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Cavitation in Vial Drop Subjected to Mechanical Shock

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University of Denver

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Cavitation in Vial Drop Subjected to Mechanical Shock

A Thesis

Presented to
The Faculty of the Daniel Felix Ritchie School of Engineering and Computer Science
University of Denver

In Partial fulfillment
of the Requirements for the Degree
Master of Science

by
Houman Babazadehroknii

November 2014
Advisor: Corinne S. Lengsfeld
Cavitation is a phenomenon that occurs when the local pressure falls down below the critical pressure. Previous work from the Randolph lab demonstrated that protein aggregates can form when a vial of therapeutic solution is dropped onto a hard surface. The process by which this occurs is most likely shock induced cavitation. During this process, hot spots can be created with temperatures and pressures reaching thousands of Kelvin and hundreds of atmospheres, respectively, leading to degradation of protein therapeutics. This work will extend previous efforts by exploring differences generated by change in vial materials, solutions, drop methods and fill volumes. Also this phenomenon will be computationally modeled by ANSYS program to investigate the created low pressure regions in solution inside the vial after the impact, and validated with the data in experiments. To accomplish the task of the experiments, water, histidine buffer, and a limited number of runs were performed with monoclonal antibody (mAb1). Video was collected under variable conditions: vials consisting of glass and plastic materials, fill volume, drop height, drop method and impact angle. Cavitation intensity was observed using a Phantom 7 high-speed camera recording. The results indicate that reducing the potential energy transmitted from the dropped vial to the solution cause the solution to be less likely to cavitate, and the intensity of cavitation would significantly vary by changing the abovementioned parameters.
ACKNOWLEDGMENTS

The author would like to thank Dr. Corinne Lengsfeld for her continued support, his wife for her encouragement and the entire lab group that the completion of this project could not have been accomplished without their support.
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CHAPTER 1: INTRODUCTION

Pharmaceutical treatment of diseases underwent a revolution between the late 1980’s and today. This era was responsible for the advent of Biologics as drug therapies. Rheumatology, oncology, cardiology, dermatology, gastroenterology and neurology have experience major medical benefits as a result of the Biologics approach. Biologics as defined by the FDA are different from small molecules (i.e., Aspirin) or antibiotics. These medicines are derived from living materials and have complex structures. Therapeutic proteins dominate the biologics FDA approved market place. Therapeutic proteins replace the role of normal produced protein in the body which are absent as a result of a disease. These therapeutic proteins bind to cells or other molecules in the body to shut down or up regulate specific functions related to the disease state. Table 1-1 provides a survey of biologics currently approved for use in the United States, the disease under treatment, and molecular type [1 and 2].
Table 1-1. Survey of biologic currently approved for use in the US

<table>
<thead>
<tr>
<th>USAN/INN</th>
<th>Trade Name</th>
<th>Indication</th>
<th>Technology</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>Orenica</td>
<td>Rheumatoid arthritis</td>
<td>Immunoglobulin CTLA-4 fusion protein</td>
<td>T-cell deactivation</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira</td>
<td>Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn’s disease</td>
<td>Monoclonal antibody</td>
<td>TNF antagonist</td>
</tr>
<tr>
<td>Alefacept</td>
<td>Armevive</td>
<td>Chronic plaque psoriasis</td>
<td>Immunoglobulin G1 fusion protein</td>
<td>Incompletely characterized</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Epogen</td>
<td>Anemia arising from cancer chemotherapy, chronic renal failure, etc.</td>
<td>Recombinant protein</td>
<td>stimulation of red blood cell production</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel</td>
<td>Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis</td>
<td>Recombinant human TNF-receptor fusion protein</td>
<td>TNF antagonist</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
<td>Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis</td>
<td>Monoclonal antibody</td>
<td>TNF antagonist</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin</td>
<td>Breast cancer</td>
<td>Humanized monoclonal antibody</td>
<td>GER2/neu (erbB2) antagonist</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Stelara</td>
<td>Psoriasis</td>
<td>Humanized monoclonal antibody</td>
<td>IL-12 and IL-23 antagonist</td>
</tr>
<tr>
<td>Denileukinidiftitox</td>
<td>Ontak</td>
<td>Cutaneous T-cell lymphoma (CTCL)</td>
<td>Diphtheria toxin engineered protein combining Interleukin-2 and Diphtheria toxin</td>
<td>Interleukin-2 receptor binder</td>
</tr>
</tbody>
</table>
Therapeutic proteins are expensive to produce in large part because the processing effort involved from growing, harvesting and purifying the molecules from living materials. Moreover, these molecules have a narrow range of conditions in which the molecule will remain potent. Proteins are large molecules comprised of amino acid residues. The primary structure or sequence of these amino acids results in three dimensional folding structure that is essential for molecular activity. These secondary, tertiary and quaternary structures governing function are not entirely rigid and formed by numerous weak bonding and interactions. The function that a protein can perform spans catalytic or metabolic reaction, structural or mechanical functions, DNA replication, signaling or immune response, transportation of molecules among others. But once formed proteins may only exist for a prescribed period of time and then are degraded and recycled by cellular process. It is a proteins susceptibility to structural change that makes them expensive to manufacture and deliver as an active therapeutic agent [3-7].

