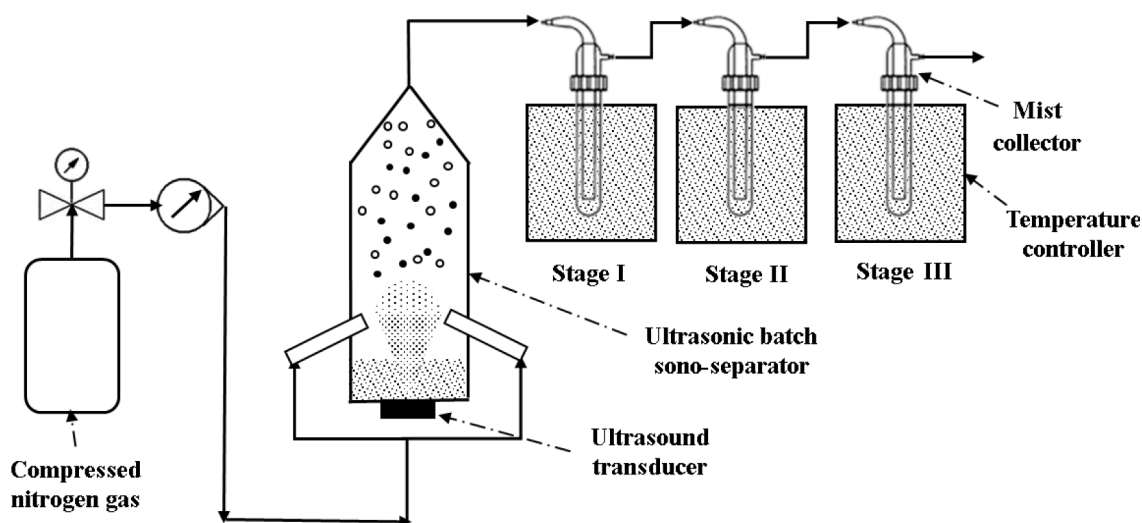


Fig. 2. Schematic of the experimental setup for ultrasonic batch sono-separator with three mist collectors connected in series [51].

refractometer. In addition, the flow rate of nitrogen gas used in the sparging experiments was not reported. The authors reported that the bubble residence time in the sparging experiments was sufficient for the ethanol concentration to get close to the VLE composition. However, the duration of experiments in the ultrasonic misting and sparging experiments is not reported. In such cases, the separation efficiencies obtained using these two methods cannot be compared. The results obtained by Spotar et al., [66] showed that ultrasonic misting and bubbling provide a similar degree of separation for ethanol-water mixtures. The ethanol concentration in the mist was reported to be lower than the value at VLE and the results reported by Sato et al., [61] could not be replicated. The experimental results obtained from this study are not comparable with other studies on ultrasonic misting for many reasons. In the misting experiments, cotton was allowed to soak in the mist, and a sample was collected every 15 min by squeezing. Cotton may absorb or adsorb ethanol and water mixture and thus it is not possible to recover the sample entirely. In addition, air with a relative humidity of 80–95% was used as carrier gas. This will lead to condensation of water vapor and decreases the concentration of ethanol in the condensate. Finally, the frequency and type of the ultrasonic transducer used in this study could not be confirmed from the manufacturer's website.

Several studies on the separation of ethanol-water solutions using air bubbling have shown that the residence time and temperature of bubbles govern the separation efficiency [1,10–11]. When bubbles at high temperature are injected into the bulk solution, the energy is transferred to the surrounding liquid either as latent heat of evaporation or as sensible heat. The former method results in mass transfer in the form of evaporation of liquid mixture from surface to the interior of the bubble and occurs at low bubble residence time. The latter method of sensible heat transfer causes a rise in the temperature of the bulk solution and occurs at high bubble residence time. In these studies, the temperature of the microbubbles is maintained at 90 °C such that it is higher than the normal boiling point of ethanol and lower than that of water. The depth of bulk solution is maintained in the range of 3–10 mm. When the thickness of the bulk solution in the unit is 10 mm, there was no separation of the azeotropic mixture. This is because of the increased residence time of bubbles leading to sensible heat transfer. When the depth of the liquid was 3 mm, the evaporation was favorable and led to maximum separation efficiency. For a bulk solution of a concentration of 95 vol% of ethanol, the residual concentration was obtained as 93 vol%. This shows that vapor with a high concentration of ethanol was removed in this process. The authors have reported that this method is a low-cost alternative to separation by distillation. Thus, separation using bubbling is competitive when compared with ultrasonic misting. However, an in-

depth study is required to compare the energy requirements for the separation of ethanol-water solutions using these methods.

Yasuda et al., [86] explored the combination of ultrafine bubbles (UFB, diameter <1 μm) and ultrasonic misting for the separation of ethanol-water mixtures. The ethanol concentration in the collected mist obtained using ultrasonic misting with UFB was higher than without using UFB. The enrichment ratios were increased by 1.5–1.27 times for ethanol-water solutions at concentrations of 5–9 wt%. Enrichment ratio is given by the ratio of concentration of ethanol in mist with respect to that of bulk solution before ultrasonic misting. The authors explained that ethanol attaches to the surface of the UFB in the solution owing to hydrophobic attraction and the UFB aggregate due to secondary Bjerknes forces to grow into cavitation bubbles. Additional experiments were conducted by varying the carrier gas flow rate from 0.25 to 2 L/min. The results showed that for all the flow rates of carrier gas, the concentration of ethanol in the mist was higher for misting with UFB when compared to misting without UFB.

The addition of salt to the ethanol-water solutions in ultrasonic misting also enhances the separation characteristics [25]. Enrichment ratios of ~3 were obtained for the misting of ethanol-water solutions in the concentration from 1 to 4 mol/L. In the presence of 0.73 mol/L of either K<sub>2</sub>CO<sub>3</sub> or (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, enrichment ratios of 20–30 were obtained for ethanol concentrations up to 4 mol/L. The enrichment ratios increased by ~5 units with the doubling of the concentration of salt. Further, salts that show weak interaction with water molecules such as Na<sub>2</sub>CO<sub>3</sub> or NaCl, did not result in improvement in enrichment ratio. The authors explained that ethanol exists in surface excess at the interface and is removed in the form of mist. In the presence of salt, the amount of water around the ethanol molecules decreases leading to an increase in the concentration of ethanol at the interface. This was confirmed with the determination of the concentration of ethanol molecules at the interface using surface excess theory, based on the Gibbs adsorption isotherm. It is also known that the vapor pressure of water decreases, and the vapor pressure of ethanol increases by the addition of salts. This could also lead to the enrichment of ethanol. In atomization methods such as spray atomization, the increase in the vapor pressure of ethanol leads to an increase in the concentration of ethanol in mist. In spray atomization, the mist is formed with the entire bulk solution and not the surface solution. In ultrasonic misting, the enrichment of ethanol at the surface plays an important role as the mist is produced with the solution at the surface. However, the contribution from vapor pressure is not clarified. In industrial applications, using salt will lead to additional costs and need special equipment to prevent corrosion. From an energy point of view, the separation of ethanol from low concentration

solutions consumes more energy and by adding salt there could be savings in energy.

Overall, these studies show that the flow conditions of carrier gas, droplet sizes, concentration and temperature of the bulk solution, and height of inlet and outlet of carrier gas determine the concentration and separation characteristics of ethanol-water solutions using ultrasonic misting. In order to further improve the concentration characteristics, Yasuda et al., [87] suggested the use of a demister to be fixed at the top of the misting unit. This is designed to prevent the large droplets with a low concentration of ethanol from escaping the unit. This is important in the view of the production of ethanol at an industrial scale. Nii et al., [52] presented an industrial prototype for the concentration of sake, Japanese rice wine. Multiple ultrasonic transducers were used in the misting unit. The bulk solution or the feedstock contained 18 vol% and is enriched to a product with 40 vol%. The plant is operated at a production rate of 10 L/h. The flavor was reported to be well retained and the sensory attributes were reported to be different from the conventional distilled sake.

