Production of Nanoemulsions at Relevant Industrial Rates: Innovative Scale-up Strategies

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ABSTRACT

Nanoemulsions find applications across industries, with several pharmaceutical and nutraceutical applications in the market. Delphi Scientific, LLC has developed a methodology to improve large scale nanoemulsion manufacturing by addressing key issues such as high energy demand, lack of repeatability and scalability, and high cost. It includes the following steps: (a) identification of the key processing parameters that affect the formation of a particular nanoemulsion, (b) development of methods to control and scale up such parameters, and (c) design of equipment that is suitable for large scale manufacturing. This methodology was applied to several emulsion formulations. Results indicate that stable nanoemulsions with average particle size as low as 63nm were produced successfully. The homogenization energy requirements were reduced by up to a factor of 2.6 times compared to requirements of conventional methods, while scale-up to several liters per minute bacame attainable.

Keywords: nanoemulsion, scale-up, continuous manufacturing, emulsification, homogenization

1 INTRODUCTION

Nanoemulsions are used extensively in pharmaceutical and nutraceutical industries to deliver biologically active ingredients, many of which are hydrophobic and difficult of deliver using other methods. Manufacturing of such emulsions is energy demanding, expensive and often difficult to scale.

The main focus of this work is the development of manufacturing processes and equipment for the cost-effective, energy efficient and large scale production of nanoemulsions. Because of the great variability in the composition of the nanoemulsions, a single manufacturing process is not possible. Therefore, there is a need to identify the key processing parameters for a particular formulation and then determine ways on how to control such parameters accurately, both on the bench and large scales.

The basic principle of scale-up used here from bench through to commercial scale is the concept of Dynamic Similitude to ensure that mechanistic matching occurs. The mixing intensity, energy density dissipation rate, uniformity of the stress field/fluid-fluid element shear rates, transport properties and associated contact areas for heat, mass and momentum transfer, and state variables such as temperature need to be consistent between scales. In other words, it is essential to replicate the distribution of micro-environments that fluid elements encounter in each system.

2 PHYSICAL MECHANISMS

The formation of nanoemulsions includes a number of physical processes that happen in series or in parallel, and may be competive or additive based on the physical properties of the ingredients of the nanoemulsion. Such processes are the formation of droplets of the dispersed phase, coating of the droplets with surfactant molecules (stabilization), droplet coalescence and droplet growth over time [1-10].

Typically, producing nanoemulsions requires mixing the liquid phases in a turbulent field with progressivelly increasing energy densities. This is commonly implemented by the use of rotor-stator mixers that creates a coarse emulsion, followed by a high-pressure homogenizer (HPH) that ultimately creates the nanoemulsion by forcing the liquids to trasnverse microchannels at velocities exceeding 400 m/s, see Figure 1. This is a Top Down method because it is based on size reduction of large droplets. Presented in the next paragraphs are the key concepts used in this work.

A. Continuous Manufacturing. Compared to batch production, continuous manufacturing is more efficienct, offers reproducibility and easier to scale up. The most common scale up approach that taken here is the concept of staking the bench scale units and manifolding the flow of the various liquid streams that are parts of the emulsion formulation. In support of our scale-up strategies, we discuss technology platforms capable of efficiently producing stable nanoemulsions, both in terms of energy input and required concentrations of surfactant and other additives, such as viscosity modifiers. Noteworthy is the corroboration of our approaches to production of

nanoemulsions by others such as A. Hakansson, et al. [1], and Bai and McClements [2]. Furthermore, we will discuss some of the common pitfalls associated with improper selection of criteria often used in a variety of scale-up strategies. A series of straightforward calculations associated with a ten-fold throughput rate are presented for illustration of this assertion and to substantiate our current scale-up strategies.

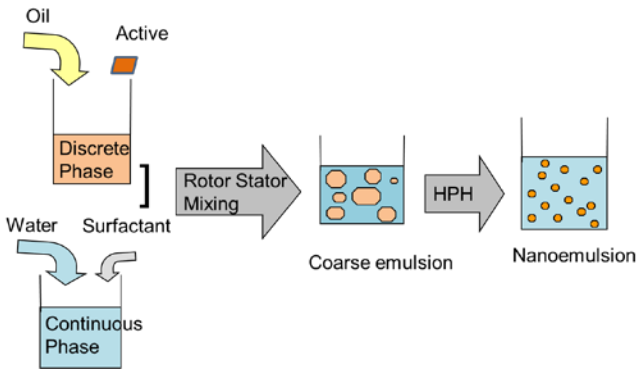

Figure 1. Conventional, Top Down method used to produce nanoemulsions.