Physical and chemical instabilities are all dependent on the thermodynamic balance between enthalpic and entropic changes provided by molecules surroundings. Proper hydration is essential for creating the correct folded state but also for maintaining this structure under different conditions. For example, heat denaturation degrades the protein structure through changes in the surrounding water network. All mechanisms that alter the molecular interaction between the amino acids can have a detrimental effect on functional stability. Salinity of the solution, pH, ambient pressure, free radical attack among others are known to change protein folding and thus function [6-8].

Early in the development phase of protein therapeutics it was discovered that degraded protein may form aggregates or solid particles. These large visible aggregates
were directly linked cause severe immune response and even death. The FDA stepped in and set regulations on particulate greater than 25um. For a long time the prevailing consensus was this regulation was sufficient, until recent studies began to provide hard evidence to the contrary. Chronic diseases provide a place to gather the most compelling data. In June 2013, a clinical studied revealed that 50% of rheumatoid arthritis patients discontinue medication within first two years. Nearly 60% of these patients sited loss of immunity or safety issues as the reason for discontinued use. A 12% decline in infliximab effectiveness in Crohn’s disease has been observed with each year of treatment, suggesting that in less than six years the therapy will no longer be effective in a significant number of patients even with escalation of doses [9].

The question that cannot be ignored any longer is what is causing this decline in efficacy for protein based therapeutics in chronically ill patients? The FDA suspects that this is linked to sub visible protein particle formation and as such has issued a summary statement that specifications should be established for sub visible particles between 0.2 and 25 micron for parenteral and inhale products. Filtration of particulate is the dominate method for improving product quality in the biopharmaceutical industry. However, the stability of the protein during post filtration processes such as vial filling, shipping and delivery may be sufficient to induce aggregation of sub visible particles. From a single vial the total mass of delivered aggregate is unlikely to induce an immune response, but the sum total of solids delivered to patients with chronic diseases (i.e. repeated and long term dosing) maybe problematic[10]. The current work investigates scenarios of particle generation by cavitation with in vials dropped onto a hard surface. A scenario highly likely for arthritic patients and any situation with repeated dosing. As stated above, one of
the causes of aggregation in proteins is partially unfolding of molecules. So many researchers have investigated to overcome the fraction of these molecules, but the molecules bonding would fracture under severe conditions, for example by changing the characteristics of filling and shipping of vials in commercial manufacturing, vial materials, and even small changes in mechanical systems of the manufacturing process. By abovementioned factors, the proteins particles would change in size that leads to adverse effects during the therapy [11 – 13].