### 2.1.1. Analysis of characteristics of mist generated during ultrasonic misting of ethanol-water solutions

Ultrasonic misting produces droplets of diameters,  $d_p < 10 \mu\text{m}$  with a narrow size distribution from liquid sheets [52]. When liquid is irradiated with the US, a fountain jet rises from the liquid surface due to acoustic pressure waves and breaks up at the apex because of gravitational effects [78]. Large liquid ligaments and drops are returned to the bulk liquid. Small low inertia droplets quickly surround the jet to form a dense fog. In industrial applications, it is desirable to control the size of droplets and their characteristics such as droplet size distribution. This requires a close study of the mechanism of breakup of liquid sheets and the formation of mist droplets. Three theories namely, capillary wave, cavitation, and conjunction theories have been proposed to explain the mechanism of liquid disintegration and droplet formation (Fig. 3). The common methods used to characterize the ultrasound-generated mist are listed in Table 2.

The capillary wave hypothesis favors a strong correlation between the mean droplet size and capillary wavelength. Liquid droplets are assumed to be formed by unstable oscillations at the crests of capillary waves. Lang, [38] measured the surface disturbance caused by the capillary waves using a photography technique. The molten wax was used as the liquid medium and ultrasonic frequencies in the range from 13 to 780 kHz were tested. A theoretical equation correlating the ultrasonic frequency,  $f$ , and macroscopic properties of bulk solution such

**Table 2**

Methods used to analyze the characteristics of mist generated during ultrasonic misting of ethanol-water solutions.

Reference	Method	Instruments
Kirpalani et al (2002 and 2011)	high-frame rate video capture at 2000 frames/s	digital camera: Redlake (PCI-8000S)
Yasuda et al (2004a, 2004b, and 2005)	laser diffraction laser light scattering	Sympatec LDI SPR7340, Nikkiso Co., Ltd.
Nii et al [52]	laser diffraction	AEROTRAC SPR 7340, Nikkiso Co., Ltd.
Yano et al [80]	Small-angle x-ray scattering (SAXS)	high precision powder diffractometer at the Japan Synchrotron Radiation Research Institute
Suzuki et al [68] Kobara et al [36]	visual observations $d_p$ : 10–700 nm, light scattering $d_p$ : 0.3–10 $\mu\text{m}$ , laser diode light scattering	photographs SMPS model 3936NL76-N (TSI) model 3016, LIGHTHOUSE
Bando et al [8]	visual observation	high-speed video camera

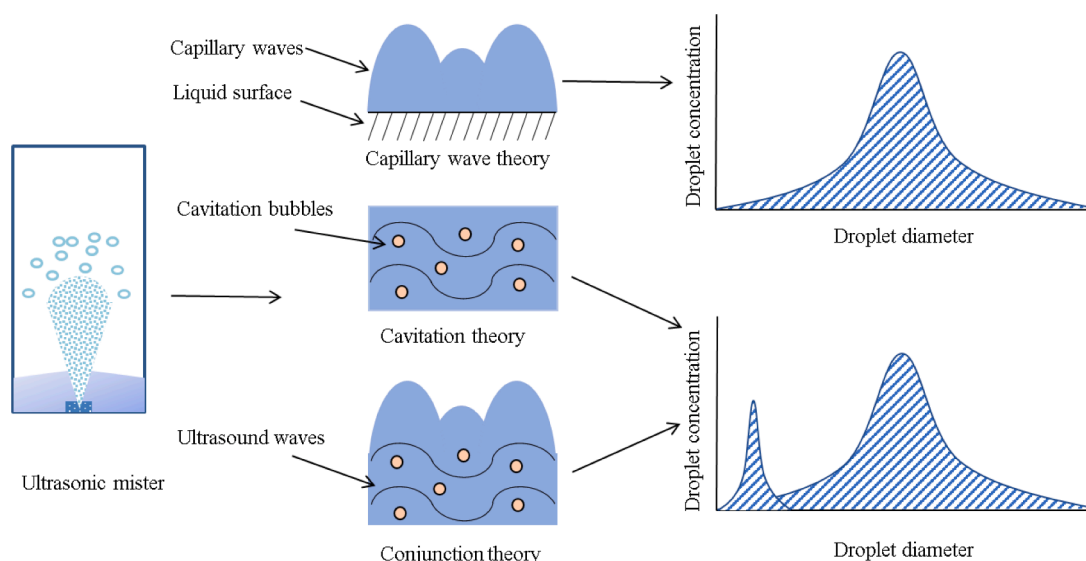
as surface tension,  $\sigma$ , density,  $\rho$ , and  $d_p$  of droplets generated during ultrasonic misting was proposed. This equation was derived from Kelvin's equation for the wavelength of capillary instability generated by ultrasound.

$$d_p = \alpha \left( \frac{\sigma}{\rho f^2} \right)^{1/3} \quad (1)$$

or,

$$d_p = 0.34 \left( \frac{8\pi\sigma}{\rho f^2} \right)^{1/3} \quad (2)$$

Using this equation, the diameter of droplets,  $d_p$ , generated by ultrasonic misting of pure water and anhydrous ethanol at 2.4 MHz is estimated to be around 2  $\mu\text{m}$  [80]. However, studies using visual inspection reported that the droplets generated from misting of pure ethanol were smaller compared to that of water [80]. Later, Kobara et al., [36] estimated the  $d_p$  as 2.3  $\mu\text{m}$  for water and 1.7  $\mu\text{m}$  for ethanol using the same equation. A. Suzuki et al., [67] used Lang's equation and estimated the  $d_p$  in the misting of amino acids, phenylalanine, and tryptophan, as 3  $\mu\text{m}$ . However, the experimental results gave different estimates for  $d_p$  as 1.03 and 0.38  $\mu\text{m}$  for phenylalanine and tryptophan,



**Fig. 3.** Analysis of mist characteristics in the ultrasonic misting of ethanol-water solutions.

respectively.

When ethanol is mixed with water, surface tension decreases, and solution density slightly decreases. Therefore, according to Lang's equation, the  $d_p$  should decrease with an increase in the concentration of ethanol in the solution. Yasuda et al., ([83]2005, [82]2004a, and [84]2004b) reported a median droplet diameter of 4.4  $\mu\text{m}$  at a solute molar fraction of 0.1 for ethanol. This value is within the range of value obtained using Lang's equation. Visual observations of ultrasonic misting of ethanol-water solutions by Suzuki et al., [68] showed that with an increase in the concentration of ethanol above 10 mol %, the visibility of mist was reduced. Kirpalani and Suzuki, [33] measured the  $d_p$  obtained in the ultrasonic misting of ethanol-water solutions. In their method, droplets with  $d_p$  of <175  $\mu\text{m}$  were measured, and the minimum cut-off value was not reported. They have observed droplets for ethanol concentrations up to 25 mol % and higher than that the droplets could not be visualized or measured. Nii et al., [52] determined the size distribution of droplets obtained in the misting of ethanol-water solutions using an ultrasonic transducer. For ethanol-water solutions of 5 and 10 mol %, the peak  $d_p$  were obtained as 6 and 3  $\mu\text{m}$ . Yasuda et al., [83] observed that for ethanol-water solutions, the  $d_p$  decreased with an increase in viscosity of the bulk solution, which increases with the increase in the concentration of ethanol. Lang's equation was modified as:

$$d_p = 2.8 \left( \frac{\sigma}{\rho f^2} \right)^{1/3} \left( \frac{\mu}{\mu_w} \right)^{-0.18} \quad (3)$$

The calculated results agreed with the experimental data within an error of  $\pm 20\%$ .

