High Pressure Homogenization – An Update on its Usage and Understanding

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Abstract

Despite being a technology of several decades, high pressure homogenization (HPH) remains widely used in food and pharmaceutical industries, often as an essential unit operation in liquid product processing. Continual advances in the technology are made on multiple fronts, on equipment innovations by the manufacturers, new applications by users, and advances in process understanding by multidisciplinary scientists alongside subject matter experts amongst industry practitioners. While HPH is comparatively simple conceptually, the homogenization process involves complex engineering physics which is influenced by the varied processing conditions and highly diverse inputs with each use-

case requiring its own treatment. The successful application of a HPH process indubitably requires practitioners to draw upon insights from multiple domains and the optimization for each case. Thus, this timely review aims to outline the more recent trends and advancements in HPH process understanding and novel applications involving HPH from both academic and industrial perspectives.

1. Introduction

High pressure homogenization (HPH) was first introduced in the early 20th century by Auguste Gaulin (Gaulin, 1904) for processing milk using pressures up to 30 MPa to improve product stability. The basic operational principle of HPH remains unchanged since and it involves using a high-pressure pump to force the fluid through a small orifice. The early successes expanded the user-base of HPH and it has become an integral unit operation in liquid product processing in several industries such as food and beverages (F&B) (Harte, 2016; Levy et al., 2020; Patrignani and Lanciotti, 2016), pharmaceuticals (Kluge et al., 2012; Yadav and Kale, 2020), waste water treatment (Zhang et al., 2012), material production and processing (Azoubel and Magdassi, 2010; Phanthong et al., 2018; Xu et al., 2011) and biotechnological processing (Kelly and Muske, 2004; Samarasinghe et al., 2012). This list is certainly non-exhaustive and will likely continue to expand.

In conjunction with the introduction of new HPH applications, much work from both industry and academia is required to better understand the impact of the HPH process. Various research studies have considered theoretical aspects of the homogenization process such as fluid flow in the HPH valve (Håkansson et al., 2010; Taghinia et al., 2016) and the mechanisms of complex processes such as emulsification (Gupta et al., 2016a;

Håkansson et al., 2013). Other studies were directed at the operational aspects of HPH such as exploring methods for process optimization (Davoudpour et al., 2015; Dopp and Reuel, 2018) and improved process monitoring and characterization (Besseling et al., 2019; Ralbovsky et al., 2022). Concomitant equipment innovations such as the design of new homogenization valve geometries (Donsì et al., 2012; Gall et al., 2016; Yadav and Kale, 2020) and ultra-high pressure homogenization (UHPH) which employs homogenization pressures between 300-400 MPa (Georget et al., 2014) reflect the continued dynamism and ingenuity of the equipment manufacturers. These efforts by various stakeholders facilitate improvements for existing applications as well as exploring new opportunities.

This review will provide a concise overview of the latest developments and applications involving HPH with the requisite contemporary explanation of the HPH process and its uses. The update by the authors will therefore mainly focus on publications of the last one to two decades. It should be noted that in many of the applications mentioned, HPH forms only part of the overall processing strategies. Often, published studies involved lab or pilot-scale facilities where alternative / smaller-scale operations and methods are adequate for the task. Consequently, for a given application, there might be comparatively fewer studies in the literature that specifically use HPH even though it is a viable option. In a sense, this presents an exciting opportunity for researchers as HPH is a well-established, robust and highly-scalable process option that allows for routine use and continually tested for possibilities to accelerate the development and commercialization of new processes or products.

2. Recent Applications of HPH

This section outlines some of the new and emerging applications of HPH, which can be categorized into three areas: 1) Food and Beverage, 2) Pharmaceutical and Biotechnology, and 3) Materials and Chemicals. A schematic of these applications can be found in Figure 1.

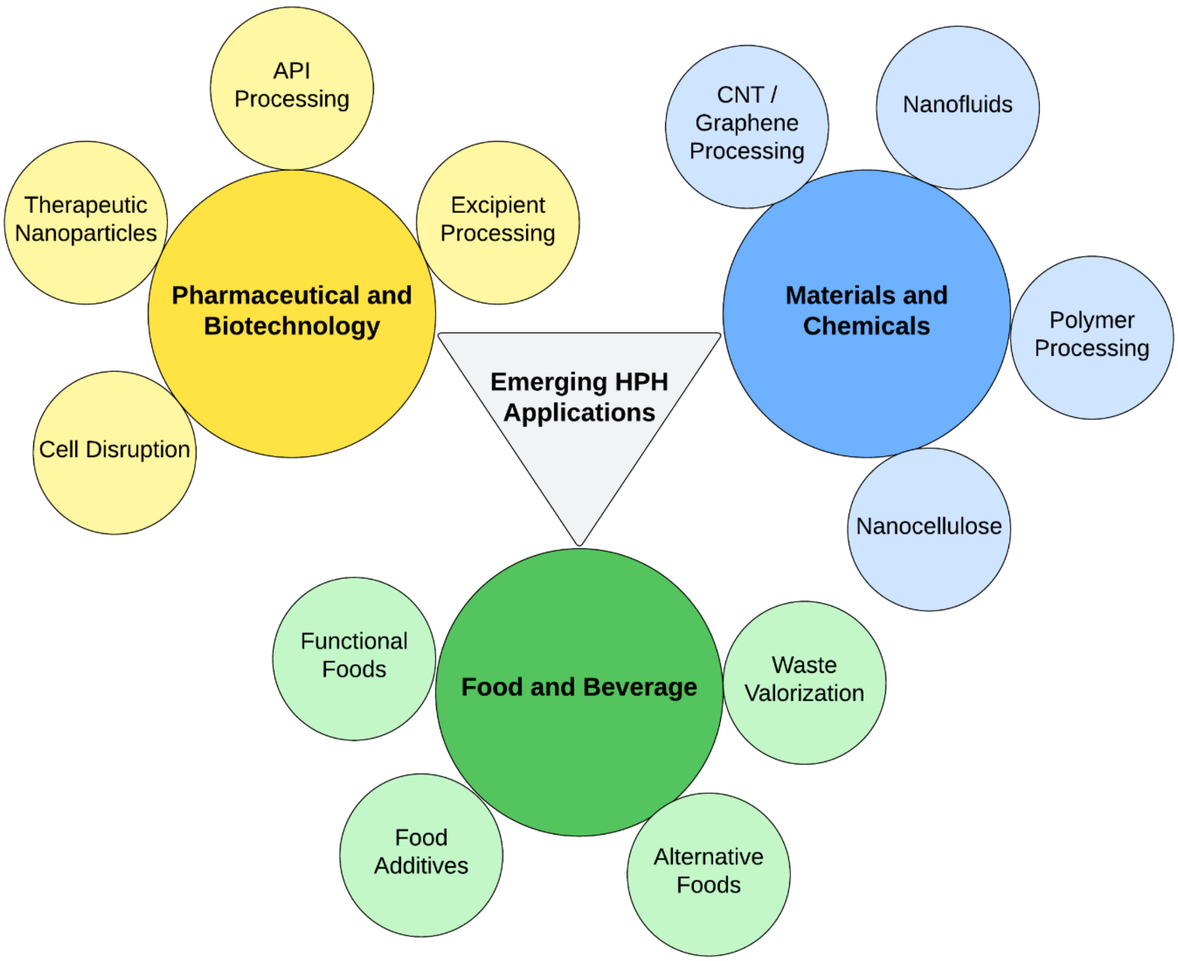

Figure 1. Summary of emerging industrial and academic applications of HPH.

When conceptualizing a new use-case employing HPH, in addition to considering the relevance and felicity of homogenization effect(s) in relation to the planned application, it is helpful to consider the following factors to determine feasibility: a) pumpability, b) power consumption, and c) life time of wear parts (e.g., homogenizer / pump valves and dynamic gaskets / o-rings). A summary of factors influencing the feasibility of an HPH process is presented in Figure 2. The first factor is related to the technical feasibility of operating an HPH process: Feeds that have properties such as high viscosity or large / hard particles typically have poor pumpability and cannot be reliably fed into the homogenizer. The other two factors impact the commercial viability of an HPH process with excessively high power consumption and/or excessively rapid wear on consumable parts can lead to prohibitively high costs and production downtimes. Section 4.2 presents a series of case studies where various process and product related issues were resolved to enable successful HPH application.

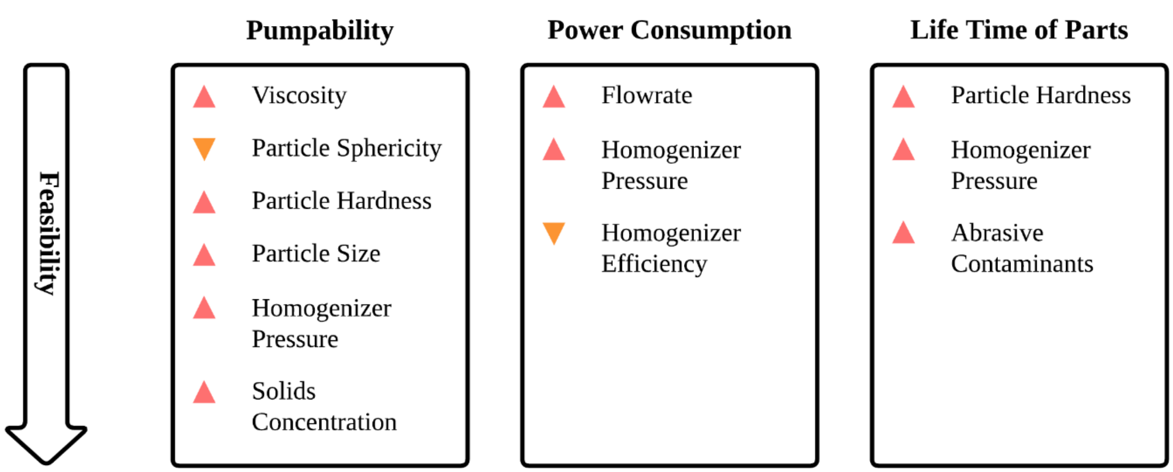

Figure 2. Summary of product and process factors adversely influencing the feasibility of developing a high-pressure homogenization process.