**Known ways to cause instability**

The stability of proteins is known to be limited by conformational instabilities and colloidal instabilities. The conformational and colloidal instabilities are recognized as protein unfolding, conformational entropy and the interactions between structured proteins. And the susceptibility to degradation in these proteins is from the weakness in their structures [14 and 15]. The advantages of this kind of therapy cause to increase the rate of productions, so that the instability in these proteins rises. The change in the scale of the productions needs a huge development in the system. So this development has impressive effects on the efficiency of the proteins, and has to be investigated in case of analyzing the impacts of the effects, like the damage caused by the created cavitation. In addition factors like high temperatures and huge vibrations lead protein aggregation. Aggregation and other physical instabilities like denaturation can break the bonds holding the structure of the proteins’ molecules. So they become unfolded which may have adverse results in patients [6, 7 and 16]. Hence this research will concentrate on physical instabilities in order to avoid protein degradation.
Cavitation

Cavitation is a phenomenon which occurs in liquids when the local pressure falls down below the critical pressure. This low pressure region generates a bubble (or bubbles) through a phase change process similar to high temperature boiling. The bubble will either become stable or collapse as the local pressure elevates, Fig. 1-1, and as the bubble collapses the walls of the bubble move rapidly towards the center. These walls represent a change in phase from liquid to gas and a density different of approximately 1000 times. The speed at which the walls move is close to that of the speed of sound; therefore the resulting collapse is a highly violent and energetic process. Hot spots are created where the local temperatures and pressures can reach thousands of Kelvin and hundreds of atmospheres, respectively. The local environment is suitable to disassociate water sustaining radical formation and setting up strong gradients in temperature and pressure more than sufficient to degrade long molecules. Visible signs of cavitation destruction are the surface pitting and erosion of even the strongest metal parts.
Figure 1-1. Non-stable or stable situations through the pressure changes

Cavitation can be induced through hydrodynamic, acoustic or mechanical means. Hydrodynamic cavitation can occur in any fluid flow system where the velocity increases sufficiently to drop the local pressure below the critical pressure, for example by increasing in pipe elevation and kinetic energy that is results of change in area constrictions and fluid characteristics. The most recognizable example of hydrodynamic cavitation is the bubbles created behind a high speed propeller. The bubbles form on the tip of the propeller blade where the velocity is the highest and the pressure is the lowest. These bubbles detach from the blade and collapse as the pressure returns to ambient. However other examples exist in sharp edged fuel injector orifices or after sharp turns in ejectors for high velocity fuel filling systems [17]. In addition acoustic cavitation occurs in liquids irradiated with high-intensity ultrasound. The amplitude of the pressure
fluctuation as well as the frequency or rate of change in pressure determines whether the acoustic field will be sufficiently strong to generate a bubble and or its collapse. Acoustic cavitation has been well established to degrade macromolecular therapeutics such as plasmid DNA [18] and protein [16]. Also cavitation can be occurred by mechanical forces that induce a strong pressure or shock wave within the fluid media. The most common example of this behavior is when a valve rapidly closes. The fluid moving forward through the value prior to closure is rapidly decelerated by the valve surface causing a large stagnation pressure that will bounce off the valve wall and retreat downstream through the fluid circuit. This pressure wave induces a low pressure region in its wake and can be sufficiently strong to generate bubbles that collapse after the fluid field pressure returns to ambient. Another example of cavitation induced by mechanical shock would be that of a fluid vessel under free fall impacting a solid or weakly energy absorbing surface.

Previous work of cavitation; mitigation techniques of aggregation

Previous work in our research group characterized protein aggregation under acoustic irradiation using an ultrasonic nebulizer. The work investigated the changes in solution properties such as viscosity density and surface tension in addition to the presents of impurities and protein concentration on aggregation. The work demonstrated conclusively that protein particle formation into the sub visible size range could result from cavitation within protein solutions. There was a strong correlation between the amount of free radicals produced (i.e., cavitation intensity) and the number of particles generated by irradiation. Moreover the work suggests that samples with foreign
particulate also elevated the rate of particle formation during irradiation [16]. This was the first work that conclusively linked cavitation processes to protein particle generation.