Most studies reported that ultrasonic misting produces droplets in the size of micrometers with a normal distribution [80,83]. However, the analytical methods used in these studies were limited in their ability to detect droplets of sizes less than the order of micrometers [33,52]. Bando et al., [8] reported that liquid droplets were generated from the surface of the fountain jet. There were 3 groups of droplets generated in the range of micrometer to millimeter diameter. The droplets in the micrometer range were generated because of liquid pinching from the crest of capillary waves. The droplets in the range of several tens and hundreds of micrometers were generated due to the violent movement of the fountain surface. The droplets in the millimeter range were formed from the detachment of the tip of the liquid fountain. Kobara et al., [36] determined the droplet sizes in the ultrasonic misting of water, and 5 and 50 mol % of ethanol solutions. For pure water and 5 mol % ethanol solution, two peaks were observed at 30 nm and 1  $\mu\text{m}$ . This shows that ultrasonic atomization of pure water and aqueous solutions of ethanol produces two sizes of droplets. With an increase in the concentration of ethanol, the droplet size was reported to decrease. Also, with the increase in the concentration of ethanol from 5 to 50 mol %, the size distribution of larger droplets did not shift to the smaller side, but the generation of such larger droplets reduced. These observations contradict the capillary wave theory and  $d_p$  values obtained using Lang's equation. It should be noted that Lang's equation was derived for experiments using ultrasonic frequencies below 800 kHz and it does not consider the physical properties of solution and frequencies over 1 MHz that are typically used in ultrasonic misting experiments.

Lang's equation does not directly correlate the effect of bulk solution temperature with  $d_p$ . With an increase in the temperature of the bulk solution, surface tension decreases, this leads to a decrease in  $d_p$ . Suzuki et al., [68] studied the effect of bulk solution temperature on  $d_p$ . At 10  $^\circ\text{C}$ , the mist droplets were not visible and increasing temperature to above 30  $^\circ\text{C}$  increased droplet size and led to the formation of dense mist. Kobara et al., [36] also studied the effect of temperature of bulk solution on the droplet size in the ultrasonic misting of ethanol-water solutions. At 10 and 20  $^\circ\text{C}$ , droplets in the range of 10–100 nm predominated and a few coarse droplets in the range of 1  $\mu\text{m}$  were generated. Among the nano-sized droplets, the median size of droplets decreased from 41.9 to 26 nm with an increase in temperature from 10

to 50  $^\circ\text{C}$ . Coarse micrometer droplets were generated at 50  $^\circ\text{C}$  only and not observed at lower temperatures. The dependence of  $d_p$  on temperature,  $T$ , is given by Kelvin's equation:

$$d_p = \frac{4\bar{v}\sigma}{RT\ln S} \quad (4)$$

where  $\bar{v}$  is molecular volume and  $S$  is super saturation degree. This equation is based on the relationship between  $d_p$  and equilibrium vapor pressure. It considers a static interface between liquid and gas phases. According to this equation, the  $d_p$  decreases with an increase in temperature. However, this holds only in the case of nanosized droplets, but the generation of coarse droplets as in the studies conducted by Kobara et al., [36] is contrary to this equation. This shows that for describing  $d_p$  an alternative interpretation is needed rather than the equation based on VLE.

Yano et al., [80] analyzed the size of droplets obtained in the misting of ethanol, water, and their mixtures using small-angle x-ray scattering (SAXS). In the misting of pure ethanol highly uniform liquid droplets with  $d_p$  of  $1 \pm 0.2$  nm were obtained. This value is  $10^{-3}$  times less than that obtained from Lang's equation. On the other hand, for misting of water the size of droplets was in the order of micrometers. In the case of ethanol-water mixtures of 20 mol % concentration and temperature of 20  $^\circ\text{C}$ , the  $d_p$  was around 1 nm containing a concentration of 62 mol %. With an increase in temperature of the bulk solution to 50  $^\circ\text{C}$ , the  $d_p$  increased to 100 nm and concentration in the droplet decreased to 42 mol%. This shows that with an increase in temperature, vaporization and generation of water-rich droplets are enhanced. Yano et al., (2005) and (2007) explained the formation of mist droplets enriched in ethanol based on surface excess theory. Experimental studies using the x-ray diffraction technique revealed that the microscopic composition of the fountain jet is similar to that of the bulk liquid without ultrasonic irradiation [79]. However, droplets in the diameter range of 1 nm are generated at the surface of the capillary fountain jet where surface excess of ethanol leads to the formation of a monolayer. This monolayer occurs at a bulk ethanol concentration of  $\sim 10$  mol % and regenerates within 4 ms [79,80].  $\mu\text{m}$  droplets are generated from the bulk solution. In addition, with the increase in temperature of the bulk solution, the hydrogen bonds in the bulk liquid weaken leading to the easier formation of micrometer-sized droplets. Similar results have been reported by Nishi et al., [53] and Wakisaka and Matsuura, [73] based on the mass spectra of clusters obtained for ethanol-water solutions.

Kobara et al., [36] explained the effect of ethanol concentration and temperature of bulk solution on  $d_p$  from a microscopic heterogeneous structure viewpoint. At low concentrations of ethanol in water,  $\sim 7$  mol %, ethanol molecules exist as part of a hydrogen-bonded network. Ultrasonic misting produces micrometer-sized droplets due to the strong hydrogen bonding network of water molecules in such dilute solutions. The increase in the concentration of ethanol leads to self-association of ethanol, a notable decrease in surface tension, and a decrease in  $d_p$ . This also leads to microscopic phase separation of solution into ethanol-rich and water-rich phases, leading to preferential atomization from the ethanol-rich cluster. Wakisaka and Matsuura, [73] explained that microscopic phase separation between ethanol-rich and water-rich clusters also takes place more significantly at lower temperatures. At higher temperatures, the ethanol-rich clusters interact with water-rich clusters leading to the generation of coarse micrometer-sized droplets.

A recent study by Zhang et al., [89] showed that the droplet size distribution is dependent upon the ultrasonic and operational parameters such as input power, the flowrate of the bulk solution, viscosity, and surface tension. The capillary and cavitation activity influence the effect of these factors on droplet size distribution. Capillary waves and low-intensity cavitation events lead to a narrow range of droplet size distribution and small droplet sizes. On the other hand, high-intensity cavitation events lead to wide droplet size distribution and large droplet sizes.



### 2.1.2. Mechanisms for ultrasound-mediated separation of ethanol-water mixtures

Kirpalani and Toll, [34] postulated a mechanism based on the conjunction theory for the separation of ethanol-water solutions. They have reported that the mist droplets enriched in ethanol are generated periodically from the surface of the fountain jet and not the bulk solution. The first step in this process is the formation of cavitation bubbles with surface excess of ethanol in the bulk solution. These bubbles grow as they travel through the bulk solution. They move upwards in the fountain jet and collapse periodically at the surface into a cloud of micro-bubbles and releases vapor and droplets enriched with ethanol. Suzuki et al., [68] and K. Suzuki et al., [67] have presented experimental evidence based on the temperature profile of fountain jet to support this mechanism. When the bulk solution temperature was 24 °C, the temperature in the fountain jet was reported to be in the range of 27–47 °C. The temperature in the jet increased with an increase in the distance from the surface of the transducer. The maximum temperature was recorded in the fountain jet above 0.035 m from the surface of the transducer. Kirpalani and Suzuki, [33] measured the temperature along the surface of the bulk solution and radial to the fountain jet for two bulk liquid temperatures of 10 and 24 °C. The base of the ultrasonic jet temperature was higher by 14 °C compared to the bulk solution. The temperature of the surface of bulk liquid remained the same. The mechanisms proposed in literature on ethanol enrichment in ultrasound-generated mist are shown in Fig. 4.