2.1. Food and Beverage Applications

Having its roots in the F&B sector, HPH continues to remain an integral unit operation in many well-established applications such as ensuring food safety and improving physico-chemical properties of foods such as fruit juices and dairy products (Comuzzo et al., 2014; Levy et al., 2020; Patrignani and Lanciotti, 2016; Salehi, 2020). Thus, many publications still explore areas for improvement or advancement in these more traditional F&B applications. For brevity, this review will avoid dwelling in these areas but emphasize instead on new and emerging applications.

Alongside the concerns about food sustainability and climate change, developments into alternative foods such as plant-based dairy and meats (Aschemann-Witzel et al., 2021), lab-cultured meats (Chriki and Hocquette, 2020), precision-fermented proteins (Lawton, 2021; Teng et al., 2021; Zollman Thomas and Bryant, 2021) and insect proteins (Loveday, 2019) are gaining significant consumer and commercial interest. The application of HPH in processing alternative foods is functionally identical to traditional foods as similar process objectives are desired such as improved product stability and sensory properties (Codina-Torrella et al., 2017; Levy et al., 2021), enhanced structural and physico-chemical properties (Dong et al., 2011; Song et al., 2013) and improved processability (Gul et al., 2017). The similarities in process objectives and implementation are encouraging as considerable literature and industrial know-how in processing traditional foods can be relevant in facilitating process development and scale-up of alternative foods production. Similarly, HPH has also been found to be useful in the valorization of meat scraps and waste into nutritional and functional products (Chen et al., 2020) which serves to improve sustainability in the meat industry.

HPH has also contributed to the development and production of innovative foods with improved health benefits such as functional foods, often with enhanced sensory properties and stability. Nanoemulsions, dispersions of two immiscible liquids emulsified with droplets of around 100nm (Gupta et al., 2016b), have facilitated this trend. These nanoemulsions benefit relevant food products by incorporating lipophilic ingredients as an optically transparent form which can improve product appearance and stability, protect sensitive compounds and enhance bioavailability of functional ingredients (Aswathanarayan and Vittal, 2019; Donsì et al., 2010; Yang et al., 2012). HPH has been used for preparing nanoemulsions of functional ingredients such as fatty acids and carotenoids in food products (Silva et al., 2012), flavoring and coloring agents (Aswathanarayan and Vittal, 2019), and various cannabinoids (Banerjee et al., 2021; Lewińska, 2021). An interesting recent application is the use of essential oil nanoemulsions as a natural antimicrobial additive to foods (Aswathanarayan and Vittal, 2019; Donsì and Ferrari, 2016) which can be leveraged to meet increasing consumer desire for foods with natural ingredients.

2.2. Pharmaceutical and Biotechnological Applications

Recent pharmaceutical uses of HPH have relied on established capabilities of HPH related to comminution by high shear, in novel applications and improving existing products or processes. Broadly, pharmaceutical usage of HPH can be divided into two categories: excipients, particularly polymeric types, processing and active pharmaceutical ingredients (APIs), especially as nanoparticulate systems, for enhanced drug delivery. More recently, HPH uses in the biotechnology and biopharmaceutical industries are also more common.

2.2.1. Processing Excipients

Polymers and gums such as alginates and cellulosic derivatives are common pharmaceutical excipients used for drug delivery systems. These polymeric systems are widely used as thickeners or stabilizers in the vehicle liquid for drug delivery and tissue engineering (Curvello et al., 2019), suspensions (Lin and Dufresne, 2014) or transdermal products (Raghav et al., 2021). HPH is often used in the production and/or modification of these polymers. In oral solid dosage forms, polymeric excipients are also used as fillers, binders and disintegrants among others (Debotton and Dahan, 2017).

HPH is often applied in the modification of polymers and gums as it can alter the characteristics of polymers by the intense high shear and turbulence. Examples of such modifications include changes to rheological properties (Eren et al., 2015; Porto et al., 2015), viscosity reduction (Harte and Venegas, 2010; Inguva et al., 2015), zeta potential (Prateepchanachai et al., 2017), molecular weight, and hydrodynamic radius reduction (Belmiro et al., 2018). These modifications can improve processability and enable new formulation strategies such as incorporating excessively viscous polymer gels into formulations (Inguva et al., 2015) or enhancing product quality by improved film strength and water resistance (Shahbazi et al., 2018). However, the HPH process is also recognized to have the potential to adversely impact certain excipients such as protein emulsifiers (Ali et al., 2018) and such a possibility should be considered.

2.2.2. Processing of APIs

Size reduction capabilities of HPH on APIs confer several advantageous properties to the final drug product. A particularly noteworthy application is in the formation of nanocrystals and nanosuspensions of APIs. By preparing the API as a nanosuspension, the dissolubility is increased which improves the bioavailability of poorly water-insoluble drugs. By improving drug solubility, commercialization of drugs would be possible as previously, they were deemed unviable due to poor solubility (Rabinow, 2004). While this paradigm of thought is not new, recent literature reports focused on developing a better understanding between the product and process such as the impact of formulation choices (Paredes et al., 2016; Sun et al., 2011; Van Eerdenbrugh et al., 2008), HPH operating conditions (Kluge et al., 2012; Oktay et al., 2019), and process type and configuration e.g. HPH vs other techniques for producing nanoparticulates (Kakran et al., 2012; Y. Li et al., 2015; Salazar et al., 2012; Zhou et al., 2018).

Another noteworthy HPH application for the processing of APIs is in the formation of nanoemulsions. The hydrophobic drug is dissolved in an oil phase which is then emulsified as an oil-in-water (O/W) nanoemulsion for use in a variety of drug delivery systems such as sprays, creams and capsules (L. Chen et al., 2020; Singh et al., 2017). The benefits of pharmaceutical nanoemulsions include improved bioavailability, stability and controlled release (Gué et al., 2016; Singh et al., 2017). Examples of pharmaceutical nanoemulsions processed using HPH include nanoemulsions of various APIs (Kotta et al., 2015; Sharma et al., 2015; Tagne et al., 2008; Tran et al., 2017), DNA/nanoemulsion complexes for gene therapy (Schuh et al., 2018) and vaccines (Fox et al., 2013; Haensler, 2017; Peshkovsky and Bystryak, 2014).

Outside the pharmaceutical sector, recent studies exploring various aspects of the nanoemulfisication process have yielded better process and product understanding by optimizing emulsifier type and use concentration (Qian and McClements, 2011; Silva et al., 2015; Uluata et al., 2016), HPH operating conditions and equipment design (Donsì et al., 2012; Silva et al., 2015; Wan et al., 2019), process type and configuration (Calligaris et al., 2018, 2016) and the development of semi-empirical scaling laws (Gupta et al., 2016a). Many insights from these studies provide guidance on HPH use to prepare nanoemulsions for both the pharmaceutical and allied industries.

2.2.3. Nanoparticle Systems

Nanoparticulate systems in the pharmaceutical industry form an important platform for achieving a range of clinical and therapeutic objectives to introduce improved and/or targeted drug delivery or efficacious and safer imaging agents (Bobo et al., 2016). This review avoids the discussion of the various types of nanoparticulate systems and their different therapeutic and clinical functions as there are already some excellent reviews (Bhatia, 2016; Bobo et al., 2016; Mitchell et al., 2021). In summary, HPH has emerged as a viable mechanism for the processing of three classes of nanoparticulate systems: lipid-based nanoparticles (Pardeike et al., 2009), polymeric nanoparticles (Vinchhi et al., 2021), and inorganic/hybrid-type nanoparticles (Grüttner et al., 2007; Qi et al., 2014).

The involvement of HPH in processing therapeutically relevant nanoparticles has grown incrementally. Most literature reports focused on developing nanoparticulate products and formulations for different APIs (Vinchhi et al., 2021; Soni et al., 2020), using lipid-based and polymeric nanoparticles for gene therapy (del Pozo-Rodríguez et al., 2016)), molecular targeting agents (Grüttner et al., 2007; Natarajan et al., 2008), and imaging agents (Lee et al., 2004; Yang et al., 2019). The HPH process has been explored within the context of nanoparticle production in order to develop improved process insights for scale-up, process control, and optimization (Homayouni et al., 2014; Hu et al., 2016; Lomis et al., 2016; Qi et al., 2014; Soni et al., 2020).

2.2.4. Biopharmaceutical and Biotechnology Applications

Most recent biopharmaceutical and biotechnology applications involving HPH have relied on its well-established cell disruption/lysis capability. The applications include the production of cell-free protein synthesis systems using various cell types (Carlson et al., 2012; Failmezger et al., 2018; L. Zhang et al., 2020), downstream processing for recombinant protein and virus-like particle production, by batch or continuous operation (Effio and Hubbuch, 2015; Tam et al., 2012; Wilken and Nikolov, 2012) along with extraction of oils and other products from algae (Günerken et al., 2015; Samarasinghe et al., 2012; Spiden et al., 2013; Yap et al., 2015).

Many studies also analyze process and product specific nuances, exploring avenues for improved efficiency, quality, and control. These include investigating the interplay between upstream and downstream unit operations on inclusion body quality and yield (Eggenreich et al., 2020; Slouka et al., 2018), characterizing the impact of process-induced chemical modifications to monoclonal antibodies (Hutterer et al., 2013), improved cell disruption process monitoring strategies (Eggenreich et al., 2017), and strategies for process optimization (Dopp and Reuel, 2018; Metzger et al., 2020; Pekarsky et al., 2019).

2.3. Advanced Materials and Chemical Applications

2.3.1. Advanced Polymer Production and Processing

Natural biopolymers are again being explored as alternative and sustainable materials for many uses such as synthetic polymer replacements (Vinod et al., 2020), therapeutic applications, and electronic materials (de Amorim et al., 2020). HPH, sometimes with other techniques like enzymatic hydrolysis, has been successfully applied to the production of biopolymers such as nanocellulose (Kawee et al., 2018; Lenhart et al., 2020; Li et al., 2012; Wang et al., 2019), starch nanoparticles (Ahmad et al., 2020; Apostolidis and Mandala, 2020; Shi et al., 2011; Wang et al., 2021), chitin nanofibers (Mushi et al., 2019; Ono et al., 2020; Salaberria et al., 2015; Satam and Meredith, 2021), and silk nanofibers (Uddin et al., 2020).