In collaboration with Ted Randolph’s group, we previously observed the formation of cavitation bubbles and collapse in vials in free fall impacting a weakly energy absorbing surface. The experimentally effort utilized a Lansmont Shock Tower and a high speed microscope to capture the images at the rate of 6000 frames per second. 3 containing 1ml solutions of anti-streptavidin where observed after impact from a variety of different drop heights. Processed solutions were analyzed for molecular changes. Variable levels of molecular oxidation were observed from the protein molecules collected from the inner surfaces of the vial [19].

Most recently our group simulated hydrodynamic cavitation under vial filling operating conditions. The work concluded that there was a strong probability of cavitation in pharmaceutical filling machine system including vials and syringes filling but offered a series of simple mitigation options. [20].

Scope of current work

The current effort builds extends our previous efforts to further explore the variable impacting cavitation in vial drop scenarios with the specific goal of defining some mitigation strategies. Experimentally the work repeats the drop tower experiments but adds hand-dropped methods and explores in detail changes in vial materials, solution properties and fill volume in a vial drop. Fluid and Solid Interaction modeling will be developed a validated with experimental data to later be used to optimally design shipping equipment.
CHAPTER 2: EXPERIMENTAL METHODS

Introduction

Previous work observing protein aggregations in partially filled vials using a standard drop tower protocol [21] observed bubble formation and collapse, particulate formation, and protein oxidation. When a vial in free fall impacted a surface there was a rapid deceleration which induced a high intensity pressure wave emanating from the contact surface. As this wave propagated through solution, a low pressure region formed behind the pressure wave. Strong shock waves frequently reduced the local pressure sufficiently to nucleate bubbles which subsequently collapsed when ambient pressure returned, whereas weak pressure waves might not. This work will extend previous efforts by exploring differences generated by change in vial materials, solutions, drop methodology and fill volumes. Specifically, the work will explore the hypothesis that increases in the energy per unit mass will enhance the probability of cavitation.

Experimental Methods

Solutions

In the current investigation deionized water purified using a Millipore 20 model direct Q 3 UV system was utilized for all samples. Buffer solutions were made using the deionized water and prepared to 10 mM histidine buffer at pH 6. Protein solutions were
prepared with a monoclonal antibody (mAb1) at a concentration of 1 mg/mL in a 20 mM histidine buffer at pH 6. Each of these solutions has different properties in regards to density, viscosity, surface tension and vapor pressure (approximate values are listed in Table 2-1).

### Table 2-1. Properties of abovementioned solutions at 20 °C

<table>
<thead>
<tr>
<th>Solution</th>
<th>Density (Kg/m3)</th>
<th>Viscosity (cP)</th>
<th>Surface tension (mN/m)</th>
<th>Vapor pressure (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purified water</td>
<td>998</td>
<td>1.002</td>
<td>72.86</td>
<td>2300</td>
</tr>
<tr>
<td>Buffer</td>
<td>1060</td>
<td>5.65</td>
<td>36.70</td>
<td>Unknown</td>
</tr>
<tr>
<td>Protein</td>
<td>1500</td>
<td>10</td>
<td>Less than water</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**High Speed Imaging**

High speed images were collected using a Phantom (V7.1 Monochrome Camera) and an EX Sigma 105 mm lens at a framing rate of 63,492 pictures per second (pps) based on the size of the images collected at a resolution of resolution of 128x128 pixels. This framing rate leads to time duration between images of 15 um. For the resolution and pps mentioned above, the duration of recorded video is 1.022 seconds. So after pushing the trigger button, the camera starts recording for approximately 1 second at the sample rate of 64K pps whenever the vial falls down and can be observed in the frame. The camera was placed 2 meters away from the vial drop area leading to a magnification such that a 2-cm diameter in bottom of vial had an image diameter of approximately 80 pixels.
Lighting was provided using three 250-Watt lights from the sides. The lights were mounted in 0.5 to 1 meters away from the drop area and the angles of these lights were set to be in 60 degrees from the axis of the camera and the drop area to the sides.