This indicates the presence of cavitation bubbles in the jet. Micro-bubble cloud travels in the jet and collapses in regions where acoustic energy is accumulated thereby releasing an ethanol-rich mist. With increasing the temperature, the collapse of microbubbles results in ethanol-rich vapor and mist. An increase in droplet vaporization was also anticipated due to the change in thermal profile along the jet. It was explained that with an increase in the temperature in the fountain jet, the viscosity decreases, and vapor pressure increases. This leads to an increase in the vaporization rate of ethanol and the separation of ethanol-water mixtures. Yano, [79] have also reported that the microscopic composition, obtained using x-ray diffraction technique, of fountain jet is identical to the bulk solution without ultrasonic irradiation. Their experiments have concluded that separation of ethanol-water occurs at the onset of or just following the formation of mist.

Yasuda et al., [87] postulated that during ultrasonic misting, solutes such as alcohol adsorb on the surface of cavitation bubbles. This leads to the formation of film around the mist droplets. However, a detailed explanation of the formation of droplets and enrichment mechanism was not provided. Yasuda et al., (2004a) and (2004b) studied the separation characteristics of several solute groups such as alcohols, ketones, amides, polyols, carboxylic acids, and inorganic salts in ultrasonic misting. Solutes such as alcohols were reported to be enriched in the mist while polyols were diluted in the mist. When comparing the separation characteristics of primary alcohols i.e., methanol, ethanol, and 1-propanol, at the same concentration in the bulk solution, 1-propanol was present at the highest concentration and methanol was present at the lowest concentration in the mist. Based on these results, the hydrophilic and hydrophobic characteristics of solutes were reported to govern the separation characteristics. In addition, for alcohols, the hydrophobicity of alcohols increases with an increase in the chain length of alcohols [39]. These results support the earlier claim by Yasuda et al., [87] that the hydrophobic solutes adsorb and form a film around the mist droplets. In the later studies, Yasuda et al., (2005, and (2004b) modeled the mist droplets to contain a solute shell and a solution core. In the case of alcohols, the surface solute amount on the shell was highest for hydrophobic solutes such as alcohols and lowest for hydrophilic solutes such as polyols. The mechanism of solute shell formation on droplet surface was not supported by experimental evidence in their study. However, the solute shell was formed due to several factors. These factors consist of a combination of solute adsorption on the surface of cavitation bubbles and incensement of surface area due to vibration of capillary wave

on the surface of the bulk solution, phase separation near the surface in bulk solution due to compression waves of ultrasound, supply of solute to the surface in bulk solution by ultrasonic streaming, and adsorption of solute vapor on the surface of droplets. In later studies, Yasuda et al., [85] explained that in the case of alcohol-water solutions, the micro-heterogeneity in the bulk solution causes the separation. When comparing bulk solutions of different alcohols at same concentration, the concentration of alcohol-rich clusters is higher for the most hydrophobic alcohol. In the ultrasonic misting of methanol- and ethanol-water solutions, the concentration in the mist was high for ethanol compared to methanol. It was concluded that during ultrasonic misting, the alcohol-rich clusters are preferentially misted when compared to water.

Koga et al., [37] and Yano, [79] explained that the formation of surface excess of ethanol in aqueous solutions causes the enrichment in ultrasonic misting. They have explained that the surface and bulk structures in alcohol-water solutions are correlated. The presence of hydrophobic solute in an aqueous solution increases the order of water surrounding the solute and locally enhances the hydrogen bonding network. This is known as hydrophobic hydration or iceberg formation. The strong hydrogen bonding network of water causes the surface excess of solutes and leads to the formation of a monolayer. At this point, the solute molecules aggregate, and the bulk solution starts to lose ideality. The aggregations of solute molecules formed at surface excess grow and destroy the percolation of the hydrogen bonding network of water in bulk solution. This disturbance in the hydrogen bonding of water in bulk solution increases with an increase in the concentration of solute. However, in order to maintain the monolayer, a strong hydrogen bonding network in the bulk solution is required. This leads to a decrease in the surface excess with an increase in the concentration of solute.

Adsorption isotherms obtained using experimental data have shown that the surface excess of alcohols increases with an increase in the concentration of alcohol in the bulk solution, reaches a maximum, and then decreases [79]. The concentration of alcohols at which surface excess begins to form depends on the hydrophobicity of the alcohol. This follows as methanol < ethanol < 2-propanol < 1-propanol < *tert*-butanol. Also, the concentration range for surface excess formation follows the same order. The maximum value of surface excess for solutions such as methanol-, ethanol-, 1-propanol, and 1-butanol is around  $0.8 \times 10^{-5}$  mol/m<sup>2</sup> corresponding to a monolayer. This value also corresponds to the maximum in the adsorption isotherm and the concentration where the bulk solution loses ideality. The mole fraction of this maximum in surface excess coincides with the corresponding minimum in the excess partial molar volumes of alcohols. This shows that at the same concentration in bulk solution, the molecular space of alcohols reaches minima in bulk solution and surface layer simultaneously.

A. Suzuki et al., [67] asserted that the enrichment mechanism in ultrasonic misting involves separation at the gas-liquid interface. The surface-active substances adsorb from the bulk liquid and are enriched in collected droplets. The enriching mechanism is affected by the adsorption equilibrium between the bulk liquid and droplet surface and the specific surface area of liquid droplets. The adsorption equilibrium is governed by the physicochemical properties of the solutes and the specific surface area of droplets is governed by the liquid properties and operating conditions.

Hamai et al., [25] compared the concentration of ethanol in droplets and mist. The results showed that the concentration of ethanol in the mist was higher than the vapor. This is because ethanol exists in surface excess at the interface and is removed in the form of mist. In their studies, the enrichment ratios doubled in the presence of salt such as K<sub>2</sub>CO<sub>3</sub>. This is because, with the addition of salt, the amount of water around the ethanol molecules decreased leading to an increase in the concentration of ethanol at the interface. The concentration at the interface was determined using surface excess, which is based on the Gibbs adsorption isotherm. In addition, salts that weakly interact with water molecules such as Na<sub>2</sub>CO<sub>3</sub> or NaCl did not result in an

