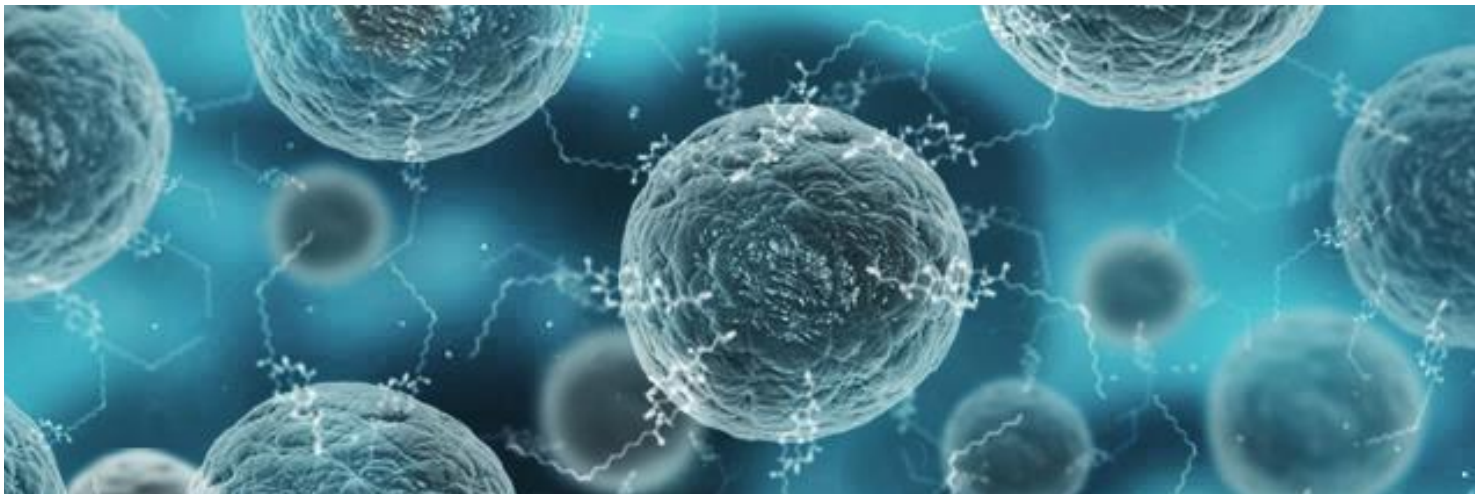

MAKING STABLE EMULSIONS

A Guide to Formulation and Processing Conditions Optimization

Dr. Alexey Peshkovsky

INDUSTRIAL SONOMECHANICS

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GLOSSARY OF TERMS AND ABBREVIATIONS

Brownian motion
Irregular motion of small particles suspended in a liquid medium that occurs due to their bombardment by molecules of the medium.

Colloidal Systems
A homogeneous mixture of substances, one of which (the dispersed phase or colloid) is uniformly distributed in an extremely finely divided state through the other (the continuous phase or dispersing medium).

Emulsification Process
The process of making an emulsion.

HLB
Hydrophile-Lipophile Balance.

Interfacial Tension
The adhesive force acting in a mixture of substances (phases) that occurs at their surfaces (interfaces) and holds the surface of a particular phase together.

Isotropic
Having equal physical properties along all axes.

MDS
Mean Droplet Size.

Oleate
A salt or ester of oleic acid – a monounsaturated omega-9 (one double bond at the ninth carbon) fatty acid with an 18-carbon chain.

Shear forces
Unaligned forces pushing one part of a body in one direction and another part of the body in the opposite direction.

Stearate
A salt or ester of stearic acid – a saturated (no double bonds) fatty acid with an 18-carbon chain.

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INTRODUCTION

One of the biggest challenges faced by product developers and process engineers in a wide variety of industries is achieving long-term stability of products based on combinations of oil and water, also known as emulsions.

This guide will answer the most common questions related to making emulsions and achieving their stability. It is detailed, yet easy to follow, even if you are not familiar with the process and related terminology.