Vials

Vials were filled with solutions using a micropipette to volumes of 1 mL, 2 mL, 3 mL, 5 mL or full then sealed using standard procedures consisting of a stopper and metal clamping ring. Figures 2-1, 2-2 and 2-3. The metal clamp was crimped using a 20 mm vial crimper for flip-off seals (Kebby 20002). Three vial types were explored, Figure 2-4: 3 mL glass vial (West Pharmaceutical), 5 mL glass vial (West Pharmaceutical) and a 5 mL plastic vial (West Pharmaceutical). Table 2-2 lists all the relevant specifications regarding each vial type.

Figure 2-1. 3 ml glass vial, 1ml, 2ml and fully filled
Figure 2-2. 5 ml plastic vial, 1ml, 3ml, 5ml and fully filled

Figure 2-3. 5 ml glass vial, 1ml, 3ml, 5ml and fully filled

<table>
<thead>
<tr>
<th>Vial name</th>
<th>Material</th>
<th>Capacity</th>
<th>Mass</th>
<th>Spring constant</th>
<th>Natural frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 ml</td>
<td>Glass</td>
<td>2.4 ml</td>
<td>4.48 g</td>
<td>5.8E+6 N/m</td>
<td>494.8 Hz</td>
</tr>
<tr>
<td>5 ml plastic</td>
<td>Plastic</td>
<td>6 ml</td>
<td>7.6 g</td>
<td>5.45E+5 N/m</td>
<td>473.7 Hz</td>
</tr>
<tr>
<td>5 ml glass</td>
<td>Glass</td>
<td>7.4 ml</td>
<td>11.79 g</td>
<td>7.45E+4 N/m</td>
<td>115.9 Hz</td>
</tr>
</tbody>
</table>

As shown in Table 2-2, the spring constants and natural frequencies of the vials are tabulated. These values were calculated as follows. The vial was considered as a pipe while the boundary conditions of the pipe are fixed in both supports (fixed – fixed);
The area moment of inertia can be found as:

\[
I = \frac{\pi}{64} \left[ D_o^4 - D_i^4 \right]
\]  

(1)

So the natural frequency can be achieved,

\[
f_0 = \left[ \frac{1}{2\pi} \\left( \frac{22.37}{L^2} \right) \right] \sqrt{\frac{EI}{\rho}}
\]  

(2)

Also to calculate the spring constant, the below equation should be applied

\[
K = \frac{1}{\frac{L^4}{3EI}}
\]  

(3)

The geometry characteristics of vials are calculated and can be found in Table 2-3.

<table>
<thead>
<tr>
<th>Vial name</th>
<th>Material</th>
<th>Diameter</th>
<th>Height</th>
<th>Mass</th>
<th>Elasticity of material</th>
<th>Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 ml</td>
<td>Glass</td>
<td>0.75 cm</td>
<td>3 cm</td>
<td>4.48 g</td>
<td>70 GPa</td>
<td>5000 Kg/m3</td>
</tr>
<tr>
<td>5 ml</td>
<td>Plastic</td>
<td>1 cm</td>
<td>3.8 cm</td>
<td>7.6 g</td>
<td>2.3 GPa</td>
<td>2500 Kg/m3</td>
</tr>
<tr>
<td>5 ml</td>
<td>Glass</td>
<td>1 cm</td>
<td>4 cm</td>
<td>11.79 g</td>
<td>70 GPa</td>
<td>4500 Kg/m3</td>
</tr>
</tbody>
</table>

Figure 2-4. The size of vials in comparison with a penny
**Vial Drop Procedures**

Two procedures for vial drop were investigated: one using a drop tower, Figure 2-5, the other dropped by hand. Drop heights varied between 100 cm, 80 cm, 60 cm, 40 cm, 20 cm, and 10 cm to investigate the influence of potential energy on the resulting cavitation. In the hand dropped scenario impact angle could not be controlled thus difference resulting from impact angle could be investigated. Impact angle is defined as the angle created between the bottom surface of the vial and the flat impaction surface.