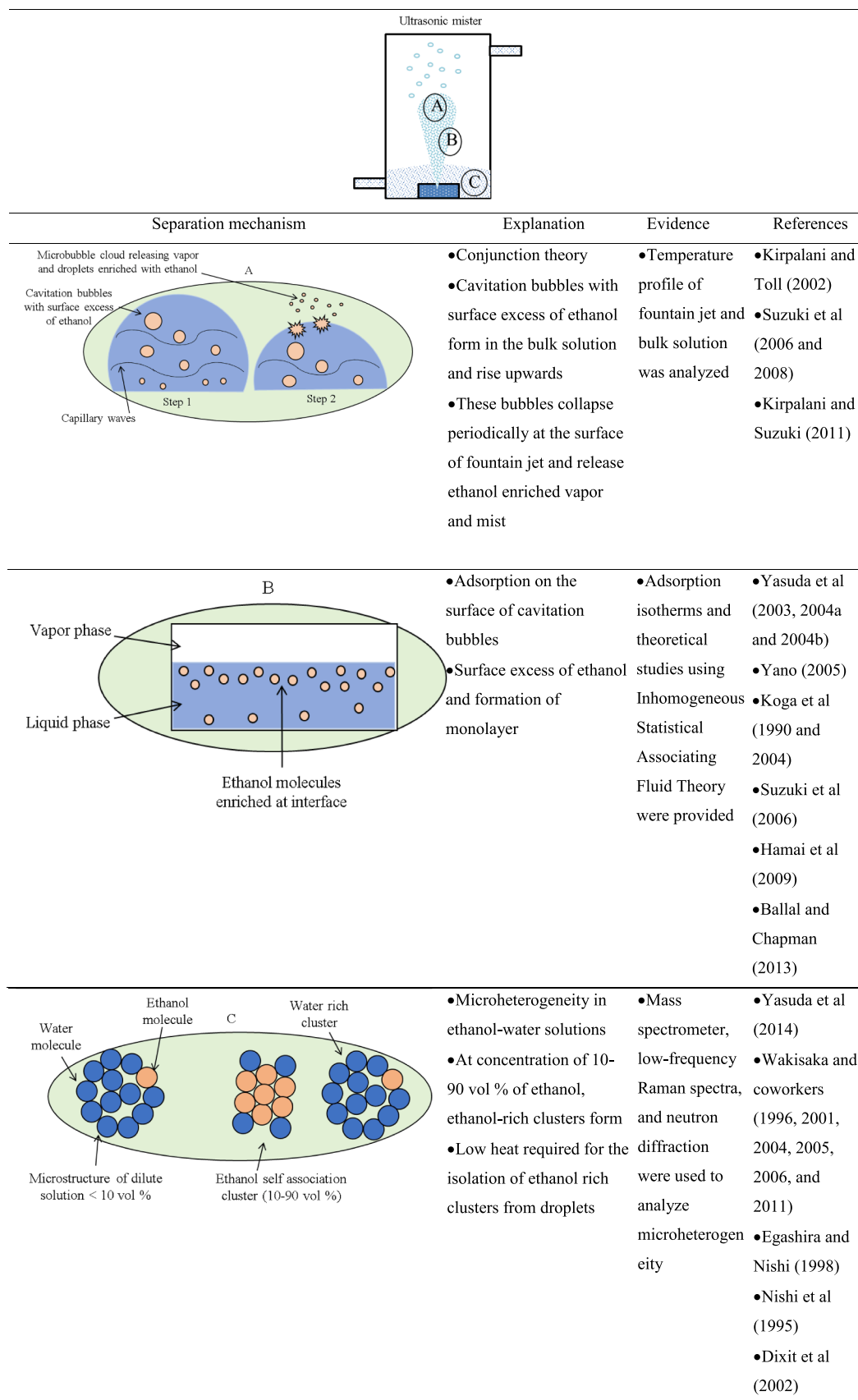


Fig. 4. Mechanisms of ethanol enrichment in ultrasonic misting proposed by various research groups.

improvement in enrichment ratio. They have reported that the vapor pressure of water decreases, and the vapor pressure of ethanol increases by the addition of salts. This could lead to the enrichment of ethanol. In other kinds of atomization methods such as spray atomization, the increase in vapor pressure of ethanol can lead to an increase in the concentration of ethanol in mist as the mist is formed with the bulk solution and not the surface solution. In ultrasonic misting, the mist is generated from the fountain jet. Hence, a clear explanation is not provided by this study.

Ballal and Chapman, [6] studied the microstructure of water-ethanol mixtures at the interface using an inhomogeneous Statistical Associating Fluid Theory (iSAFT). When present in pure forms, ethanol, and water form complex hydrogen-bond networks. However, in binary mixtures, the presence of hydrophobic alkyl groups of alcohols complicates the structuring of the solution. Ethanol-and water-rich regions exist in binary mixtures and the thermodynamics and structure of these regions are different. The hydrophobic segments cluster together and leave some hydrogen bonding network of water leading to negative excess entropy. This anomalous structuring has been explained as the basis of enrichment of ethanol in the ultrasonic misting process. In this process, ethanol is separated from water in the form of mist at a vapour-liquid interface. The authors reported that ethanol orients perpendicular to the interface and is preferentially concentrated at the vapour-liquid interface. In this orientation, the water is kept away from the interface. The surface mole fraction of ethanol, i.e., the average mole fraction of ethanol in the first 3 molecular layers next to the interface, was almost equal to the mole fraction of ethanol obtained in the mist by Sato et al., [61]. This shows that ethanol molecules are preferentially separated in the ultrasonic misting process. In addition, they have extended this study to methanol-, 1-propanol-, and 2-propanol-water mixtures. The surface mole fraction of these alcohols increased with an increase in their chain length and ultrasonic misting enriches the alcohols that are present at high concentrations at the interface. On the other hand, as the chain length of alcohol increases, the vapor pressure decreases and the concentration in the vapor phase decreases. This shows that the vapor pressure of solutes does not have any effect on the enrichment using the ultrasonic misting process.

Wakisaka and coworkers ([74](2011), [75](2004), [72](2001), [71](1996); [73](2006); and [76](2005)) explained that the micro-heterogeneity in the form of ethanol- and water-rich clusters in alcohol-water solutions is responsible for the enrichment of ethanol in the ultrasonic misting process. This research group has designed a special mass spectrometer that isolates molecular clusters from liquid solutions and analyzed their mass [71]. The bulk solution passes through a heated nozzle to generate a flow of liquid droplets. The temperature of the droplets was estimated to be 90–100 °C lower than the nozzle temperature. Inside the mass spectrometer, strongly interacting molecules in the liquid droplets remain as clusters but weakly interacting molecules are vaporized as monomeric molecules. The clusters were ionized and then analyzed by the mass spectrometer.

Initially, the mass spectra of pure water were observed at four nozzle temperatures of 125, 150, 175, and 195 °C. At 125 °C, water clusters with smaller mass numbers,  $\leq 500$  atomic mass unit (amu), were only observed. This is because the thermal energy supplied by the nozzle at this temperature is too small to fragment the water droplets into clusters. When increasing the temperature to 150 °C, water clusters with larger mass numbers and higher signal intensities were formed. The clusters formed at this temperature predominantly consisted of 21 and 28 molecules, an inherent property of pure water. At 195 °C, the hydrogen bonding network of water is destroyed, leading to vaporization and decomposition of water clusters.

The cluster structures of ethanol-water solutions of various concentrations were studied and three types of cluster structures were observed at <10, 10–90, and >90 vol% of ethanol. In the concentration range of <10 vol% of ethanol, the mass distribution of clusters was identical to that of pure water. The clusters consisted of a total of 21 molecules of

ethanol and water, with the number of ethanol molecules varying from 1 to 5. In this concentration range, the ethanol molecules were substituted for a part of water molecules in the hydrogen bonding network, and this network remained undisturbed and similar to that of pure water. At a concentration of 10 vol% of ethanol, two types of clusters, ethanol self-association/ethanol-rich, and ethanol-water clusters were observed. The microscopic phase separation at the cluster level was also observed at this concentration. In the concentration range of 10–90 vol%, ethanol-rich clusters were mainly observed. These clusters consisted of 2 to 8 ethanol molecules, representing dimeric to octameric molecular structures. This shows that the hydrogen bonding network of pure water was changed to accommodate the ethanol self-association clusters. At a concentration of >90 vol% of ethanol, ethanol-rich clusters were mainly observed. Interestingly, when the concentration of ethanol was 100 vol %, ethanol-self association clusters consisting of >4 molecules, i.e., larger than tetrameric structures were hardly observed. This shows that the self-association of ethanol is promoted by the presence of water.

The effect of temperature on the cluster structures was studied by varying the temperature of the nozzle. At a concentration of 5 vol% of ethanol and nozzle temperature of 135 °C, the cluster structure and hydrogen bonding network were undisturbed. At a temperature of 160 °C, the thermal energy destroyed the hydrogen bonds in the cluster and the hydrogen bonds between the ethanol and water molecules were broken. This temperature corresponds to the vaporization of ethanol molecules from clusters. At a concentration of 10–90 and >90 vol% of ethanol and a lower nozzle temperature of 110 °C, the ethanol self-association clusters were predominant. With an increase in temperature to 130 °C, the ethanol-rich clusters interacted with water clusters to promote the formation of ethanol-water clusters. The  $\Delta H$  for the isolation of clusters from liquid droplets was lower for smaller clusters compared to larger clusters. At a concentration of 10–90 vol%, the smaller clusters were composed mainly of ethanol molecules and microscopic phase separation existed between ethanol-rich and water-rich clusters mixtures. This shows that in this concentration range ethanol can be isolated from binary at lower temperatures using ultrasonic misting.