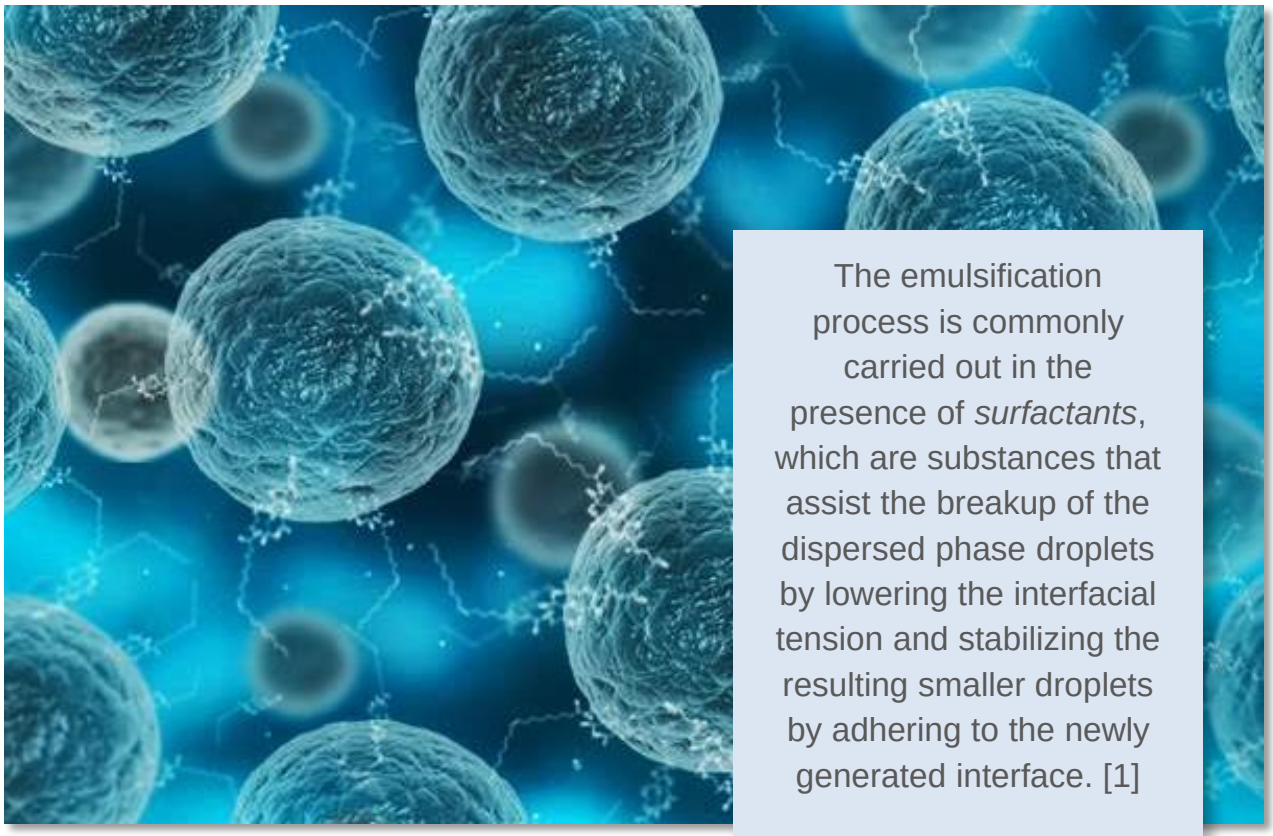
We will begin by introducing the basic definitions and concepts used in the field of emulsion manufacture. We will then describe the optimization theory and outline each step required for the development of a high-quality emulsion product. The guide will conclude with a practical optimization example, including detailed descriptions of experimental procedures and results.

Please note that this is only a general guide based on our experience. While we find the steps described here useful for the optimization of many emulsification processes, your particular situation may be different. We do hope, however, that even if this guide cannot completely address your needs, it can still be useful in conjunction with additional resources you may require.

BACKGROUND

The definition of "emulsion"

Emulsions are colloidal systems, commonly comprising two immiscible liquids (e.g. oil and water). They are produced by introducing high shear forces into a pre-mixture of the liquids, one of which becomes the so-called *continuous phase* (i.e. water) and the other the *dispersed phase* (i.e. oil) that exists in the form of droplets. The dispersed phase may have droplet sizes between about 20 nanometers (nm) and several millimeters (mm) [1].



The emulsification process is commonly carried out in the presence of *surfactants*, which are substances that assist the breakup of the dispersed phase droplets by lowering the interfacial tension and stabilizing the resulting smaller droplets by adhering to the newly generated interface. [1]

The definition of "nanoemulsion"

Nanoemulsions are emulsions with narrow droplet size distributions centered below ~ 300 nm, which have special properties, such as low viscosity, high interfacial surface area and long-term kinetic stability (see page 9) [2].