Often, native biopolymers do not possess the requisite physico-chemical properties for subsequent processing or for the final product. Structural modifications by chemical treatment to alter rheological properties or adding modifiers like plasticizers and similar materials to form composites may be necessary (Aaliya et al., 2021; George et al., 2020; Harish Prashanth and Tharanathan, 2007; Kaur et al., 2012). In most cases, HPH is used primarily for the production of the material of interest and subsequent processing steps may utilize other techniques (Rizal et al., 2021; Rocca-Smith et al., 2019). In certain cases, HPH was also used in subsequent modification and processing steps such as in the modification of starch nanoparticles (Apostolidis and Mandala, 2020; Shahbazi et al., 2018), rheological and structural modifications of polymer dispersions (Fu et al., 2011), and formation of nanofibrillated cellulose composites with nanoclays (Garusinghe et al., 2018; Shanmugam et al., 2021; Yong et al., 2018).

Nanocellulose deserves particular attention as a cellulosic material of nanoscale dimension. Three main forms in the prevalent in the literature: nanocrystalline cellulose

(NCC), bacterial nanocellulose (BNC), and nanofibrillated cellulose (NFC) (Phanthong et al., 2018; Thomas et al., 2020). The different types of nanocellulose have attracted significant interest from academia and industry due to many advantageous properties such as being a biodegradable natural product of high strength and stiffness along with the possibility of surface chemical modifications (Phanthong et al., 2018; Salas et al., 2014). Nanocellulose has been utilized in many sectors such as foods (Gómez H. et al., 2016), composite materials and packaging (Kargarzadeh et al., 2017; F. Li et al., 2015), electronics (Sabo et al., 2016), biomedical and pharmaceutics (Jorfi and Foster, 2015; Kamel et al., 2020), and environmental remediation (Mahfoudhi and Boufi, 2017). As previously mentioned, HPH has been established as the convenient, scalable and comparatively environmentally-friendly technology to process and produce nanocellulose and its derivatives.

HPH has also found application in the broader sustainability trend of upcycling and valorizing agri-food remains or waste into usable materials like bioplastics (Otoni et al., 2021). Examples of HPH use in this context include the production of nanocellulose and other nanofibers from agricultural wastes and other sources (Hongrattanavichit and Aht-Ong, 2020; Li et al., 2012; Pacaphol and Aht-Ong, 2017; Salaberria et al., 2015), bio-based adhesives from soybean meal (Y. Zhang et al., 2020), and biopolymer films from fruit and vegetable wastes (Kang and Min, 2010; Wu et al., 2020).

2.3.2. Nanoscale Materials and Fluids

HPH has been applied to the scalable production of many exciting nanomaterials through liquid-phase exfoliation such as boron nitride nanosheets (Guerra et al., 2018; Shang et al., 2016), transition metal dichalcogenide nanosheets (Piao et al., 2018; Shang et al., 2016), and graphene and its variants (Arao et al., 2016; Chen et al., 2020; Qi et al., 2017; Shang et al., 2015). Subsequent application of these nanomaterials often requires the dispersion of the nanostructured material in some media and in some cases, the dispersion produced from the liquid-phase exfoliation step can be used directly (Backes et al., 2020; Johnson et al., 2015). Correspondingly, HPH is suitable for use to directly produce a wide variety of dispersions and has been demonstrated as an effective technique for dispersing and potentially modifying nanomaterials (Azoubel and Magdassi, 2010; Li et al., 2019; Schlüter et al., 2014; Tölle et al., 2012). Many studies have reported successful use of HPH as a processing step to produce advanced materials such as graphene films and inks (Tölle et al., 2012), polymer composites incorporating nanomaterials for improved mechanical, thermal and electrical properties (Appel et al., 2012; Chatterjee et al., 2012; Clausi et al., 2020; Shayganpour et al., 2019; Wu et al., 2021; Xu et al., 2020), and nanofluids which will be discussed. One particularly noteworthy application which has gained significant industrial traction recently, but is comparatively less explored in the academic literature is the production of graphene / carbon nanotube slurries for electrode coatings in batteries (Park et al., 2022; Wen et al., 2023).

Nanofluids contain various types of nanoparticles like metal nanoparticles and their oxides or carbon nanotubes/graphite in a base fluid. These fluids have emerged as a promising advanced thermal fluid to improve the heat transfer performance and thermal efficiency in systems for engine cooling or building temperature management (Saidur et al., 2011). HPH has successfully been used to produce nanofluids containing carbon nanoparticles like carbon nanotubes, diamond, graphite, or graphene (Fontes et al., 2015;

Oliveira et al., 2017; Sica et al., 2021) and metal oxides (Fedele et al., 2011). Similarly, homogenization has been applied for the production of phase change material emulsions which are currently being researched for use as advanced thermal fluids and energy storage media (Wang et al., 2019).

3. Advances in Process Understanding

3.1. Theory and Modeling of HPH

The HPH process involves complex fluid mechanics (primarily shear, turbulence, cavitation, and impact) which can be engineered to obtain desired process and product outcomes. The interested reader is referred to Figure 9.1 in Mulder and Walstra, (1974), Phipps, (1985), and Clarke et al., (2010) for descriptions of the various proposed phenomena occurring in the homogenization valve. With improvements in computational and experimental resources available to researchers, extensive computational fluid dynamics (CFD) simulations and experiments have been performed to elucidate theoretical features of fluid flow in the homogenizer, to better understand how HPH operation relates to product characteristics and seek avenues for process improvement. Despite these advances, it is often helpful to first consider the governing physical laws and theory prior to numerical simulations / experiments. Meaningful insights in the form of scaling relationships and qualitative understanding of flow features relevant to the process of interest can be obtained with significantly less effort.

We intend for this section to be more pedagogical in nature, with the material presented to help the interested reader understand both qualitatively and quantitatively various aspects of the HPH process. A discussion of scaling-based approaches and their developments in the context of emulsification is omitted as there are several articles and reviews presently available in the literature that discuss the topic in great detail and in an accessible manner e.g., see (Gupta et al., 2016a; Håkansson, 2021, 2019; Walstra, 2005).

Before outlining the physical governing equations and relations, it is helpful to first consider the geometry of the homogenizer valve. The specifics of the fluid dynamic effects are often a function of the valve geometry in addition to operating conditions and fluid properties. Figure 3 presents schematics for the geometry of several types of homogenization valves explored in the literature. For the purposes of this section, we intend to focus on radial diffuser type valves (see Figure 4 for a schematic of a typical radial diffuser type homogenizer valve with key measurements outlined), however the analysis and approaches presented are generalizable to other valve types.

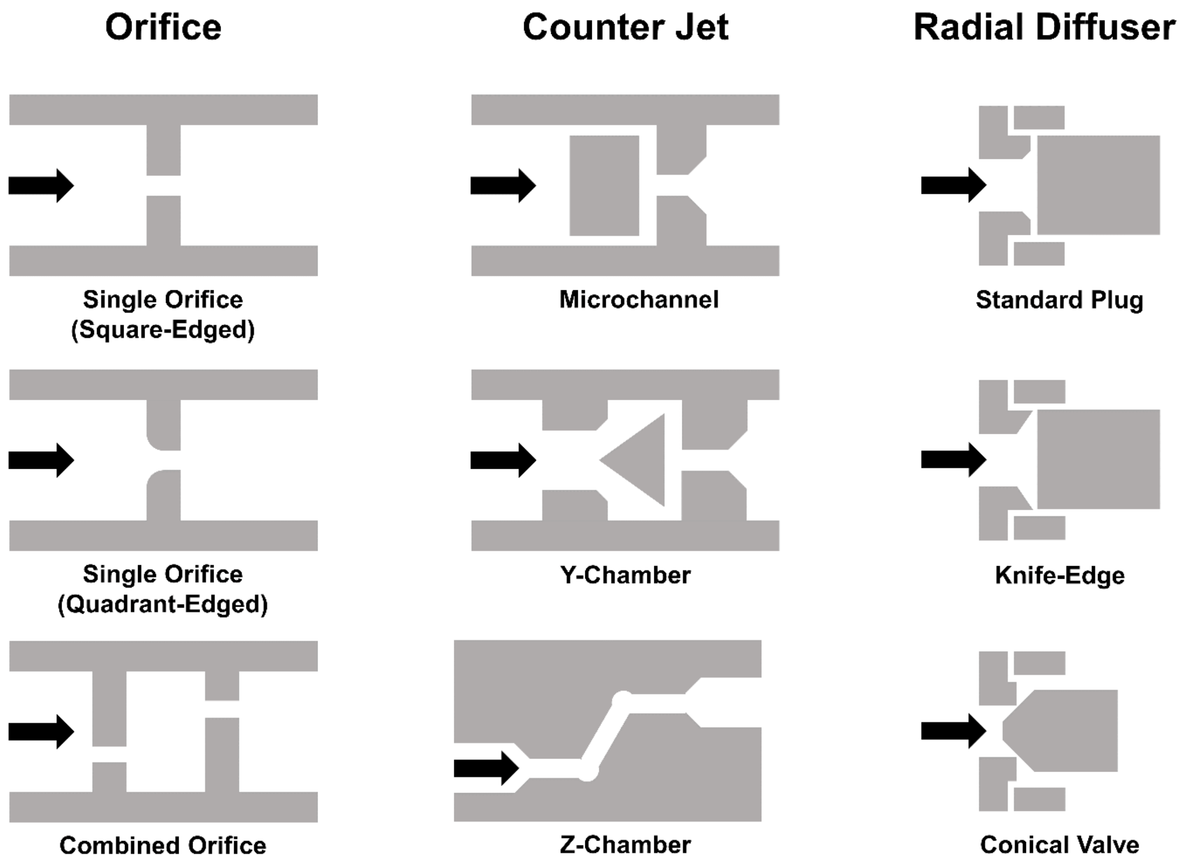

Figure 3. Schematic of different valve geometries segmented into three broad categories: orifice, counter jet, and radial diffuser type valves. Drawings are not to scale. Even more valve geometries have been explored in the literature (e.g., see Mincks, (2002) and Yadav and Kale, (2020)). Equipment manufacturers can help users in designing a suitable valve for their application.