Hand dropped samples were organized in 3 groups to investigate the cavitation and tested at least three times. In these groups of tests, the heights of free-fall vary from 10 cm to 80 cm and due to the size and fill volume of vials, the height differed. For example, for 3 ml glass vial the minimum and maximum height were designed to be 10 cm and 40 cm respectively. While for full 5 ml plastic and glass vials these values were 20 cm and 60 cm respectively. And for other fill volumes of 5 ml vials the maximum height of drop was considered as 80 cm. This procedure was applied because of considering the hypothesis in impact of energy of drop. The dropped vials hit a 10 inches by 10 inches steel plate.

In addition a Lansmont shock test system (Monterey, CA) was utilized with standard procedures. These kinds of systems apply up to 10,000 g (gravity of earth) and due to the payload and sizes of the system vary. The model applied in these tests was Lansmont Model 15D while the max acceleration and payload are 2000g and 40 lb respectively. Sealed 3 mL vials were loaded into a confinement fixture and locked into place. The sample block was raised via the computer to the desired height, while in this
case it was set to 100 cm. When deemed safe the emergency latch was released by a hydraulic mechanism and the block falls to the impact surface. The impact surface is connected to pneumatic springs that are calibrated to absorb the extra kinetic energy of the block but not the sample. All samples were tested three times except the protein solutions. Protein solutions after testing were evaluated by the Dr. Randolph’s group for particulate using a Flow Cam system in their research.

Figure 2-5. Drop methods: (a) A Lansmont Shock Tower, (b) Video recording area for the tower and (c) video recording area in hand drop method
Cavitation Characterization

To characterize the resulting cavitation the high speed video was analyzed to determine (1) the number of cavitation bubbles, (2) average size of the bubbles, (3) the lifetime of the bubbles before collapse, (4) the frequency of bubble oscillation, and (5) the probability of cavitation. Probability of cavitation was calculated by number of drops that lead to bubble formation divided by the total number of drops at those conditions. Additional experiments were conducted to explore the minimum drop height required to cavitate the solution for each condition explored.

Results

Lansmont Drop Tower Results

Table 2-4 provides a comprehensive set of data characterizing the cavitation behavior of 3 mL glass vials dropped using the Lansmont Drop Tower. The result in this set of data showing no cavitation includes several times for each test. And Figures 2-6, 2-7 and 2-8 provide image sequences from those experiments. Each frame presented is 30 µs apart and the sequence begins at impact. As it can be seen in Table 2-4, the formation periods of different greatest created bubbles and their frequencies were measured and tabulated. In 1 ml filled vial by water, no cavitation observed. While for that of buffer and protein, in all cases the cavitation was observed. Also the duration of the formation, growth and collapse of the greatest bubbles in buffer is much longer than that of protein.
Table 2-4. The data set for 3 ml vial using drop tower. - No data collected.

<table>
<thead>
<tr>
<th>Fill volume (ml)</th>
<th>Fluid Content</th>
<th>Frame Rate (KHz)</th>
<th>T (µs)</th>
<th>Frequency (KHz)</th>
<th>Cavitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>water</td>
<td>66.6</td>
<td>-</td>
<td>-</td>
<td>4 No</td>
</tr>
<tr>
<td>2.4</td>
<td>buffer</td>
<td>66.6</td>
<td>220</td>
<td>4.5</td>
<td>2 Yes</td>
</tr>
<tr>
<td>1</td>
<td>buffer</td>
<td>66.6</td>
<td>180</td>
<td>5.5</td>
<td>2 Yes</td>
</tr>
<tr>
<td>2.4</td>
<td>protein</td>
<td>66.6</td>
<td>165</td>
<td>6.0</td>
<td>Yes</td>
</tr>
<tr>
<td>1</td>
<td>protein</td>
<td>66.6</td>
<td>75</td>
<td>11.1</td>
<td>2 Yes</td>
</tr>
</tbody>
</table>

Figure 2-6. 3 ml glass vial dropped via tower and filled 1 ml by buffer

Figure 2-7. 3 ml glass vial dropped via tower and fully filled by protein

Figure 2-8. 3 ml glass vial dropped via tower and filled 1 ml by water

Hand Dropped Results – Influence of Solution Type

Table 2-5 provides a comprehensive set of data characterizing the cavitation behavior of 3 mL glass vials dropped by hand. The results in this set of data showing no
cavitation include several times for each test. And Figures 2-9 and 2-10 provide image sequences from those experiments. Each frames presented are 30 and 208 µs apart for vial filled by water and buffer respectively and the sequences begin at impact. As it is shown in Table 2-5 and Figures 2-9 and 2-10, using buffer led to a huge increase in the intensity of cavitation and a decrease in duration of cavitation for the greatest created bubbles. In addition in those experiments that buffer was used as solution, the size of bubbles was greater than when the solution was water.