Nanoemulsions with droplets smaller than 100 nm are optically translucent, achieving progressively higher degree of clarity and stability as the droplet sizes are diminished [3]. They can be separated in yet another special class of emulsions – *translucent nanoemulsions*.

The definition of "microemulsion"

Microemulsions are clear, thermodynamically stable (see page 9), isotropic liquid mixtures of oil, water, surfactant(s) and, frequently, co-surfactant(s). Due to similarity in appearance, microemulsions are sometimes confused with translucent nanoemulsions.

Emulsion application examples

Emulsions are widely used in the pharmaceutical, cosmetics, food, metalworking, agricultural, fuel and many other industries, either as final products (e.g. drug delivery systems, cosmetic formulations, food and beverage products, agricultural agents, emulsified fuels, metalworking fluids, candles with emulsified water) or as transient states in mass transfer-limited chemical processes (e.g. crude oil desulfurization, biodiesel production, plant oil extraction).

The definition and types of "stability"

Stability refers to the ability of a system to resist change in its properties over time. When it comes to emulsions, two types of stability must be distinguished: thermodynamic and kinetic.

Thermodynamic stability is a term used to describe a system that is neither consuming nor releasing energy because it is already in its lowest energy state. This means that the system is permanently stable unless a change is introduced externally. Microemulsions are thermodynamically stable.

Kinetic stability is related to the rate at which a spontaneous change occurs in a thermodynamically unstable system. When the rate of change is extremely low, the system can be considered kinetically stable. Nanoemulsions are thermodynamically unstable, but kinetically stable.

Emulsion instability pathways

Thermodynamically unstable emulsions exhibit four main instability pathways (Figure 1): coalescence, flocculation, creaming and disproportionation (Ostwald ripening). The latter is usually relatively minor and will not be covered in this guide.

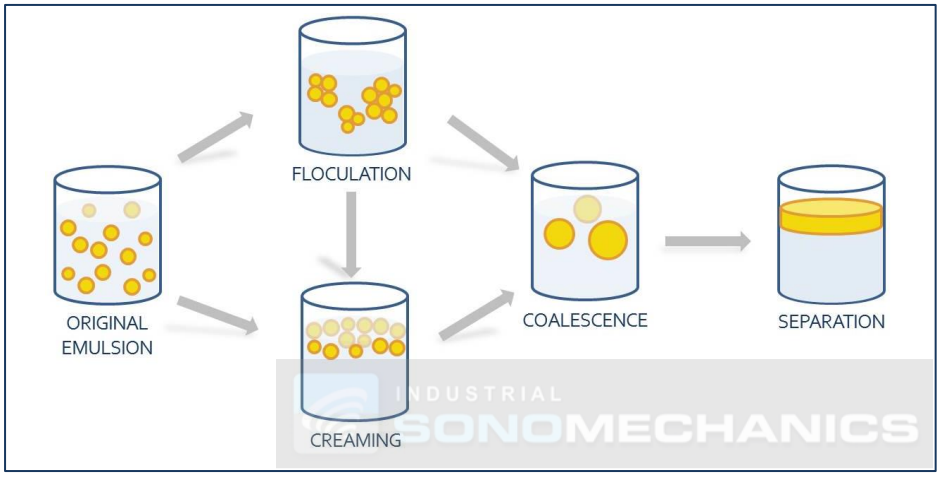


Figure 1. Emulsion instability pathways

Flocculation is defined as droplet aggregation in the form of clusters (flocs) resulting from inter-droplet attraction. During flocculation, the droplets do not combine, but remain as separate entities.

Creaming occurs when droplets have sufficient buoyancy to simultaneously migrate in the same direction (for most oil-in-water emulsions, to the top).

Coalescence takes place when dispersed phase droplets collide with each other and progressively combine into larger droplets, finally separating as a bulk layer. Creaming and flocculation are common precursors to coalescence.

Nanoemulsions: kinetic stability

Kinetically stable nanoemulsions are susceptible to the abovementioned instability processes. However, the rates at which these processes occur are so low that nanoemulsions can be considered stable for most practical purposes. A shelf life of one year or more is common for these products.