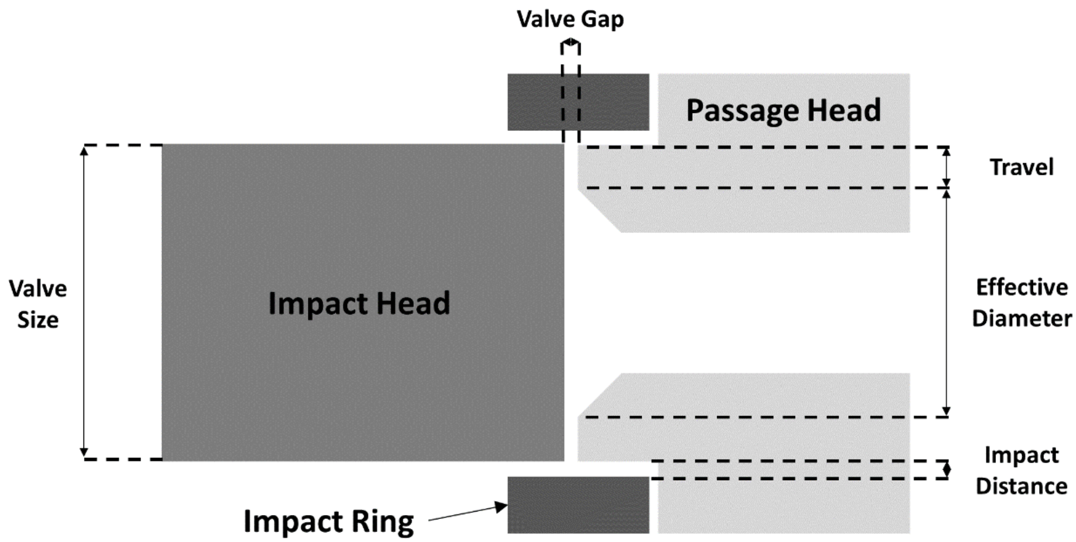

Figure 4. Schematic of a radial diffuser type homogenizer valve. Drawings are not to scale. The valve diameter, effective diameter, travel, and impact distance are important valve design parameters that can be adjusted to achieve the desired fluid dynamic effect for a specific application. The valve gap is an emergent property of the system and is a function of the operating conditions (temperature, homogenizing pressure), valve geometry, and product.

3.1.1. Characterizing the Fluid Flow

3.1.1.1. Pressure Drop and Homogenizer Valve Gap

Referencing Figure 4, as the fluid flows through the homogenizer valve, it accelerates as it enters the homogenizer valve gap. The fluid then decelerates as it exits the gap as a radial jet that impinges on the impact ring, leaving the homogenizer at low velocity and pressure. In that process, the fluid experiences inlet, frictional, and expansion pressure losses (Jahnke, 1998; Kleinig and Middelberg, 1996). Operationally, the homogenization pressure Δp_H and valve geometry (see Figures 3 and 4) are the main degrees of freedom when designing an HPH process. Consequently, for a radial diffuser type valve, the valve gap is an emergent property for a given set of feed, valve geometry, and operating conditions. Note that setting the valve gap when designing an HPH process with a radial diffuser valve is equivalent to operating a fixed orifice valve. For a given application and equipment configuration, there is typically a target valve gap which helps achieves optimal homogenization effect (e.g., see Figure 4 in Pandolfe, (1988)). However, details regarding the optimal valve gap and geometry for a given application are often proprietary information with limited publicly available data especially for newer applications.

One of the simplest procedures for evaluating the valve gap can be constructed using Bernoulli's equation,

$$p_0 + \frac{1}{2}\rho v_0^2 = p_1 + \frac{1}{2}\rho v_1^2 = Constant, \tag{1}$$

where p_0,p_1 and v_0, v_1 are the fluid pressures and velocities at the upstream of the valve and at the entrance / inside of the valve gap respectively. A reasonable approximation, even at low Δp_H such as 30 bar is that $p_0 \gg p_1$ and $v_1 \gg v_0$ (Masbernat et al., 2022; Mulder and Walstra, 1974). Rearranging equation 1 and substituting $p_0 - p_1 = \Delta p_H$ gives

$$\Delta p_H = \frac{1}{2}\rho v_1^2. \tag{2}$$

The average velocity at the entrance of the valve gap, v_E, can be evaluated from the continuity equation,

$$v_E = \frac{\dot{V}}{\pi d_{eff} h}, \tag{3}$$

where $\dot{V}$ is the volumetric flowrate, d_{eff} is the effective diameter of the homogenizer valve, and h is the homogenizer valve gap (see Figure 4). Combining equations 2 and 3 and rearranging for h,

$$h = \frac{1}{\sqrt{2}\,\pi} \frac{\sqrt{\rho}\,\dot{V}}{d_{eff}\sqrt{\Delta p_H}}. \tag{4}$$

Equations 2 and 4 can be modified by including a valve coefficient k to better describe real flow effects (Jahnke, 1998),

$$h = k\,\frac{1}{\sqrt{2}\,\pi} \frac{\sqrt{\rho}\,\dot{V}}{d_{eff}\sqrt{\Delta p_H}}\,, \qquad \Delta p_H = \frac{1}{2k^2}\rho v_E^2, \tag{5}$$

where k is a function of the valve geometry and takes on values ranging from 0.5 – 1.0, and for whole turbulent flow conditions k can be set to ~0.75 (Jahnke, 1998). The simplistic approach presented thus far is useful for understanding the factors impacting the valve gap and can be reasonably accurate for simple cases (Mulder and Walstra, 1974). However, this analysis neglects important details of the fluid flow such as whether it is in the laminar or turbulent flow regime and is also insufficient for describing the total pressure drop across the valve. Thus, the development of empirical correlations was pursued to characterize the total pressure drop and valve gap. The general form of the correlation is expressible as

$$\frac{2\Delta p_H}{\rho v_E^2} = \xi_i + \xi_f + \xi_e, \tag{6}$$

where ξ_i, ξ_f, and ξ_e correspond to inlet, friction, and expansion loss coefficients respectively (Jahnke, 1998; Stevenson and Chen, 1997). ξ_i is given as (Jahnke, 1998),

$$\xi_i = \left(\frac{1}{\alpha} - 1\right)^2, \tag{7}$$

where α is the contraction coefficient defined as the ratio of the width of the vena contracta of the fluid as it enters the valve, h' , and the valve gap. The contraction coefficient describes the “lower gap height” due to flow contraction at the inlet and takes on values ranging from 0.58 for sharp inlets to 0.8 for normal valve geometries. It is also a function of flow and pressure conditions.

To evaluate ξ_f, the flow regime in the valve gap needs to be characterized through the Reynolds number Re_h,

$$Re_h = \frac{v_E h}{\nu} = \frac{\dot{V}}{\pi d_{eff} \nu}, \tag{8}$$

where ν is the kinematic viscosity of the fluid. Based on value for Re_h of the flow, where $Re_h < 1000$ is considered laminar, $1000 < Re_h < 5000$ is considered transitional, and $Re_h > 5000$ is considered turbulent, a suitable correlation can be applied for evaluating ξ_f. The most commonly used correlations were outlined by Phipps, (1975) and are given by:

For $Re_h < 1000$,

$$\xi_f = \frac{12}{mRe_h} ln\left(\frac{d_A}{d_{eff}}\right), \tag{9}$$

for $1000 < Re_h < 5000$,

$$\xi_f = \frac{5}{mRe_h^{3/5}}\left(1 - \left(\frac{d_{eff}}{d_A}\right)^{2/5}\right), \tag{10}$$

for $Re_h > 5000$,

$$\xi_f = \frac{0.076}{mRe_h^{1/4}}\left(1 - \left(\frac{d_{eff}}{d_A}\right)^{3/4}\right), \tag{11}$$

where $m = \frac{h}{d_{eff}}$, and d_A is the valve size (see Figure 4). Lastly, ξ_e is given by

$$\xi_e = k' \left(\frac{d_{eff}}{d_A} \right)^2, \tag{12}$$

where k' is the efflux coefficient and is often set to 1 (Phipps, 1975).

The overall correlation given by equations 7 and 9-12 have been used to estimate valve gaps (Donsì et al., 2009; Floury et al., 2004; Kleinig and Middelberg, 1996; Stevenson and Chen, 1997) and is able to perform reasonably well for simple fluids e.g., water. Even in cases where the flow is more complex e.g., with the presence of particulate material, this method is still able to provide order-of-magnitude estimates of the valve gap (Floury et al., 2004). Alternative approaches have also been proposed to develop relationships and correlations for the pressure drop and valve gap based on friction factors (conceptually similar to equations 9-12) (Masbernat et al., 2022; McKillop et al., 1955; Rovinsky, 1994) and more empirical methods (Kelly and Muske, 2004). However, the case still remains that for more complex fluids e.g., multiphase systems, valve gap estimation is challenging and remains largely empirically-driven.

3.1.1.2. Homogenization Heating Effects

The temperature rise of the product stream, ΔT, as a result of the HPH process can be understood by considering the distribution of the energy input (i.e., pressure) which falls into three categories as the fluid flows through the valve: temperature rise in the product stream, heat loss to the environment, and work done to achieve the homogenization effect (e.g., particle size reduction). Mathematically, the relation between HPH power consumption P, and the three effects is

$$P = \frac{\Delta p_H \dot{V}}{\eta} = \rho c_p \dot{V} \Delta T - UA\Delta T_E + Z, \tag{13}$$

where η is the efficiency, Δp_H is the homogenization pressure, $\dot{V}$ is the volumetric flowrate of the product, ρ is the density of the product, c_p is the specific heat capacity of the product, U is the heat transfer coefficient, A is the heat transfer area of the homogenizer, ΔT_E is the average temperature difference with the environment, and Z is the energy expenditure for homogenization. The maximum temperature rise can be estimated by neglecting heat loss to the environment and energy expenditure for homogenization in equation 13,

$$\Delta T_{Max} = \frac{\Delta p_H}{\rho c_p}. \tag{14}$$

For water and aqueous product streams, equation 2 yields a rule-of-thumb of $\Delta T_{Max} \approx 2.5K\ /100\ bar$ which is in line with experimental observations of 1.5-2.0K / 100 bar (Osorio-Arias et al., 2021). Equation 14 can also be modified to account for multicomponent systems where the densities and/or heat capacities of each component are significantly different,

$$\Delta T_{Max} = \frac{\Delta p_H}{\sum_i x_i \rho_i c_{p,i}}, \tag{15}$$

where the subscript i corresponds to component i and x_i is the mass fraction of component i in the feed. More accurate, but empirical polynomial fits relating Δp_H and ΔT can be constructed for specific product and HPH equipment combinations (e.g., see Table 7 in Osorio-Arias et al., (2021)).