Egashira and Nishi, [18] have also proposed the microscopic phase separation as the underlying mechanism for the separation of ethanol-water mixtures and explained the role of water in cluster formation based on the low-frequency Raman spectra of these mixtures. They have reported that the binary mixture consists of ethanol groups and water groups at the isosbestic point. Nishi et al., [54] have reported that the hydrogen bonds between water clusters and ethanol clusters are weak and the lifetime of hydrogen-bonding networks of ethanol clusters was longer than that of water clusters. They have proposed that water molecules might exist as stabilizers for ethanol clusters. Dixit et al., [17] have also confirmed the incomplete mixing of alcohol-water solutions at the molecular level using neutron diffraction experiments. Their results indicated that in concentrated solutions of alcohol and water, water molecules exist as small hydrogen-bonded strings and clusters in a “fluid” of closely packed hydrophobic groups.

## 2.2. Ultrasonic misting for the separation of organic molecules

There has not been much research conducted on the separation of organic molecules other than ethanol using the ultrasonic misting process. A. Suzuki et al., [67] and Yasuda et al., (2004a) have studied the separation characteristics of several classes of chemical compounds such as organic acids, polyols, ketones, amino acids, amides, salts, alcohols, etc. However, their studies were not detailed to explain the concentration mechanism and basis of separation characteristics of those compounds.

Organic molecules such as amino acids are used widely in the pharmaceutical and food industries. Conventional separation methods such as crystallization, adsorption, and membrane separation are used to recover amino acids from dilute solutions. A. Suzuki et al., [67] reported

that ultrasonic misting is effective to recover amino acids from dilute solutions. Amino acids namely, tryptophan and phenylalanine, were used in their study. The enrichment ratios increased with a decrease in the concentration of the bulk solution. At concentrations of  $10^{-6}$  to  $10^{-4}$  M, the concentration in the mist increased by 10–100 times. The pH of the bulk solution played an important role in the enrichment of phenylalanine. Due to its surface activity, phenylalanine was present at a high concentration at the gas-liquid interface at pH 10. On the other hand, the pH did not affect the adsorption equilibrium in the enrichment of tryptophan.

Naidu et al., [51] conducted studies on the separation characteristics of several groups of organic molecules such as alcohols (methanol, ethanol, 1-propanol, and 1-butanol), carbohydrates (glucose and sucrose), carboxylic acids (acetic acid), ketone (acetone), lactone (gamma-valerolactone (GVL)), and polyols (ethylene glycol and glycerol). In the case of alcohols and acetone, the mist was found to be enriched with the solutes. This shows that biofuels such as ethanol and butanol can be separated using this non-thermal and non-equilibrium method. On the other hand, organic acids, polyols, lactones, and sugars were diluted in the mist or enriched in the bulk solution. This will provide the basis for the concentration of these solutes in a non-thermal and non-equilibrium method. The role of various physicochemical parameters of the solution, such as Henry's law constant, vapor pressure, and octanol-water partition coefficient, on ultrasound-assisted separation of solutes, was also determined. Among these properties, the octanol-water partition coefficient ( $\log P_{ow}$ ) of the tested organic molecules was found to control the separation characteristics. The compounds with higher  $\log P_{ow}$  were enriched in the collected mist and those with lower  $\log P_{ow}$  were diluted in the collected mist. In biobased methods to produce chemicals or fuels, the product usually contains a mixture of solutes. In such cases, the application of ultrasonic misting can separate these solutes by enriching the components in mist and bulk solutions. Further studies on the ultrasonic misting of multicomponent solutions can provide the basis for the application of this process for the separation of products obtained through fermentation methods.

### 2.3. Literature gaps and future research

In order to scale-up and develop a continuous ultrasonic misting unit, further research needs to be conducted.

- In the ultrasonic misting process, smaller droplets are known to contain a high concentration of solute compared to larger droplets. The droplet size distribution is important to design efficient mist collection methods. It is recommended that further research be conducted on the dependence of droplet size distribution on operation parameters such as ultrasonic frequency and depth, concentration, and nature of solute in the bulk solution.
- In industrial applications, continuous and large-scale units are preferred over batch units due to their low operational cost. This will also give a competitive advantage for the ultrasonic misting process over the conventional distillation process. Continuous units with high throughput are needed to be designed for industrial applications. In addition, the acoustic cavitation in liquids that are either stagnant or flowing needs to be studied in detail.
- The amount and concentration of solute in the product depend on the efficiency of the mist collection method. Further research needs to be conducted on the design of efficient mist collection methods. Different mist collection methods such as collection using cooling, adsorption, etc. need to be studied.
- In the staged mist collection method, the concentration of product in the first stage is low due to the collection of vapors instead of droplets. Additional studies that incorporate recycling of the condensate from the mist collection unit to the misting unit need to be conducted.

- The broth in the fermentation process is dilute and contains a mixture of different chemicals. The composition of droplets generated during ultrasonic misting and the composition change during mist collection needs to be studied.
- The design of ultrasonic misting units and optimization of parameters such as carrier gas flow rate, carrier gas flow dynamics, bulk solution volume, etc. are needed to be studied.
- Ultrasonic misting technology is relatively new and pilot testing under field conditions and full-scale tests are recommended.
- Power electronics or circuits used to drive a large number of piezoelectric transducers do not exist currently. Working with electrical engineers becomes indispensable in future efforts to scale up ultrasonic separation technology.

### 3. Ultrasonic atomization to produce pharmaceuticals

One of the fields in that ultrasonication has been employed is pharmaceutical processing. In recent years, there has been an increase in the number of studies focusing on the utilization of ultrasonic atomization either as an individual processing technique or in combination with various processing methods mainly for drug delivery purposes. In this section, an overview of the applications of ultrasonic atomization in this field is provided focusing on the advantages and capabilities of ultrasonication for creating novel drug delivery methods.

Drug solubility and permeability are the two critical factors that significantly influence the absorption of the drug, which has been posing a major issue in the development of pharmaceutical products. Several strategies have been employed to address the low solubility and insufficient permeability problems of drugs including but not limited to solid lipid nanoparticles, liposomes, and nano emulsions. One method to enhance the drug absorption is by decreasing the size of drug particles to nanoscale, which can facilitate an improvement of their solubility by increasing the surface area [55]. Ultrasonic atomization alone or combined with other methods is one of the processes that has been implemented for obtaining ultrafine particles. It has been claimed that ultrasound-assisted atomization has relatively fewer energy requirements for droplet production compared to other conventional techniques [13]. Previous studies also demonstrated that ultrasonic atomization can be used in various matrixes such as in high viscous polymer solutions and can be applied in creating alginate micro-systems for drug delivery [3,15].

A comprehensive review on the applications of ultrasonication for nanosizing of drug formulations has been recently published by Partheniadis et al., [55]. According to that, nanosized formulations were designated for various delivery methods such as oral, rectal, intranasal, and transdermal. The ultrasonic atomization has been implemented for pulmonary delivery systems. Compared to the conventional production techniques, ultrasonic atomization can easily create smaller and more uniform droplets and facilitate more efficient transportation of drugs. Additionally, unlike other methods to produce small particles for nasal drug delivery, like spray drying, solvent extraction or evaporation, oil-in-water emulsion, and hot melt, it has been established that the ultrasonic atomization process does not involve high-temperature applications or phase separation inducing agents (Gogate, 2015 [22]). Due to these advantages, it can be easily operated at larger production scales and utilized in the production of nano- to micro-sized droplets [20]. However, it is important to highlight that process parameters such as feed flow rate, power, and frequency of ultrasound can impact the final particle size of the droplets. Therefore, identifying and applying appropriate conditions carry great importance in terms of achieving the targeted particle size with the ultrasonic atomization process.