Kinetic stability of nanoemulsions can be attributed to the nature of their droplet size profiles. Because of their small sizes and narrow size distributions, the Brownian motion undergone by dispersed phase droplets can overcome creaming and flocculation processes that otherwise would cause droplet coalescence and eventual separation as a bulk layer. Nanoemulsions, therefore, can be thought of as “self-stirring” systems.

Repulsion forces created by surfactants covering the surfaces of the droplets also help prevent coalescence and promote stability.

Microemulsions: thermodynamic stability

These special colloidal systems are translucent and thermodynamically stable. Microemulsions are formed by “solubilizing” dispersed phase molecules with a mixture of surfactants, co-surfactants and co-solvents.

It should be emphasized, however, that the required total concentration of surfactants in a microemulsion is several times higher than that in a nanoemulsion and commonly exceeds the concentration of the dispersed phase.

Because of many undesirable side-effects caused by concentrated surfactants as well as the associated expense, the use of microemulsions is disadvantageous or prohibitive for many applications.

In addition, unlike nanoemulsions, microemulsions are easily destabilized by dilution, heating or changing pH levels [4].

Technologies used for the production of nanoemulsions

The production of nanoemulsions requires significant energy depositions and strong shear forces that can overcome the interfacial tension during the finely dispersed droplet formation [5].

Although methods that do not involve high shear forces exist, they are not applicable to industrial production because they require elevated surfactant concentrations and involve complex preparation procedures [6, 7]. The shear forces necessary for the emulsification process can be provided by such means as stirring, high shear mixing, high-pressure homogenization or high-amplitude ultrasonic processing (sonication). The latter two methods have been demonstrated to be superior to all others, being able to produce nanoemulsions with the smallest droplet sizes and the highest stability [8].

In this guide, we will concentrate on the **ultrasonic method** and describe common strategies used for optimizing nanoemulsion formulations and preparation procedures.

OPTIMIZATION THEORY

Simplification of the procedure

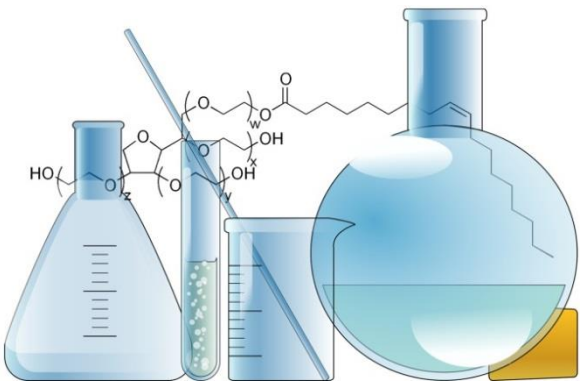
As a general rule, the higher the dispersed phase content, the larger the minimum achievable droplet size (everything else being equal) and, therefore, the lower the kinetic stability of the emulsion. The inverse is commonly true for the combined surfactant content.

In addition, the type and concentration of the dispersed phase as well as the maximum allowed surfactant content are frequently predefined by the application.

We can, therefore, simplify the formulation optimization procedure by considering the following parameters as fixed:

- Dispersed phase type (e.g. type of oil in an oil-in-water emulsion);
- Dispersed phase concentration (% content of the oil in the emulsion);
- Combined surfactant concentration (cumulative % content of all surfactants in the emulsion).

As an example, in this guide we will use a model emulsion comprising 10% of soybean oil, total 10% of surfactants and 80 % of water. This relatively high combined surfactant concentration will allow us to achieve extremely small droplet sizes and produce a translucent nanoemulsion.



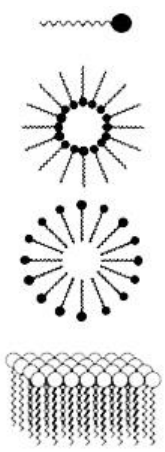
Note that the same amount of liquid dispersed in the form of larger droplets will have a smaller combined surface area to cover by surfactants. As a result, non-translucent nanoemulsions require significantly smaller amounts of surfactants (4 – 5 times) than translucent ones.

For demonstrating droplet size minimization strategies, the translucent nanoemulsion model is advantageous because experimental success can be visually evaluated by observing light penetration though the produced samples.

Our attention will now be devoted to describing procedures used for selecting surfactant types and determining their relative concentrations.

Surfactant chemical types and proportions

In order to minimize the Mean Droplet Size (MDS) and increase the kinetic stability of an emulsion, it is essential to use the right chemical types of surfactants and combine them in the right proportions.