3.1.1.3. Turbulence in the Homogenizing Valve

The fluid leaves the valve gap as a radial jet into the post-valve gap region and impinges on the impact ring. Wall interactions may also be significant with flow separation and reattachment (Håkansson et al., 2012). The fluid experiences the highest intensity of turbulence in this region. Fluid flow in the valve gap can be either laminar or turbulent based on the valve gap and geometry (see Section 3.1.1.1), while the flow in the inlet chamber is mostly laminar or has a low turbulence intensity (Håkansson et al., 2012).

A key quantity for understanding turbulent flow in the homogenizer valve and its effect is the energy dissipation rate ϵ. Håkansson et al., (2011) provides an excellent overview of methods to estimate ϵ and derived properties from scaling relations (mean approach), CFD (local approach), and experimental methods (direct approach). Historically, the mean approach has been the most commonly employed method due to its ease-of-use as no detailed information on the fluid flow is needed to generate useful analytical relationships. The mean energy dissipation per unit volume $\bar{\epsilon}$, can be related to the homogenization pressure and flowrate by

$$\bar{\epsilon} = \frac{\Delta p_H \dot{V}}{V_{diss}}, \tag{16}$$

where V_{diss} is the valve gap volume $V_{diss} = \frac{\pi}{4}\left(d_A^2 - d_{eff}^2\right)h$ (Raikar et al., 2010). Another form of $\bar{\epsilon}$ commonly used in the literature is expressed in terms of v_E and is given by (Håkansson et al., 2011)

$$\bar{\epsilon} = c_1 \frac{v_E^3}{h}, \tag{17}$$

where c_1 is a constant and has been set to 0.05 (Mohr, 1987a) or 0.0125 (Innings and Trägårdh, 2007). Estimates of h can be found using the approaches outlined in Section 3.1.1.1. Note that equations 16 and 17 are conceptually equivalent as Δp_H can be related to v_E using Bernoulli's equation (Innings and Trägårdh, 2007). Conceptually equivalent relationships have also been used with the form $\bar{\epsilon} \propto \Delta p_H^{3/2}$ (Casoli et al., 2010; Jahnke, 1998; Mulder and Walstra, 1974; Raikar et al., 2009). From this estimate of the energy dissipation rate, several useful properties can be estimated to characterize the turbulent fluid flow and its impact e.g., emulsification. The Komolgorov microscales (length λ, time t_λ, and velocity v_λ), which characterize the smallest eddies in the flow, can be expressed in terms of the kinematic viscosity, ν, and $\bar{\epsilon}$:

$$\lambda = \left(\frac{\nu^3}{\bar{\epsilon}}\right)^{1/4}, \quad (18)$$

$$t_\lambda = \left(\frac{\nu}{\bar{\epsilon}}\right)^{1/2}, \quad (19)$$

$$v_\lambda = (\nu\bar{\epsilon})^{1/4}. \quad (20)$$

A drop / particle will experience turbulent inertial (TI) stresses, τ_{TI}, arising from pressure fluctuations across the particle diameter d_P from eddies smaller than d_P and turbulent viscous (TV) stresses, τ_{TV}, from eddies larger than d_P. These stresses are given by,

$$\tau_{TI} = \frac{\rho\langle vv\rangle_d}{2} = \rho\bar{\epsilon}^{2/3} d_P^{2/3}, \quad (21)$$

$$\tau_{TV} = \mu G_d = \mu\sqrt{\frac{\bar{\epsilon}}{\nu}}, \quad (22)$$

where $\langle vv\rangle_d$ is the mean squared velocity fluctuations of eddies up to size d_P, G_d is the time-averaged velocity gradient and μ is the dynamic viscosity of the fluid. The evaluation of $\langle vv\rangle_d$ is based on the result from Komolgorov, (1949) and Hinze, (1955), while G_d is based on Shinnar, (1961). From the relations given in equations 21 and 22, subsequent analysis of the impact of turbulence on the product can be performed. This analysis has primarily been carried out in the context of emulsification where a stress balance can be carried out to characterize droplet breakage (Håkansson, 2019).

The mean approach based on scaling methods, derived results (e.g., Komolgorov-Hinze theory), and extensions are not only comparatively simple, they have found widespread use, providing physical insight and reasonable quantitative predictions for many systems (Håkansson, 2019). Advances in characterizing turbulence in HPH valves have been pursued experimentally using particle image velocimetry (PIV) on scaled models and/or modified homogenizer valves (Håkansson et al., 2012, 2011; Innings and Trägårdh, 2007; Kelemen et al., 2015) or with CFD (further discussed in Section 3.1.2.) and provide significant insight to the flow characteristics. These methods can also be used to generate more accurate estimates of $\bar{\epsilon}$ (Olad et al., 2022a) which are then used to compute a property of interest using the methods outlined, or alternatively the local flow data can be used directly (e.g., see Casoli et al., (2010)).

3.1.1.4. Shear in the Homogenizing Valve

Shear stress is the force per unit area acting on a fluid element in the direction parallel to the fluid element surface. Shear is one of the main fluid dynamic effects occurring in a homogenizing valve and can contribute to achieving the desired homogenization effect such as in the exfoliation of advanced 2D materials (Biccai et al., 2018). High shear stresses arise in the region of the inlet chamber near to the gap entrance and in the boundary layer in the valve gap (Vinchhi et al., 2021). Turbulent shear effects are also present in the outlet region and are discussed in Section 3.1.1.3. Depending on the context, the shear stress, τ, and/or the shear rate, G, can be of relevance. It is important to remember that these two values are related by constitutive relationships such as Newton's law of viscosity for Newtonian fluids given by

$$\tau = \mu G = \mu \frac{dv}{dy}, \tag{23}$$

where $\frac{dv}{dy}$ is the velocity gradient in the direction perpendicular to the shear force. In the absence of CFD simulation data, detailed information of the shear rates/stress is unavailable, motivating the use of mean / max methods. The mean shear stress, $\bar{\tau}$, can be estimated by considering a force balance across the annular region which gives

$$\bar{\tau} = \frac{2h\left(d_{eff}p_0 - d_A p_2\right)}{d_A^2 - d_{eff}^2}, \tag{24}$$

where p_2 is the back pressure in the valve. The maximum shear rate G_{max} is given by

$$G_{max} = c_2 \frac{v_E}{h}, \tag{25}$$

where c_2 is a constant with a typical value ~ 0.5 and is a function of the valve geometry (Håkansson, 2022a, 2017). CFD simulations can be used to generate more accurate estimates for the mean/maximum shear rates/stress and also to map the location and quantity of shear effects (Håkansson, 2022a; Kelly and Muske, 2004).

3.1.1.5. Cavitation in the Homogenizing Valve

As a consequence of the high fluid velocity in the homogenization valve gap, the static pressure of the fluid decreases significantly (see equation 1). In many cases the pressure can decrease below the vapor pressure of the fluid, causing the fluid to "boil" and form vapor bubbles (cavities) which can collapse, resulting in a shockwave and/or microjet that contribute (or in some cases diminish) to the homogenization effect and cause equipment wear (Innings et al., 2011). Detailed insight on the cavitation phenomena in the homogenization valve such as the location is still limited (Håkansson et al., 2010) and active research using experimental and computational methods are being undertaken. Experimental approaches include flow visualization (Håkansson et al., 2010; Schlender et al., 2015b) and examining valve wear. Valve wear believed to have been caused by cavitation has found to take place at the valve gap entrance, exit, and at the outlet region before the radial jet impinges on the impact ring (Casoli et al., 2010; Innings et al., 2011). The presence of particulate matter in conjunction with cavitation can significantly accelerate wear of the homogenizer valve (Innings et al., 2011).

The presence of cavitation can be understood by considering two dimensionless numbers, namely the cavitation number C_v, and the Thoma number Th, which are given by

$$C_v = \frac{p_2 - p_v}{0.5\rho v_E^2}, \tag{26}$$

$$Th = \frac{p_2 - p'}{p_0 - p'} \approx \frac{p_2}{p_0}, \tag{27}$$

where p_v is the saturation vapor pressure of the fluid and can be determined using the Antoine equation and p' is the pressure in the valve gap. Theoretically, cavitation can initiate when $C_v < 1$ as this is indicative of conditions where boiling is possible. However, cavitation effects have been observed when $C_v > 1$ and has been attributed to the presence of dissolved gases and is also a function of valve geometry (Yan and Thorpe, 1990).

It is also important to simultaneously consider the Thoma number as it helps to quantify the cavitation suppression effects of factors such as valve geometry (Jahnke, 1998; Mohr, 1987b) and the process configuration. For example, the presence of a second homogenizing stage or downstream unit operations which introduce additional back pressure, can suppress cavitation (Jahnke, 1998). It can be helpful to explore the role of C_v and Th when carrying out process development (e.g., see Nacken et al., (2015) and Balasundaram and Harrison, (2006)) as there can be optimum values of these parameters that help achieve the desired homogenization effect (Jahnke, 1998).