Mezhericher et al., [48] explored the use of a novel liquid atomization method for generating submicron aerosol droplets. The experimental setup consisted of an atomizing chamber containing the liquid from which the aerosol droplets were produced. The generated droplets were transferred to a drying pipe with the help of compressed air

directed into the chamber. In the drying pipe section, the droplets were dried by removing the solvent from them. The dried aerosol droplets were then collected by an electrostatic trap mounted at the top of the drying pipe section. The effect of process parameters, such as different precursor solutions, their concentrations, and compressed air pressure levels, on the morphological properties and particle size distributions of generated droplets, were investigated. Additionally, the findings were compared with already established atomization methods. It was demonstrated that the proposed method offered advantages over the conventional production methods in terms of generating much smaller droplets, higher production capacities, and better energy efficiency. The results also showed that with this method, it is possible to simultaneously produce and dry aerosol droplets at room temperature with a final particle size ranging between 100 and 500 nm. It was claimed that the ultrasonic technique can be utilized in pharmaceutical manufacturing, especially for the applications requiring low-temperature and short-time processing to form aerosol particles.

Microencapsulation is another application area that ultrasonic atomization that has been employed in the pharmaceutical industry, which can be described as a process by which an active compound is entrapped within a spherical particle, coated with a thin film. Microcapsules do not only protect the encapsulated active substance against any damages or deteriorations, but it also assists in the controlled release of the integrated drug over time and offers a simple drug delivery method [64]. Depending on polymer characteristics, targeted particle sizes and chemical properties of the drug, such as its solubility in the polymeric material, physicochemical processes, like solvent evaporation or phase separation, and mechanical processes, for instance, spray drying, can be used to prepare microencapsulated systems. In general, all these methods are based on five essential steps, namely, incorporation of bioactive compounds, droplets formation, solvent removal, microparticles harvest, and drying [15]. As a novel technology, ultrasonic atomization has been investigated for droplet formation in a microencapsulation process. It has been established that ultrasonic atomization can produce micro encapsulates with more uniform size and shapes, and provide a narrower particle size distribution (Gogate, 2015). With its relatively higher encapsulation efficiency compared to conventional techniques, it also decreases the probability of loss for encapsulated substance [21,56].

Several studies investigated the application of ultrasonic atomization for encapsulating various active compounds for drug or vaccine delivery, such as darbepoetin alfa, pDNA, indomethacin, and theophylline [9,13,23,27]. In a recent study, micro-encapsulates made of poly( $\epsilon$ -caprolactone) (PCL) were produced by using ultrasonic atomization to deliver resveratrol (RSV). RSV is a phytoalexin found in numerous vascular plants and considered as a potential compound to inhibit the free radical damage responsible for anti-inflammatory effects [42]. In this study, the ultrasonic atomization was selected to prepare RSV-loaded microcapsules for several reasons, including its simplicity, versatility, mild production conditions, capability to provide uniform particle size distribution, high loading efficiencies, and finally fast and continuous production ability. The RSV-loaded micro encapsulates were prepared by using a coaxial ultrasonic atomizer nozzle (Sono-Tek Corp., Milton, NY, USA) equipped with a 60 kHz frequency power supply. According to the results, the generated micro encapsulates had a proper size and morphology for local delivery into the joint by intra-articular administration. While they did not show cytotoxicity, their stability and antioxidant properties were retained by microencapsulation.

#### 4. Application of ultrasonic atomization in medical devices

Inhalation therapy has been one of the most common drug administration methods for centuries. It carries great importance for lung diseases, such as asthma, cystic fibrosis, and chronic obstructive pulmonary disease. Drugs for inhalation such as  $\beta_2$ -agonist drugs, corticosteroids, and anticholinergic drugs, and inhalation of antibiotics have

been available for a long time. In addition to these drugs, due to their ability for fast and increasing extended delivery of therapeutic agents by using aerosols, the pulmonary route has become an attractive method for systemic administration [40]. There are mainly three types of devices are commonly employed for the delivery of these therapeutic agents in the form of aerosols to the respiratory tract, namely, nebulizers, pressurized metered-dose inhalers (pMDI), and dry powder inhalers (DPI) [28]. Medical nebulizers are devices that can convert the drugs from a liquid to a fine mist to facilitate their immediate release and administration, and to assist their inhalation into the respiratory tract easily [32]. The effectiveness of nebulizers in treating various illnesses including pneumonia, asthma, cystic fibrosis, and obstructive lung diseases has been investigated in various studies [50,62,65].

As illustrated in Fig. 5, medical nebulizers can be classified into three major groups depending on the type of force used for aerosol production from a solution: jet, ultrasonic, and mesh nebulizers [28,59]. Jet nebulizers use pressurized air to transfer drugs in liquid form from a nebulizer reservoir to a capillary tube. In this type of nebulizer, the pressurized gas goes through a narrow sectional area at a high velocity, and with the impact of low pressure it creates, the liquid drug moves up to the baffles and is aerosolized into droplets of varying sizes. Droplets with large particle sizes are either divided into smaller droplets at the baffle and pass to the capillary tube or return to the reservoir to be nebulized again [24,28]. Despite their common utilization for treating pulmonary diseases and their effectiveness in delivering drugs that cannot be transferred with pMDIs and DPIs, they still have disadvantages over other nebulizers, such as their need for compressed air and additional tubing and inefficiency in drug delivery [4].

On the other hand, mesh nebulizers use micropump technology to generate aerosols. They are either static or vibrating depending on the type of plate or membrane incorporated in their system. As shown in Fig. 5, vibrating mesh nebulizers contain an AC power source and a piezoelectric actuator with a mesh mounted on one side which produces aerosols from the drug solution stored in the reservoir [49]. Compared to jet nebulizers, they are quieter and more compact. Although they are relatively more efficient than other nebulizers in terms of their low residual drug volumes and great inhaled mass, they are not suitable for delivering viscous drugs and suspensions due to the clogging problem [4,47].

Over seventy years ago, ultrasonic nebulizers first appeared as humidifiers which were then modified and adapted to be utilized for medical purposes [16]. These devices use moderate-to-high frequency acoustic waves to produce aerosol droplets through their both capillary and cavitation effects. The acoustic waves are generated because of the conversion of electrical energy to oscillatory mechanical movement by a piezoelectric transducer incorporated in the system [12].

Depending on the design of the system, ultrasonic nebulizers can be separated into two groups, namely direct contact ultrasonic nebulizers and ultrasonic nebulizers with a water interface. As shown in Fig. 6(a), in the direct contact ultrasonic nebulizers, the piezoelectric transducer is placed at the bottom of the system, and it is in direct contact with the drug solution or suspension put into the reservoir. The major concern with this type of ultrasonic nebulizer is the increase in the temperature of the liquid in the reservoir due to the heat generated by the transducers. On the other hand, in ultrasonic nebulizers with a water interface (Fig. 6(b)), there is a volume of water between the reservoir and the transducer which facilitates transmitting the effect of ultrasonic waves to the liquid in the reservoir and acts as a cooler to maintain the temperature of the liquid throughout the process [14,88]. Another common classification of ultrasonic nebulizers is made based on the volume of the system [26]. While the small volume ultrasonic nebulizers have been commercially used for delivering inhaled bronchodilators, large volume ultrasonic nebulizers have been used for the delivery of inhaled antibiotics for treating cystic fibrosis disease and for transferring the hypertonic saline for sputum induction [7,19,77].

Ultrasonic nebulizers offer many advantages as medical devices.