Surfactant molecules consist of hydrophilic ("water-loving", polar) and lipophilic ("lipid-loving", non-polar) chemical groups. The Hydrophile-Lipophile Balance (HLB) of a surfactant is an empirical value assigned to it to describe the relationship of these groups. The higher the HLB value, the more water-soluble and less oil-soluble the surfactant. Conversely, the lower the HLB value, the more oil-soluble and less water-soluble the surfactant. Many detailed guides are available online that describe the HLB system as well as chemical compatibilities of surfactants. Our favorite one is called "*The HLB system – a time saving guide to emulsifier selection*" [9], and we recommend that you refer to it for in-depth information on this subject.

Two main conditions should be maintained in order to minimize the MDS and increase the kinetic stability of an emulsion:

1. Surfactants' lipophilic groups should be of a similar chemical type as the emulsion's oil phase.

   Lipophilic groups of surfactants are based on a particular chemical type (e.g. stearates, oleates, etc.). When this chemical type matches that of the oil phase in an emulsion, better contact is made between oil and surfactant molecules and higher stability is achieved. For example, saturated stearates work better with mineral oils (also saturated), while unsaturated oleates are better for unsaturated vegetable oils.

2. Surfactant combination's HLB should correspond to the emulsion's *Required HLB.*

   Each particular emulsion type has a Required HLB value, which corresponds to the smallest MDS (all other parameters being equal). Combining high- and low-HLB value surfactants in correct proportions makes it possible to arrive at any intermediate HLB value for the emulsion, while maintaining a constant total surfactant concentration. Approximate Required HLB values are published for many types of emulsions [8]; however, fine-tuning is almost always required and can make a significant difference.

In order to calculate how much of surfactants A (high HLB value) and B (low HLB value) one must use to attain a given HLB value of X when the total surfactant concentration is % S, the equations on the right can be helpful.

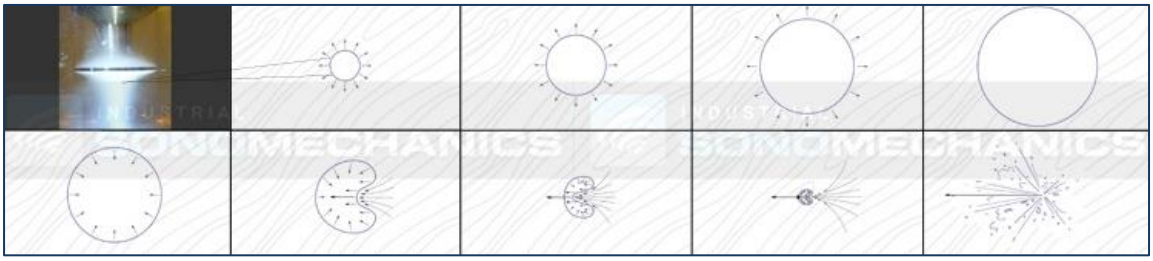
$$\%\ A = \frac{(X - HLB_B) \times \%\ S}{HLB_A - HLB_B}$$

$$\%\ B = \%\ S - \%\ A$$

For example, if the Required HLB of an emulsion is X = 12, then for a mixture of A = Tween 80 (a surfactant with HLB_A of 15) and B = Span 80 (a surfactant with HLB_B of 4.3) with the combined concentration of % S = 10, the individual concentrations will be % A = 7.2 and % B = 2.8.

Ultrasonic processing conditions

The exposure of liquids to high-intensity ultrasound generates acoustic cavitation, which produces violently and asymmetrically imploding vacuum bubbles. The implosions cause strong micro-jets that impinge one liquid into the other in the form of tiny droplets – a process that creates nanoemulsions [8].



The intensity of acoustic cavitation generated by an ultrasonic processor is proportional to the displacement amplitude of the incorporated ultrasonic horn (measured in microns). It is, therefore, reasonable to expect that the higher is this *ultrasonic amplitude* during the emulsification process, the smaller will the droplets become in the resulting emulsion. The relationship between the ultrasonic amplitude and the MDS, however, is generally not linear and must be investigated during the optimization procedure.

The *rate of processing* is commonly measured in terms of volume per unit of time (e.g. L/min) and also has a strong effect on the MDS. The lower the rate, the more time does the emulsion spend in the active cavitation zone of the ultrasonic processor, and, therefore, the smaller will the dispersed phase droplets become. On the other hand, if the rate is too low, the process may become impractical as a production method. It is, therefore, important to find the relationship between the processing rate and the MDS, and identify the highest rate at which the target MDS (and the resulting product stability) can still be achieved.