3.1.1.6. Impact in the Homogenizing Valve

The fluid leaves the homogenizer valve gap as a radial jet and impinges on the impact ring (see Figure 4). The maximum stagnation pressure of the impinging jet, p_S can be related to the velocity of the jet at the exit of the valve gap v_O using Bernoulli's equation,

$$p_S = \frac{1}{2}\rho v_O^2, \qquad v_O = \frac{\dot{V}}{\pi d_A h}. \tag{28}$$

It is helpful to calculate the Reynolds number of the jet, Re_O,

$$Re_O = \frac{v_O h}{\nu} = \frac{\dot{V}}{\pi d_A \nu}, \tag{29}$$

as the flow regime (laminar or turbulent) of the jet is of importance in characterizing aspects of the jet's behavior. For subsonic turbulent impinging jets, it has been proposed that p_S is related to the valve geometry by (Beltaos and Rajaratnam, 1974; Moore et al., 1990),

$$p_S \propto \frac{1}{X^2 h^2}, \tag{30}$$

where X is the impact distance. To date, the role of impact has been mainly studied in the context of cell disruption with p_S being correlated with the homogenization effect with only a limited number of studies available in the literature. While equation 30 was found suitable for baker's yeast (Moore et al., 1990), subsequent studies based on other organisms and CFD demonstrated limitations in its applicability (Kleinig et al., 1996; Kleinig and Middelberg, 1997; Miller et al., 2002). For example, Kleinig and Middelberg, (1997) found that the laminar jet stagnation pressure determined by CFD better described the cell disruption process than equation 30, noting that for their system, estimations of Re_O indicated that the flow is in the laminar regime.

3.1.2. Scale-Up

A key point to note during scale-up is that the homogenizer valve gap in larger-scale homogenizers is much larger than then bench/pilot scale equipment. Consequently, scale-up is non-trivial as the increase in the valve gap and changes in the valve geometry can alter important flow characteristics (Håkansson, 2017), potentially leading to poor homogenizer performance upon scale-up. To date, scale-up remains a largely empirical and iterative exercise, relying on deep product and process know-how from users and equipment manufacturers. Theoretical and computational tools such as those described thus far can help facilitate scale-up, but some experimental testing and validation on pilot/production-scale equipment is often required. An example of some of the challenges encountered during scale-up is presented in Section 4.2.

Some scale-up/down guidelines have been presented in the literature and are principally based on keeping important geometry and flow characteristics similar at different scales as quantified by relevant dimensionless groups and other parameters. One criterion which maintains similarity in the flow characteristics is to keep Re_h and the turbulent gap height (given by $\frac{h}{\lambda}$) the same (Stevenson and Chen, 1997). Preiss et al., (2021) proposed that in addition to Re_h, the Weber number and $\frac{d_{eff}}{d_A}$ should be kept constant. These approaches can help provide a good starting point for scale-up.

3.2. Mechanistic Modeling of HPH

3.2.1. Continuum-Scale Methods

The use of CFD to study HPH processes is challenging as there are multiple complex fluid dynamic effects occurring in the homogenization valve, and in many applications, two or more phases such as solid-liquid or liquid-liquid flows are present. Early applications of CFD from the 1990s and early 2000s employed single-phase Reynolds Averaged Navier-Stokes (RANS) CFD with classical turbulence models (e.g., some variant of the $k - \varepsilon$ model) to analyze the fluid flow in the homogenizer valve in terms of the various fluid dynamic effects outlined in Section 3.1 and their possible impact on homogenizer performance (Floury et al., 2004; Kelly and Muske, 2004; Kleinig and Middelberg, 1997, 1996; Miller et al., 2002; Stevenson and Chen, 1997).

As computational capabilities and modeling know-how improved, two areas of improvement in the application of CFD emerged: 1) improving the accuracy of the simulation, and 2) improving the value derived from CFD. On the first point, as RANS-based CFD methods were and still remain the most commonly used turbulence modeling approach due to their low computational cost and availability, it was important to understand its applicability and accuracy. Håkansson et al., (2012) was the first to compare RANS-CFD results with experimentally measured velocity flow fields and observed that while RANS-CFD can reasonably model flow in the inlet and valve gap, it is inaccurate in the outlet region both in terms of the velocity profile and the production of turbulent kinetic energy. More recent studies have employed more sophisticated though computationally costly methods such as Large Eddy Simulation (LES) on the whole homogenizer valve (Taghinia et al., 2016, 2015) and Direct Numerical Simulation (DNS) on the outlet region (Olad et al., 2022a, 2022b) and were able to provide much more accurate descriptions of the flow, even in the outlet region. The interested reader is referred to Olad et al., (2022a) for a state-of-the-art discussion on best practices in applying turbulence models in HPH CFD studies. Finally, a handful of studies have also explored the role of cavitation and its impact on the fluid flow using CFD and cavitation models (Casoli et al., 2010; Håkansson et al., 2010; Innings et al., 2011).

CFD has also increasingly found more utility beyond just providing descriptions of the fluid flow in the homogenizing valve and has become an integral part of the process development workflow in industry (see Section 4 for examples). CFD-based methods are being used to model and optimize homogenization performance using CFD-augmented Kolmogorov-Hinze approaches (Håkansson et al., 2011), discrete phase modeling (Casoli et al., 2010; Jiang et al., 2021), and population balance models (PBMs) (discussed subsequently). CFD is also enabling improved valve geometry designs (Håkansson, 2022a, 2022b; Pang and Ngaile, 2021) and can help provide a better understanding of the overall HPH process as factors such as the pulsatile flow caused by the piston pumps can be studied (Håkansson, 2018).

In parallel to the advancement of CFD, the use of PBMs and its coupling with CFD to describe study HPH processes has also become more common, though mainly in the context of tracking the particle size distribution during emulsification. PBMs are a highly flexible modeling method that enables the user to track the evolution of a population along one or more intrinsic variables e.g., particle size and/or composition (Inguva et al., 2022; Ramkrishna and Singh, 2014). For a single continuous intrinsic variable L, the general form of a population balance model which describes the evolution of the number density $n(L, t)$, is given by,

$$\frac{\partial n(L,t)}{\partial t} + \frac{\partial (g n(L,t))}{\partial L} = h(L,t,n), \tag{31}$$

where g is the rate of change of L with respect to time and is often referred to as the "growth rate" in the PBM literature, and h represents the various source and sink terms needed to describe the physics of the process. The incorporation of additional intrinsic variables (described by a vector $\boldsymbol{l}$ of intrinsic coordinates l_i) and its spatial distribution (which is important for coupled CFD-PBM methods) is conceptually straightforward and the general PBM can be given by

$$\frac{\partial n(\boldsymbol{l},\boldsymbol{x},t)}{\partial t} + \nabla_{\boldsymbol{l}} \cdot (\boldsymbol{g} n(\boldsymbol{l},\boldsymbol{x},t)) + \nabla_{\boldsymbol{x}} \cdot (\boldsymbol{u} n(\boldsymbol{l},\boldsymbol{x},t)) = h(\boldsymbol{l},\boldsymbol{x},t,n), \tag{32}$$

where $\nabla_{\boldsymbol{l}}$ is the gradient operator with respect to $\boldsymbol{l}$, $\boldsymbol{g}$ is the vector of growth rates, $\nabla_{\boldsymbol{x}}$ is the spatial gradient operator and $\boldsymbol{u}$ is the velocity vector.

The application of PBM-based approaches to emulsification and particle size reduction requires incorporating suitable expressions for h that capture the relevant physics of the process which includes breakage, coalescence, and the transport of an emulsifier (see Håkansson, (2019) and citations therein for details on formulating the required expressions). The PBM model can be employed by itself, using the methods presented in Section 3.1 or experimental/CFD data to formulate the relevant expressions and fit model parameters (Håkansson et al., 2009; Maindarkar et al., 2012; Raikar et al., 2010, 2009). More advanced approaches have employed one-way coupled CFD-PBM where the CFD model is first solved and the spatial information of the fluid flow is passed into the PBM model, providing spatial resolution of the particle size distribution (Becker et al., 2014; Dubbelboer et al., 2014; Håkansson et al., 2013).

PBMs as a framework to study HPH processes is comparatively immature and most studies thus far have focused on modeling a single intrinsic variable, the particle size, in the context of emulsification. The further development and application of PBMs, either by incorporating more relevant intrinsic variables and/or by describing other homogenization processes can be an exciting, albeit challenging area of research. It should be noted however, that PBM-based approaches can have limitations either due to shortcomings in the underlying models used to describe specific physical phenomena, or due to the possibility of introducing a large number of fitted parameters thus reducing its generalizability (Håkansson, 2019).

As a final point, it is possible to employ multiphase flow CFD techniques such as the volume-of-fluid interface capturing method (Malekzadeh and Roohi, 2015) or smooth particle hydrodynamics (Wieth et al., 2016) to model droplet breakage and emulsion formation. This approach is far more predictive as only a handful of physical constants such as the interfacial tension and viscosities are required to formulate the model and it can provide a complete description of droplet breakage. However, such a simulation approach is too computationally expensive at the length scale of the whole homogenization valve, but is feasible for a single drop if performed strategically and has only very recently been carried out (Lewerentz et al., 2023; Olad et al., 2023b, 2023a).

3.2.2. Meso-and Molecular-Scale Modeling

As a final point, many newer applications of HPH involve molecular length scales like the production of nanofibrillated cellulose (Abdul Khalil et al., 2014) or graphene-based materials (Shang et al., 2015). While CFD and other continuum-scale techniques might be able to provide some insights into the process (Stafford et al., 2021), it may not be adequate to provide a complete picture of the process. At these length scales, mesoscale and molecular-scale methods such as dissipative particle dynamics (J. Zhang et al., 2020) and molecular dynamics (Choi et al., 2014; Li et al., 2017) can be used in conjunction with continuum-scale methods like CFD to study HPH process in a multiscale manner. However, despite the existence of several mesoscale/molecular-scale studies for specific phenomena / system such as emulsions and colloids, there is a paucity of literature for multiscale modeling and simulations of HPH processes and this presents an exciting opportunity for new research.

3.3. Data-Driven / Empirical Modeling

In many cases, it may be impractical or even intractable to develop an adequately detailed mechanistic model for HPH processes. Thus, empirical/ semi-empirical and data-driven models that relate input and output variables are often modelled for product development and optimization (Garcia-Ortega et al., 2015). These models are also very useful for developing digital twins and process simulations for the whole process where HPH is an important unit operation. The diversity of HPH applications does mean that there is no universal model to describe the relationship between key input and output variables as the specific application determines important variables and factors.