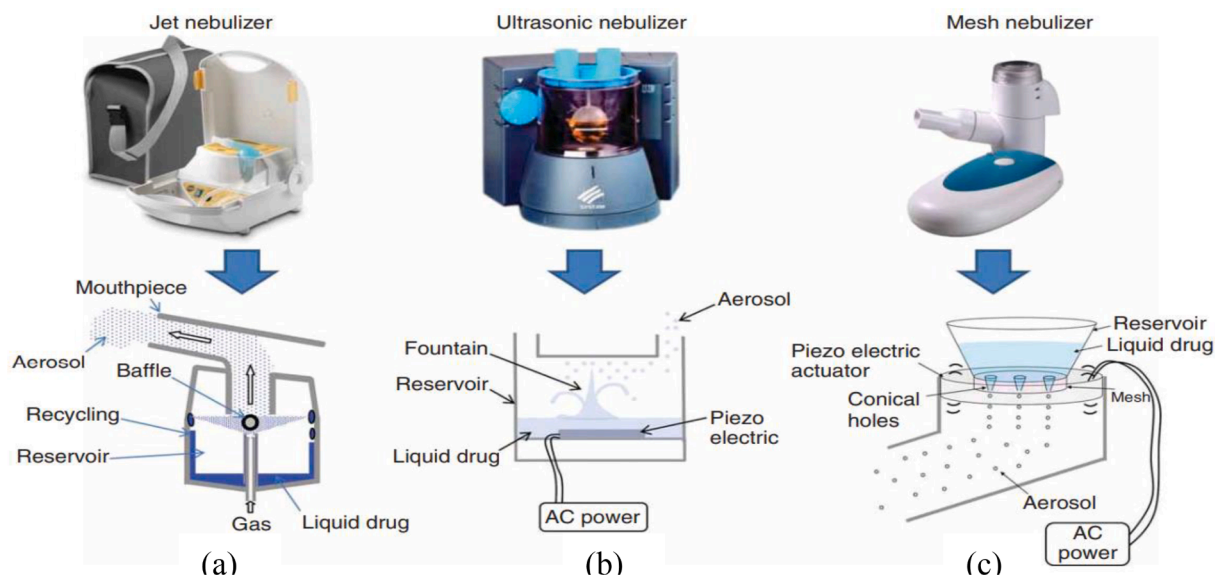


Fig. 5. Medical nebulizers (a) jet nebulizer; (b) ultrasonic nebulizer; (c) mesh nebulizer. (Retrieved from [59].

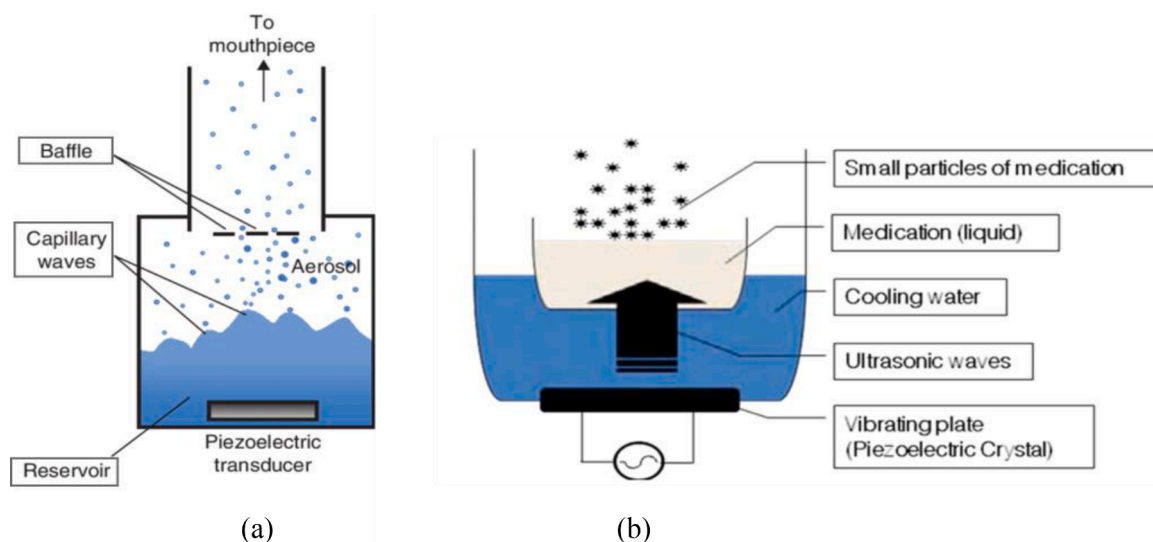


Fig. 6. The illustrations of (a) a direct contact ultrasonic nebulizer and (b) an ultrasonic nebulizer with a water interface (Adapted from Yeo et. al., 2010; Chetan and Negoias, 2011).

Their easy-to-use and compact design make them convenient to use both at home and in ICU settings. Compared to jet nebulizers, they are quieter and more efficient in terms of drug delivery performance [4]. As stated in the study of Hess, [26], several factors are affecting the characteristics of the output from the ultrasonic nebulizer, such as the physical properties of drug solution or suspension, process parameters of the transducer, and the dimension and design of reservoir, etc. The ultrasonic nebulizers have limitations associated with the stated factors. One of the major limitations of ultrasonic nebulizers is their inability to aerosolize liquids with a viscosity above 6 cP. According to Mc Callion and Patel, [46], the threshold amplitude for creating capillary waves is correlated with the viscosity of the liquid. Because high viscous liquids show more resistance against disintegration and require a higher ultrasound intensity, they restrain the atomization process, which would cause lower outputs and be less efficient compared to less viscous liquids. Another important limitation of ultrasonic nebulizers is the size of generated droplets. They produce aerosol droplets with about 1–6  $\mu\text{m}$  particle size which is not small enough for efficient and effective delivery of drugs to the lungs. Katial et al., [30] evaluated three commercial ultrasonic

nebulizers to understand the aerosol characteristics and their overall performances. They concluded that the size of generated droplets can be reduced to the respirable range by improvements in the design of the nebulizer system and modifying the process parameters.

Overall, it is likely that ultrasonic nebulizers will continue to be used as a powerful medical tool in the treatment of selected diseases. With improvements in the designs and operating systems, more precise, portable, efficient, and effective ultrasonic nebulizers are expected to be produced in the future.

## 5. Conclusion

The application of ultrasound in atomization applications proves to have significant benefits such as low energy requirement, low or no waste generation, material savings, etc. These qualities confirm the greener processing capabilities of this technology. The application of ultrasonic atomization for the separation of chemicals is a relatively new technology. In the past two decades, several studies have been conducted in this area. However, these were limited to lab-scale testing and

there is a lack of understanding of the effect of operating conditions on the separation efficiency and the mechanism by which the solute molecules are separated from their aqueous solutions in the atomization process. The review presented in this work gives an overview of experimental setups and the operating conditions used. This will stimulate future studies on the large-scale operation of ultrasonic atomization units. Most industrial applications require that the droplets are within a particular diameter range. In the literature, theories such as capillary wave, cavitation, and conjunction theories have been proposed to explain the mechanism of droplet formation and their sizes. However, this review shows that the results from several research studies do not concur with these theories. In addition, ultrasonic atomization is also used to create novel drug delivery methods, produce micro encapsulates, and medical nebulizers. This method was proven to produce ultrafine particles used for drugs delivered through oral, rectal, intranasal, transdermal, and pulmonary delivery methods. This method operates at low temperatures without any phase separation-inducing agents. Thus, the application of ultrasonic energy to produce chemicals, pharmaceuticals, and medical devices will result in improving the efficiency and environmental sustainability of the products.

### CRedit authorship contribution statement

**Haripriya Naidu:** Writing – review & editing. **Ozan Kahraman:** . **Hao Feng:** Conceptualization, Funding acquisition, Supervision.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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