Main optimization steps

The main optimization steps can be defined as follows:

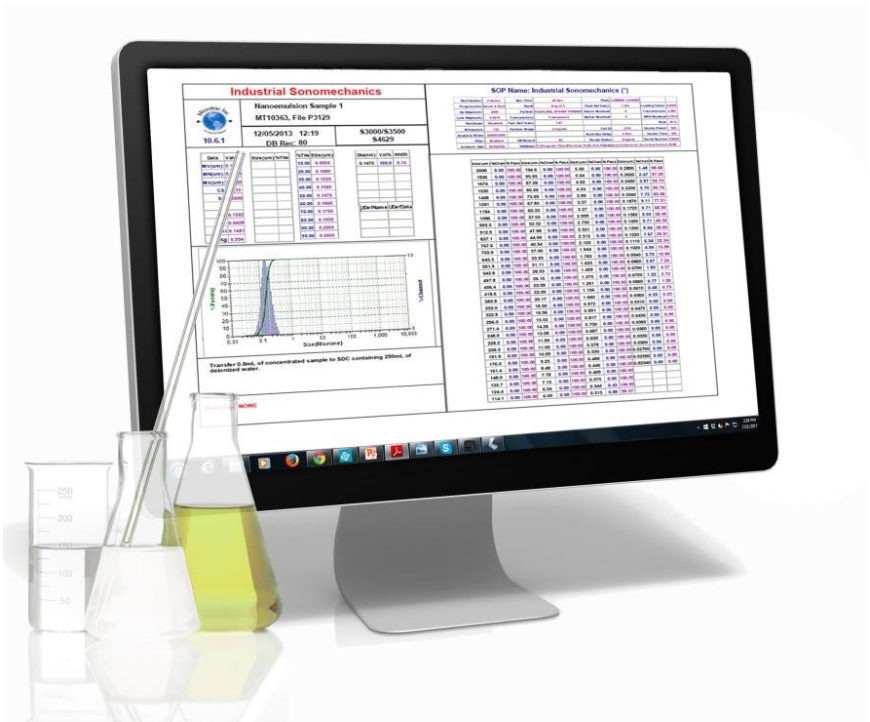
1. Based on the literature, determine the Required HLB and appropriate chemical types of surfactants for the target emulsion;

2. Experimentally fine-tune relative surfactant concentrations to obtain the optimum HLB value corresponding to the smallest relative MDS of the dispersed phase. It should be close to the Required HLB;

3. Experimentally determine the lowest optimum ultrasonic amplitude corresponding to the smallest relative MDS;

4. Maintaining the HLB and amplitude at their optimum values, experimentally investigate the dependence of the MDS on the processing rate;

5. Based on the result of the previous step, determine the correct processing rate for the desired MDS.



OPTIMIZATION EXAMPLE

Formulation and processing parameter optimization procedures will now be described for our model nanoemulsion. These procedures are universal and can be applied to most target emulsion products.

Figure 2. Laboratory-Scale Ultrasonic Liquid Processor

All experiments were conducted using a laboratory ultrasonic liquid processor (LSP-500, Industrial Sonomechanics, NY) comprising an ultrasonic generator, a piezoelectric transducer and a conventional ultrasonic horn with the tip diameter of 15 mm (Figure 2). Ultrasonic amplitudes provided by the horn were calibrated and could be set to the desired values in microns.

In all tests, 50 ml samples comprising 10 % of soybean oil, total 10 % of surfactants and 80 % of deionized water were exposed to ultrasound in identical 80 ml beakers. The beakers were placed in a water bath (not shown) to maintain the constant temperature of 65 ^{o}C.

Determining the Required HLB and appropriate chemical types of surfactants

Since our model nanoemulsion comprises soybean oil in water, according to Table 3 of "*The HLB system – a time saving guide to emulsifier selection*" [9] (under Pharmaceuticals/Fish and Vegetable Oils, Typical Blend 253), its Required HLB is 12 – 15, and oleates is the appropriate chemical family of surfactants. A convenient pair of surfactants belonging to this family is Polyoxyethylene (20) Sorbitan Monooleate (also called Polysorbate 80 or Tween 80, HLB = 15) and Sorbitan Monooleate (also called Span 80, HLB = 4.3).