Models attempted involve variables related to the particle size distribution for emulsification or nanoparticle production processes (Dubbelboer et al., 2014; Durán-Lobato et al., 2013; Lebaz and Sheibat-Othman, 2019), viscosity reduction of polymers (Harte and Venegas, 2010; Inguva et al., 2015), cell disruption for intracellular product recovery and sludge disintegration (Ekpeni et al., 2015; Kelly and Muske, 2004; Tam et al., 2012; Y. Zhang et al., 2012), and nanocellulose production (Davoudpour et al., 2015). Two modelling strategies are of particular interest; response surface model (RSM) which employs a multi-dimensional first order or second order polynomial to curve-fit experimental data conducted as part of a design of experiment (Khuri and Mukhopadhyay, 2010). The first approach is conceptually straightforward and can be implemented easily and is already commonly used to model HPH processes (Davoudpour et al., 2015; Gul et al., 2018). The second approach is machine learning based approaches e.g., neural network / gaussian processes / k-nearest neighbors that are being applied in HPH settings (Bhilare et al., 2019; Patil et al., 2016). Machine learning approaches offer the potential for better regression and predictive performance than RSM in addition to facilitating the construction of more complex models that integrate more data-streams.

3.4. Process Analytical Technology

While process analytical technology (PAT) as a concept has mainly gained prominence in the pharmaceutical and fine chemicals industries (Chew and Sharratt, 2010; Simon et al., 2015), many of the principles and techniques such as the real-time monitoring of process and product parameters and multivariate data collection and analysis methods are relevant and useful for the broader manufacturing sector (Jerome et al., 2019; van den Berg et al., 2013). The use of analytical tools for process control and monitoring for HPH is highly application specific as each product and process will require the monitoring and evaluation of different properties of the system using different platforms and technologies. Therefore, two sub-sections will describe the topic under (a) monitoring and control of the HPH process, and (b) analysis and characterization of products. A discussion of the relevant data collection, mathematical and statistical methods will not be covered as these topics have been extensively discussed in the PAT literature.

3.4.1. Monitoring and Control of the HPH Process

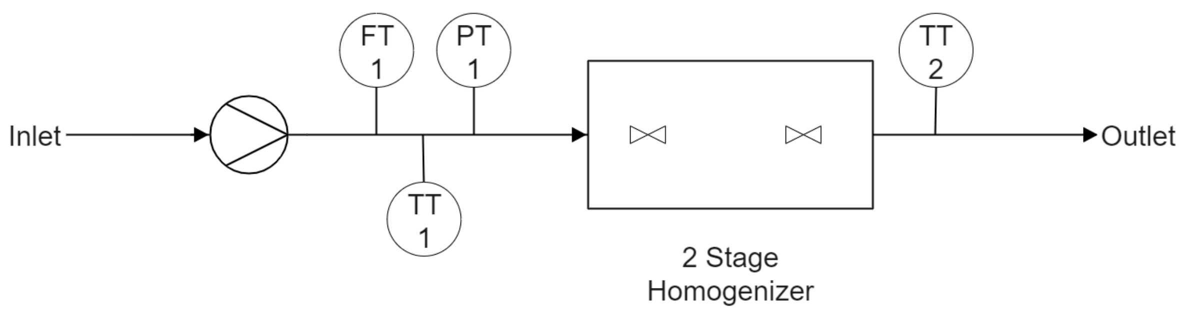

Figure 5. Schematic of 2-Stage HPH process with temperature (TT), pressure (PT) and flow (FT) sensors/transmitters.

As shown in figure 5, HPH is a conceptually simple unit operation. Various conventional sensors such as temperature, flow and pressure sensors can and are typically integrated into the equipment for standard process control and monitoring. For a given process configuration such as a single 2-stage homogenizer, the main manipulated variables are the homogenization pressure of the different stages and number of passes. The pressure can be automatically controlled with the use of a pressure controller such as in GEA

XStream Lab homogenizer as an example. Another parameter that can be easily monitored for additional process insight is the power consumption of the homogenizer. While not as extensively discussed in the HPH literature, power consumption measurement is a common PAT tool in many unit operations such as granulation (Hansuld and Briens, 2014) and mixing (Bowler et al., 2020) to characterize different stages of the process and determine the process end-point. While such analysis may not be directly applicable due to the continuous nature of HPH operations, power measurement can help to monitor the process for deviations. The HPH equipment may be monitored by its acoustic emission. The use of acoustic measurement to better understand the occurrence of cavitation during operation and its impact on the emulsification process has been expounded (Håkansson et al., 2010; Schlender et al., 2015b). While not explored thus far, possible incorporation of acoustic emissions and other monitored variables as output variables in a multivariate data-driven model of the process which can then be leveraged for enhanced process monitoring, control, and optimization.

3.4.2. Analysis and Characterization of Products

The trend to further develop and incorporate PAT for better product and process understanding has facilitated significant technological advancements in ancillary areas such as new or improved sensor technologies for inline process integration and multivariate data analytic methods to handle complex sensor data streams (Grassi and Alamprese, 2018; Rüdt et al., 2017; van den Berg et al., 2013; Zhao et al., 2015). Recently, several noteworthy studies explored new technologies and the integration of PAT for process monitoring and control (Besseling et al., 2019; Eggenreich et al., 2017;

Ralbovsky et al., 2022). Table 1 summarizes the various PAT tools employed for HPH. Considering the diversity and increasing sophistication of HPH applications that require precise control, additional work by all stakeholders is necessary to holistically fuel the exciting challenge of advancing the development and incorporation of PAT in HPH processes.

Table 1. Summary of process/product variables of interest and analytical technologies available for PAT. Where possible, examples provided are applied within the context of HPH, but some examples are drawn from other areas such as chemical synthesis.

Process/Product Variable of Interest	Available Analytical Technologies (Process Integration Format)	Comments	Examples
Temperature	Thermocouple (inline)	Sensors can be integrated at both the inlet and outlet to monitor temperature change.	(Martínez-Monteagudo et al., 2017; Poliseli-Scopel et al., 2013)
Pressure	Pressure transducer (inline)	Pressure gauges typically come standard with the HPH equipment.	
Flowrate	Flowmeter (inline)	Various flowmeters with different operating principles are available. Select a flowmeter type best suited for the application.	(Poliseli-Scopel et al., 2013; Schlender et al., 2015a)
Acoustic emissions	Microphone / Acoustics emission sensor	Signal processing such as amplification may be necessary. Currently used to characterize cavitation patterns.	(Håkansson et al., 2010; Schlender et al., 2015b)
Power consumption	Power meter		See various citations in Hansuld and Briens, (2014)
Imaging / Visualization of fluid flow	1. Particle image velocimetry (inline) 2. High-speed imaging (inline)	High-speed imaging and particle image velocimetry to characterize fluid flow features such as the velocity profile, cavitation patterns and droplet breakage.	See various citations in Bisten and Schuchmann, (2016)

Imaging of products	1. Inline imaging 2. Optical / Electron / Atomic force microscopy (offline)	Inline imaging of the HPH process remains relatively unexplored with many studies using scaled models. Offline imaging using various microscopy techniques is well-established.	(Ralbovsky et al., 2022)
Turbidity	Turbidity sensor (inline / at-line / offline), Spectrophotometer (inline / at-line / offline)		(Linke and Drusch, 2016; Spiden et al., 2013)
Particle Size	1. Dynamic light scattering (DLS) (at-line / offline) 2. Spatially resolved DLS (inline) 3. Laser scattering (at-line / offline) 4. Focused beam reflectance measurement (FBRM) (inline)		DLS: (Qian and McClements, 2011; Yu et al., 2013) Spatially resolved DLS: (Besseling et al., 2019) Laser scattering: (Samarasinghe et al., 2012) FBRM: (Ralbovsky et al., 2022)
Viscosity / Rheological properties	1. Viscometer (inline / at-line / offline) 2. Rheometer (offline)	Rheometers are better at characterizing rheological properties than viscometers; choice depends on process / product requirements.	Viscometer: (Inguva et al., 2015; Pu et al., 2015) Rheometer: (Fu et al., 2011; Qian and McClements, 2011)

Chemical properties / Composition	1. X-ray diffraction (XRD) (offline) 2. Spectroscopic techniques (Raman, UV-Vis, NIR etc.) (inline / at-line / offline) 3. Chromatographic techniques (HPLC, size-exclusion etc.) (at-line / offline) 4. Nuclear magnetic resonance (NMR) (online / at-line / offline)	The choice of analytical technique and integration format depends on the application and process requirements. Cost can also be an important factor.	XRD: (Apostolidis and Mandala, 2020; Li et al., 2012) Spectroscopic: (Ralbovsky et al., 2022; Shang et al., 2016, 2015) Chromatographic: (Eggenreich et al., 2017; Salaberria et al., 2015) NMR: (T. Li et al., 2015; Ono et al., 2020)

4. Industrial Insights and Perspectives

4.1. Industrial Outlook

The HPH industry is pushed by innovation and technological advances, pulled by the need for scale-up of successful “startup" products, and inspired by an increasing focus on sustainability at lowest possible total cost of ownership. While HPH will remain integral to multiple traditional applications, several high growth areas in the HPH market have recently emerged and include complex foodstuff products, pharmaceutical/nutraceuticals, and new industrial products related to the transition to a more sustainable and circular economy. In this regard, many of the active areas of research involving homogenizers are closely aligned with industrial trends.

Developments in traditional, high-volume, and low-complexity applications (e.g., fresh milk) are ongoing and will continue to be an important driver to meet demands for increased throughput at lower homogenization pressures while yielding the same or better homogenization effect. Simultaneously, major global dairy and food players are investing in differentiating some of their products by adding supplements like vitamins and fibers to turn them into healthier and more profitable products. These higher-end products typically require higher homogenization pressures. Key developments to take note of in this space include improved product and process understanding and more efficient homogenizer valves designed with the latest CFD tools.

Some of the emerging applications (e.g., certain novel biotech applications, new foods, battery materials, and NFC/PHA) will either fizzle out while others will grow and mature into main-stream applications with large capacity, 24/7 production plants on a global scale. Consequently, HPH machine designs and materials will evolve to better suit these emerging applications in an industrial setting.