B. Droplet formation. The ability to manipulate the mass, heat and momentum transport processes is critical in developing droplets of desired size. This translates to efficient use of energy and lower operating costs. Thus, a major objective is to minimize the amount of kinetic energy generated that is not utilized in forming new surfaces, i.e., droplets. This efficacy is obtained through focused energy density transfer rates.

The source of these useful energies is from the energy dissipation rate per unit mass that is not converted to losses, such as viscous heating from turbulent eddy collapse and wall shear. It is imperative that each fluid element processed in a continuous system be exposed to identical micro-environments if product consistency with respect to uniformity of droplet sizes, with a narrow size distribution, is desired. This is possible via exposure to the same thermodynamic state, mixing intensity, and residence time; i.e., sustaining the controlling mechanisms. Furthermore, uniformity in characteristic time and length scales for the appropriate transport processes, whether mass, heat, or momentum mechanisms are occurring in tandem, or an individual one is controlling the phenomenological events, is possible. For example, since turbulence is the intense mixing mechanism, the *microscales* of the turbulence, often called the *Kolmogorov scales* (*length*, λ_K *velocity*, u_K, *and time*, t_K), are relevant [5];

$$\lambda_K = [\nu^3/\varepsilon]^{1/4}, \quad u_k = (\nu\varepsilon)^{1/4}, \quad t_k = \left(\frac{\nu}{\varepsilon}\right)^{1/2},$$

where ν is the kinematic viscosity and ε energy dissipation rate per unit mass. Note that the size of the smallest eddies that exist in the flow can be characterized by these micro-scales [5]. The time scale is related to the life time of eddies since it is the time for the smallest velocity fluctuation to dissipate.

C. Residence Time Distributions. In addition to the characteristic Kolmogorov time, the residence time distribution (RTD) is also important. For example, mixing in a tank to create the coarse emulsion shown in Figure 1, results in a broad RTD and incomplete mixing regions are present [6]. Due to the need for uniformity of the droplet micro-environment we require a narrow RTD, which is obtainable via turbulent flow in ideal plug flow systems. Therefore, eliminating this step also emiminates a potential source of process variability.

D. Droplet Stability. Analyses of drop dispersion processes (drop deformation and breakup mechanisms) was discussed by Hinze [7] using a modified Weber number (ratio of disruptive force to deform to the stabilization force due to interfacial surface tension). Hakansson [1] provides additional discussions, such as mechanisms of fragmentation, recoalescence, and adsorption of surface active agents (SAA's). The collision frequency of bare drops with SAA's must outweigh any drop-drop interactions. Once again, emphasizing the importance of time and length scales associated with transport processes and operational parameters that establish system residence time (RT and RTD); indicative of mixing intensity and dispersion. The fundamental basis for determining the mechanisms that influence each transport variable's profile and rates can be found, for example, in the works of Bird, et. al. [8] and Deen [9]. A more focused study of these concepts as related to understanding the analyses and computational methodologies useful for design and scale-up of continuous processes, with an emphasis toward formation of nano-emulsions, is given in Fisher and Fisher [10]. All the above referenced works [1-10] have provided the influential factors that have directed the development of our approach to systems analyses, design and implementation. The following example analysis is illustrative of our scale-up strategies.

E. Scale up Strategies. For simplicity of analysis we will assume that the flow channels in our devices, are cylindrical, that droplet formation is primarily via a turbulent mechanism (energy density transfer rate), and the resultant sizes are related to the Kolmogorov scales. Our scale-up strategy is based on the premise that maintaining the identical micro-environment for fluid element at each scale will produce the desired results. Consequently, energy density transfer (dissipation) rate, ε, should yield the same Kolmogorov scales, even when dealing with multiphase systems; i.e., yielding the same quality nano-emulsion. For cylindrical systems ε is readily estimated from the turbulent perturbation velocity (U, approximately 10 % of the main stream time averaged velocity) and channel diameter (D); i.e., $\varepsilon = U^3/D$. A ten-fold scale-up on throughput would therefore require a 1.4x increase in average velocity and a 2.7x increase in diameter. Note that this would raise the Reynolds number (Re) 3.8x; a significant observation since a common misconception would be to scale via a fixed

value of Re. That approach would require a diameter increase of 10x and a velocity decrease to 0.1x. This leads to a ε ratio of 10^{-4} and subsequent 10x increase in the smallest eddy size (λ) between scales.