Optimizing the HLB

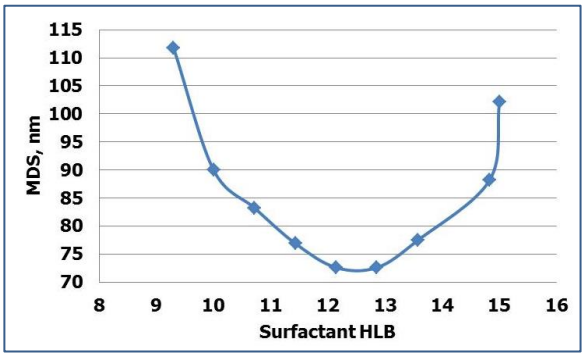


Figure 3. MDS as a function of surfactant HLB

Nine samples were prepared, in which the concentrations of surfactants (total 10 %) were varied from 10% of Tween 80 and 0% of Span 80 (mixture HLB=15) to 4.67% of Tween 80 and 5.33% of Span 80 (mixture HLB = 9.3). The ultrasonic amplitude was 90 microns and the processing time was 5 min (processing rate = 10 ml/min). As can be seen in Figure 3, the MDS exhibited a strong dependence on the HLB of the surfactant mixture. The minimum MDS was achieved at the HLB of 12.86. At this value, the resulting nanoemulsion was translucent, with the MDS of 72 nm.

Based on these results, all further experiments were carried out using the following formulation: 10 % soybean oil, 8 % Tween 80, 2 % Span 80 (HLB = 12.86), and 80 % water.

Optimizing the ultrasonic amplitude

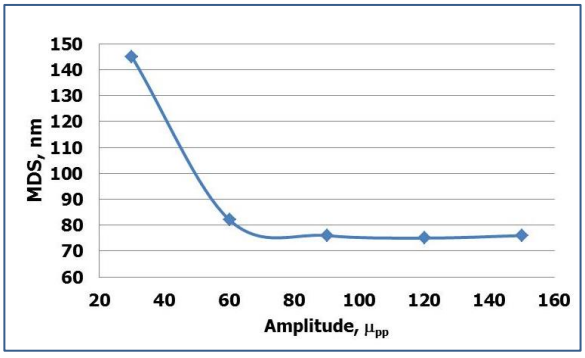


Figure 4. MDS as a function of ultrasonic amplitude

Five samples with the formulation optimized in the preceding step were prepared and exposed to ultrasonic amplitudes of 30, 60, 90, 120 and 150 microns. The processing rate for all samples was 10 ml/min. Figure 4 shows that MDS values were strongly dependent on the amplitude, decreasing from 145 nm at the amplitude of 30 microns to a plateau value of ~ 72 nm at the amplitude levels above approximately 70 microns.

In selecting the best amplitude value for the production of a nanoemulsion, it is important to make sure that the amplitude is sufficiently high to obtain the desired (commonly, the lowest) MDS, but is not excessive, as this would lead to unnecessary energy expenditure and ultrasonic horn wear. Ideally, the value should be on a plateau, with a reasonable amplitude margin above the value at which the plateau begins. Based on the experiments described in this section, the ultrasonic amplitude of 90 microns is appropriate for the production of our model nanoemulsion.

Determining the dependence of the MDS on the processing rate

The dependence of the MDS on the processing rate was investigated by sonicating five samples (with the optimized formulation and amplitude) for 2.5, 5, 7.5, 10 and 12.5 min, resulting in processing rates of 20, 10, 6.7, 5 and 4 ml/min, respectively. As can be seen from Figure 5, the MDS dropped as the processing rate was decreased, falling to 31 nm at the rate of 4 ml/min.

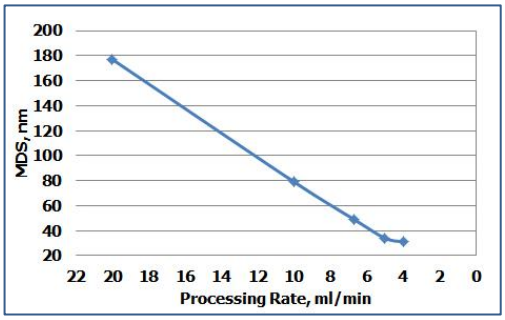


Figure 5. MDS as a function of processing rate

The nanoemulsion became increasingly translucent as the droplet sizes decreased, reaching near-transparency when the MDS was 31 nm (Figure 6).