HPH manufacturers are actively developing designs and solutions to better meet customers' expectations and to align processes with increasingly challenging regulatory guidance for simpler, more robust cleanability and achieving and maintaining sterility for longer time than presently possible. Improvements in materials of construction and design of wear parts in contact with the product are important to reducing maintenance frequency and costs. In-line measurements of product quality attributes, other than what is currently commonly available (e.g., temperature, flow, density, viscosity, turbidity etc.) will become viable even for lower margin products and will allow application of quality-by-design concepts in future homogenizer design and process control.

4.2. Case Studies from Industry

With widespread industrial application of HPH, the following case studies are presented to convey noteworthy points drawn from various recent industrial applications at different stages of operation. Multiple empirical observations and "rules of thumb" are also provided as a reference to the reader. It is hoped that both industry practitioners and R&D scientists alike will find some of the information presented in this section relevant when working HPH. In some cases, specific details are omitted as this information is proprietary and/or commercially sensitive. All identifying information has also been removed.

4.2.1. Process Scale-Up

Introduction

Scale-up of HPH processes can often be very challenging as optimal operating conditions identified at a laboratory/pilot scale may not directly translate to satisfactory product quality and/or process conditions in scale-up runs. In this case study, a pharmaceutical company scaled-up (~30X the capacity of a table-top HPH) production of an API dispersion with 1~3 µm particles. The scale-up process was challenging but succeeded with inputs from both the pharmaceutical company and equipment manufacturer.

Case Study and Results

A table-top HPH system was used to identify the optimal process operating conditions for a product of the desired quality, quantified by size and size distribution determinations. As part of the scale-up procedure, the equipment manufacturer performed CFD studies and relied on prior experience to scale up the radial diffuser homogenizing valve size and profile. Initial trials conducted on the production scale equipment failed to achieve the desired particle size reduction as the particles were too large, even with the same operating pressure and number of passes. Increasing the operating pressure was not an option as the identified operating conditions were already near the limit of the machine and higher pressures increased the polydispersity of the particle size distribution. To resolve the issue, experiments were carried out on the production machine to characterize the relationship between product flowrate and particle size distribution. The CFD model was updated using the experimental data which enabled the equipment manufacturer to modify the size and shape of the homogenizing valve, yielding the desired outcome. Shortly after, an even larger production scale HPH system (~6X larger) was ordered and the scale-up was not problematical as the updated CFD model and process insights gained from the first experience proved to remain valid at the larger scale and the first batch of product met quality specifications.

Conclusions

Scale-up, especially for complex products and mixtures, remains a highly empirical exercise, drawing upon deep process and product know-how from both the user and equipment manufacturer. The following points should be considered in scale-up:

- Modeling techniques like CFD can facilitate scale-up but remains relatively immature and need to be used in conjunction with product and process know-how.
- Radial diffuser type homogenizer valves are much more industrially validated and successfully scaled-up when compared to other types such as fixed orifice or counter jet valves.
- Radial diffuser type homogenizer valves are much more amenable to scale up compared to other valve types. There are many variants, with multiple adjustable design parameters (see Figures 2 and 3) to suit a desired application at a given production scale

4.2.2. Process Optimization

Introduction

An industrial-scale process for the production of NFC was being implemented. While the process conditions identified were successfully transferred from R&D to industrial-scale, the production process was deemed commercially unviable as the operating expenses (OPEX) was excessively high. Process optimization was necessary to reduce OPEX as much as possible along with capital expense (CAPEX) to acceptable levels.

Case Study

The process originally specified a 5,000 L/hr homogenizer rated for 150 MPa. The energy consumption per pass at 150 MPa was 46 kWh/1000L of product. The cellulose raw material had natural variations and contained abrasive contaminants. The removal of these contaminants was neither necessary (the contaminants did not impact final product quality) nor practicable (the process would then be too expensive and complicated). At these operating conditions, the machine experienced unacceptable levels of wear which resulted in significant cost for parts replacement and labor alongside production downtime.

To address this issue, multiple avenues of optimization were undertaken by both the equipment manufacturer and process development team. The equipment manufacturer carried out CFD studies to optimize the homogenizing valve geometry to enhance the desired fluid dynamic effect necessary for NFC fibrillation at gentler operating conditions. The process development team also optimized the pre-processing steps which typically consist of hydrolysis / enzymatic reduction steps.

Results

The combined efforts of the equipment manufacturer and process development team resulted in the process being able to produce NFC of acceptable quality at 60 MPa which reduced energy consumption per pass to 18.3 kWh/1000L of product. The gentler operating conditions also reduced parts wear, required labor, and frequency of maintenance by ~15X. Furthermore, as lower pressures were used, a larger machine (14,000L/hr machine rated at 70 MPa) could be supplied at lower price, thus, reducing the CAPEX per unit capacity by ~5X. These cost savings derived from optimizing both the HPH and upstream processes made the operation commercially viable and successful.

Conclusion

The following rules of thumb can be used when considering avenues for process optimization and better economies:

- At the same rated operating pressure, machine price ratio changes to the capacity ratio to the power of 0.5 or even lower: $\frac{C_2}{C_1} \sim \left(\frac{\dot{V}_2}{\dot{V}_1}\right)^{0.5}$, where C_i is the cost of machine i rated for capacity $\dot{V}_i$.
- At the same rated capacity, machine price ratio changes to the rated pressure ratio to the power of 1.5 or even higher: $\frac{C_2}{C_1} \sim \left(\frac{P_2}{P_1}\right)^{1.5}$, where P_i is the rated pressure of machine i.
- The power consumption of the HPH process can be estimated using the following formula: $\text{Power Consumption (kW)} = \frac{\dot{\text{V}}\left(\frac{\text{L}}{\text{hr}}\right)\times \text{P(bar)}}{36000\times\ \eta}$, where η is an efficiency factor and can range from ~0.50 to 0.92.
- Consider possible pre-processing steps to more efficiently utilize HPH. One common example is to use a lower-energy dissipation method (e.g., rotor-stator high shear mixer) to perform pre-dispersion/crude emulsion formation as extensively as possible prior to using a high-energy dissipation device. This strategy generally helps improve product quality and reduce OPEX and CAPEX.

- Actively consider process economics at the R&D stage to better align R&D with manufacturing.

4.2.3. Process Troubleshooting

Introduction

HPH is often used as an intermediate unit operation in the process to achieve a specific goal such as cell disruption or emulsification. Correspondingly, the final product quality in relation to HPH performance is dependent on both successful HPH operation and upstream and/or downstream operations. Two case studies are presented here which illustrate how factors upstream or downstream of the HPH process can adversely impact the quality of product and efficiency of process.

Case Study

In the first case, a manufacturer had over many years successfully produced bovine growth hormones using an E. coli culture process with HPH for cell disruption and achieved ~95% cell rupture efficiency in two passes. However, the cell rupture efficiency dropped to < 60% from one batch to the next which seriously affected productivity. Technicians from the HPH manufacturer first repaired and/or replaced all relevant mechanical parts and certified the machine as good as new. However, this did not improve cell rupture efficiency which remained < 60%. The manufacturer organized an audit led by a senior process specialist to further diagnose the problem and identified a process change upstream (initially assumed as non-material) that caused the drop in cell rupture efficiency.

In the second case, a high-fat, high-viscosity non-Newtonian emulsion food product was produced using HPH. The product had a comparatively lower surfactant loading without adverse impact on product stability as the high viscosity impeded coalescence of fat globules. The manufacturer experienced a recurring problem where emulsion failure occurred in the packaging and free oil would appear on top of the product in the package which resulted in significant costs arising from recalls and waste handling. The problem was only recently addressed during an audit and fixes were recommended.

Results

In the first case study, a new storage tank (without a cooling jacket) was installed between the fermentation vessel and downstream processes (centrifugal separation and HPH cell disruption) to reduce the time taken to empty the fermentation vessel (with cooling jacket) from ~3 h to ~15 min, enabling higher fermenter utilization. As a result, the *E. coli* cells were held in the storage tank at the fermentation temperature in a low nutrient environment for up to an additional ~3 h, during which time the cell wall morphology significantly changed, impacting cell rupture efficiency. As a diagnostic test, the new storage tank was bypassed and cell rupture efficiency was immediately restored. The long-term solution involved installing an inline cooler to chill the cell culture to < 10°C enroute to the storage tank. With the intervention, cell rupture efficiency was slightly higher than before the storage tank was installed and there was more efficient fermenter utilization.

During the audit in the second case study, it was determined that the issue arose downstream of the homogenizer as product samples were taken directly from the outlet of the homogenizer did not experience emulsion failure. The outlet of the homogenizer is connected to the fill-heads of the packaging machine by a jacketed pipe of about 50 m in length. The flow in the pipe is highly unsteady due to the filling process with intermittent start-stop breaks after every few seconds when switching between fill heads. However, the flow would also have frequent start-stop pauses over longer periods when there are packing line issues. The unsteady flow introduced sharp velocity gradients in the pipe, which when coupled with the comparatively lower surfactant content of the product, resulted in coalescence of oil droplets and emulsion failure. Changes to the process to maintain a steady flow of product in the pipe and to shorten the distance between the homogenizer and the filling line are recommended.

Conclusion

Understanding the complex interactions between HPH operation, upstream/downstream processes and the product is vital for effective operation of the entire process and to ensure continuous good product quality. Correspondingly, process design, modification and troubleshooting decisions should be made with inputs from subject matter experts (e.g., process/product technologists) to ensure holistic decision making with the equipment manufacturer. Failure to do so can result in significant costs, from lost in time and output-related issues like efficiency and quality.

5. Conclusions and Outlook

Even though HPH is a mature technology platform and has become a standard unit operation in industry, many challenges either persist or are on the horizon. From a theoretical perspective, many knowledge gaps such as a detailed understanding of fluid flow in the valve remain. Emerging applications, in particular biological and nanoscale applications, contribute many open questions and exciting research and/or commercial opportunities. The push for sustainability and economies in more conventional applications will drive innovation in process and equipment design. Continued research and development by academia, equipment manufacturers, and industry is necessary to address these challenges going forward and collaborative efforts between stakeholders will become increasingly important. Advances in adjacent fields such as PAT, computational simulations, manufacturing, and materials have been and will continue to be significant in progressing HPH technology and its use.

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