Using a single channel for scale-up is not a good strategy. It is complicated by other factors such as wall heat generation/transfer and mass diffusion as related to SAA interactions with droplets for stability. A more logical approach is to use the stacking concept; placing identical system configurations, as optimized at the bench scale, in a parallel arrangement fed by a single manifold. It is also necessary that the quality of any pre-emulsion in the feed to each channel remains consistent to that of the bench scale to avoid any additional top down processing requirements to maintain product quality. Consequently, the feed line to the manifold must be designed and scaled properly with respect to mixing intensity and RT to avoid an increase in SAA stabilized macro-droplets. This is imperative since one of our design criteria for bench scale systems is to also minimize formation of such droplets prior to hihg pressure homogenization (HPH). The presence of stabilized macro-droplets in the feed is detrimental to operational efficiency since additional energy is needed for a top down process to fragment them. The severity of this problem can be reduced using a duel feed systems to replace the pre-mix holding tank that is typically used in single feed channel systems, and inherently produce these problematic droplets. Our duel feed systems use in-line mixing devices that operate in the laminal flow regime. They provide tunable levels of macro-mixing, RT's, and when properly designed, minimize interfacial instabilities (Bird, et. al. [10]).

Based on these concenpts, an experimental prototype and testing was deviced to evaluate each in-line device for its incorporation into a full system scale-up.

3 EXPERIMENTAL APPARATUS AND PROCESSURE

Figure 2 shows the concenpt of the device used for the dual feed tests. Two liquid streams are pumped continuously at precice rates dictated by the emulsion formulation. These streams are directed to a manifold with proprietary design and finally feed a high pressure homogenizer located downstream. Thus, the continuous flows limit the variation in residence times experienced by the liquids and droplets. The homogenizer downstream ensures control of the energy rate dissipation, and therefore droplet formation.

The homogenizer used in these tests is the HP350-30 ShearJet from DyHydromatics LLC, located in Maynard, MA, USA. The homogenizer was equipped with various Reaction Chambers®, which are the processing modules, inside which the energy is dissipated. Reaction Chambers® with various consigurations and channel sizes, along with the processing pressure provide control of the energy dissipation rates. A feed manifold with the proprietary design was used in most tests to demonstrate Delphi's dual feed emulsification technology (DF).

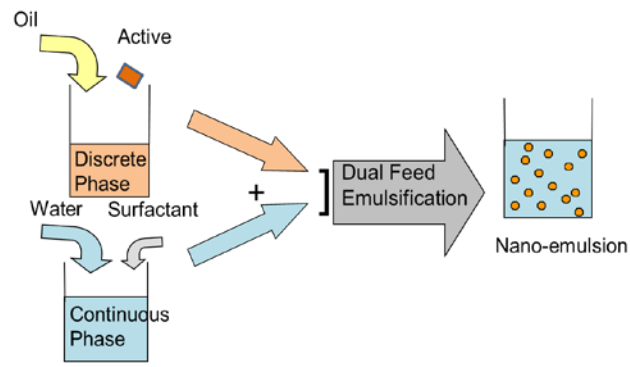

Figure 2. Continuous, Dual Feed emulsification menthod.

Additionally, control tests were conducted using the conventional configuration shown in Figure 1. This is referred to as Top Down (TD) technology, since it reduces the size of already formed droplets during the first step, which is the formation of the coarse emulsion, see Figure 1. In these tests, a rotor-stator mixer device was used for the coarse emulsion. This was a T25 digital ULTRA TURRAX ® equipped with S25N-10G head, operated at about 20,000 rpm. The initial and final temperatures at each step of the process were controlled using insulated lines and a heat exchanger downstream of the Reaction Chambers®.