The selection of the appropriate processing rate could be made at this stage, based on the target product's MDS requirement.

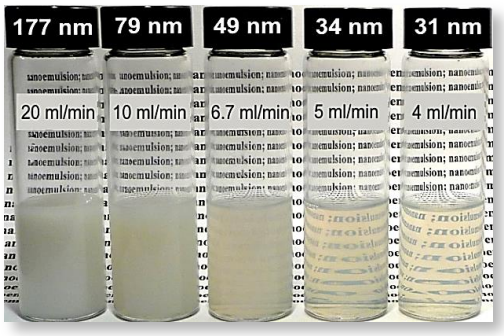


Figure 6. Nanoemulsion translucency dependence on MDS

A common application of the nanoemulsion type we used as a model is to deliver flavor oils to water-based beverages without compromising the final product's transparency. Since the nanoemulsion is diluted by the beverage, its transparency is further enhanced. The degree of clarity achieved at the processing rate of 10 ml/min is, therefore, sufficient for this application.

The product obtained at 10 ml/min has the MDS of 79 nm, is translucent in its concentrated form and quickly becomes transparent when diluted. It is kinetically stable with the shelf life of over a year.

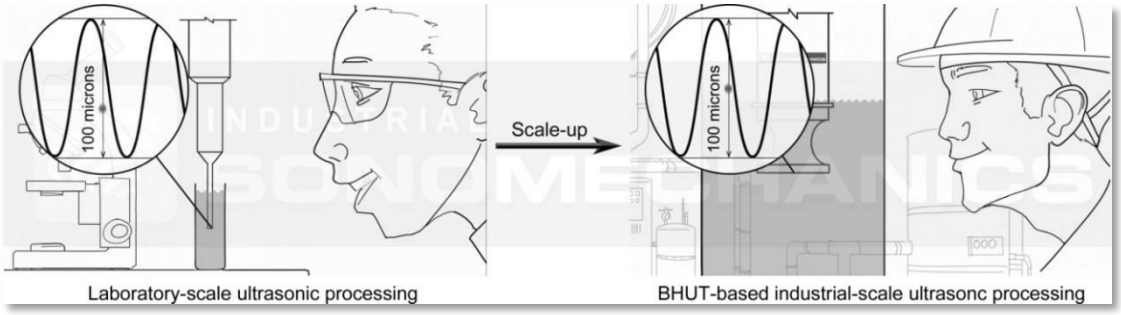
The Tween 80 and Span 80 surfactants used in this nanoemulsion are Generally Recognized As Safe (GRAS) by the U.S. Food and Drug Administration and can be used in food and beverage products.

Summary of the optimization results

The laboratory optimization results for the model nanoemulsion can thus be summarized as the following set of parameters:

1.	Surfactant chemical type ……	oleate (Tween 80 and Span 80);
2.	Surfactant mixture HLB ……..	12.86 (8 % of Tween 80 and 2 % of Span 80);
3.	Ultrasonic amplitude ……..	90 microns;
4.	Processing rate ……..	10 ml/min.

NEXT PHASE: SCALE-UP



After it is optimized in the laboratory, the process can be transferred to the pilot (bench) scale for the flow-through pre-production optimization and then to the industrial scale for continuous production. During the scale-up, it is essential to make sure that all optimized processing conditions remain the same, which will ensure that the MDS (and the resulting stability) of the final product is unchanged, while the productivity is increased by a predictable "scale-up factor".

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Industrial Sonomechanics, LLC, (ISM) is a research & development, equipment design and process consulting firm, specializing in high-intensity ultrasonic technology for liquid treatment. Our mission is to help businesses optimize ultrasound-assisted processes and implement them in commercial production. ISM offers high-intensity ultrasonic liquid processors (also known as sonicators, ultrasonic homogenizers, sonochemical reactors, ultrasonic mixers and ultrasonic systems) able to provide unprecedented processing rates and final product quality.

Application examples include the production of nanoemulsions, nanocrystals and liposomes for the pharmaceutical, cosmetic, food, printing ink, paint, coating, wood treatment, metalworking, nanocomposite and fuel industries; as well as plant oil extraction, alternative fuels manufacture, crude oil desulphurization, beverage sterilization, viscous liquid degassing, cell disruption, nano-scale dispersing, waste-water purification, and many more.

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