The particle size distributions of homogenized emulsions were measured using a Dynamic Light Scattering (DLS) instrument, Model Litesizer 500, from Anton Paar GmbH, Graz, Austria. All measurements were conducted based on the instructions of the manufacturer.

The dual feed emulsifications experiments conctucted as follows: (a) Each phase, oil and water was prepared separately based on the formulation used; if necessary each phase was heated up to the desired temperature. (b) Each phase was fed to the HPH at the appropriate rate; the HPH was equipped with the desired Reaction Chambers® and it was set to the appropriate pressure. (c) The emulsion was cooled as it flowed through the heat exchanger and was finally collected, and (d) when desired, the emulsion was then fed as a single stream to the HPH and is processed again.

The top down emulsifications experiments conctucted as follows: (a) Each phase, oil and water was prepared separately based on the formulation used; if necessary each phase was heated up to the desired temperature. (b) The two phases were combined and the mixture was processed with the rotor-stator mixer forming a coarse emulsion. (c) The coarse emulsion was fed to the HPH where it was processed under the desired conditions. (d) The emulsion cooled as it flowed through the heat exchanger and was finally collected, and (e) when desired, the emulsion was then fed as a single stream to the HPH and is processed again.

Four different emulsions were tested, shown in Table 1.

COMPOSITION			FORMULATIONS		
PROCESSING PARAMETERS	A	A	B	C	D
Oil Content (wt %)	28	28	22.5	37	10
Reaction Chambers	75.1T-200.2L	75.1T-200.2L	87.1L-200.2L	75.3T-200.2L	75.1T-200.2L
Process Pressure (psi)	20,000	20,000	20,000	20,000	20,000
Process Temperature (°C)	30-35	30-35	12-13	45-50	35-45
Number of Passes	3	8	4	3	3
Average Particle size (nm)					
Top Down	**112**	**93**	**242**	**287**	**169**
Dual Feed	**85**	**63**	**192**	**252**	**171**

Table 1. Processing parameters and particle size of emulsions

4 RESULTS

Table 2 shows results from four different emulsion formulations. Those had oil content in the range of 10-37 wt% and processed in a variety of conditions, including Reaction Chambers® types, temperatures and number of homogenization passes. All emulsions were processed at process pressures of 20,000 psi (1379 bar).

It can be seen that the Dual Feed method generally results in smaller particle sizes under similar homogenization conditions.

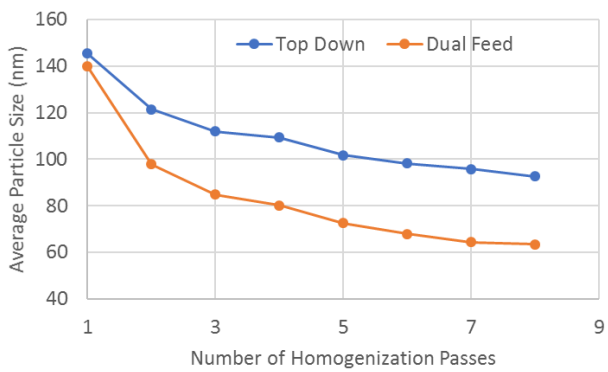

Figure 3. Average particle size of emulsion A processed using Dual Feed and Top Down methods.

Figure 3 shows the particle size of emulsion A as a function of the number of passes. The target particle size was 90 nm. With the dual feed emulsification method, the target is achieved comfortabley in three homogenization passes and is 85 nm. However, with the conventional top down method the target cannot be achieved even after eight passes, after which the average particle size is 93 nm.

Since the number of passes is proportional to the energy requirements, the dual feed requires 267% less homogenization energy. Additionally, it requires one less processing step, since it does not include the coarse emulsion step. This results in additional efficiencies in terms of time, equipment and processing space demands.

5 SUMMARY/CONCLUSIONS

The concept of continuous, dual feed emulsification was demonstred sucessefully for four emulsions, having a wide range of oil contents, 10-37 wt%. In most cases the dual feed emulsified emulsions had substantially lower particle size for the same processing conditions, therefore required lower processing energies. The homogenization energy requirements were reduced by 2.67 times (267%). This is in addition to efficiencies gained as a result of eliminating the step for the formation of the coarse emulsion. Future work includes constructing and testing a large scale prototype based on on these concepts.

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