Table 2-5. The data set for 3 ml vial dropped from 100 cm using hand drop method. No data collected.

<table>
<thead>
<tr>
<th>Fill volume (ml)</th>
<th>Fluid Content</th>
<th>Frame Rate (KHz)</th>
<th>T (µs)</th>
<th>Frequency (KHz)</th>
<th>Cavitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4</td>
<td>buffer</td>
<td>4.8</td>
<td>90</td>
<td>11.1</td>
<td>4Yes</td>
</tr>
<tr>
<td>1</td>
<td>buffer</td>
<td>66.6</td>
<td>-</td>
<td>-</td>
<td>2No</td>
</tr>
<tr>
<td>2.4</td>
<td>water</td>
<td>4.8</td>
<td>60</td>
<td>16.6</td>
<td>4Yes</td>
</tr>
<tr>
<td>1</td>
<td>water</td>
<td>66.6</td>
<td>-</td>
<td>-</td>
<td>3No</td>
</tr>
</tbody>
</table>

Figure 2-9. 3 ml glass vial dropped from 40 cm via hand and filled 3 ml by water

Figure 2-10. 3 ml glass vial dropped from 40 cm via hand and filled 3 ml by buffer
Hand Dropped Results – Influence of Vial Type

Table 2-6 and 2-7 provide comprehensive sets of data characterizing the cavitation behavior of three vial types dropped by hand from 40 cm using water and buffer as the baseline solutions. Figures 2-9, 2-11 and 2-12 provide image sequences from those experiments. Each frame presented is 15 us apart and the sequence begins at impact. As it can be seen in Figures 2-9, 2-11 and 2-12 and Tables 2-6 and 2-7, the duration of cavitation for the greatest created bubbles in glass vials and when the solution was buffer took longer than plastic vials and when the solution was water, respectively. However the average durations of cavitation for these solutions would be about a frame period, 15 µs, so they cannot be separated from each other using this resolution.

Furthermore using plastic vial led to more intense cavitation.

Table 2-6. The data set for different vials filled with water using hand drop method

<table>
<thead>
<tr>
<th>Vial material</th>
<th>Vial size</th>
<th>Fill volume</th>
<th>T (µs)</th>
<th>Frequency (Hz)</th>
<th>Cavitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass</td>
<td>3 ml</td>
<td>Full</td>
<td>45</td>
<td>22222</td>
<td>Yes</td>
</tr>
<tr>
<td>Glass</td>
<td>7.4 ml</td>
<td>Full</td>
<td>90</td>
<td>11111</td>
<td>Yes</td>
</tr>
<tr>
<td>Plastic</td>
<td>6 ml</td>
<td>Full</td>
<td>70</td>
<td>14200</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 2-7. The data set for different vials filled with buffer using hand drop method

<table>
<thead>
<tr>
<th>Vial material</th>
<th>Vial size</th>
<th>Fill volume</th>
<th>T (µs)</th>
<th>Frequency (Hz)</th>
<th>Cavitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass</td>
<td>3 ml</td>
<td>Full</td>
<td>60</td>
<td>16.6</td>
<td>Yes</td>
</tr>
<tr>
<td>Glass</td>
<td>7.4 ml</td>
<td>Full</td>
<td>100</td>
<td>10</td>
<td>Yes</td>
</tr>
<tr>
<td>Plastic</td>
<td>6 ml</td>
<td>Full</td>
<td>80</td>
<td>12.5</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Hand Dropped Results – Influence of Fill Volume

Table 2-8 provides a comprehensive set of data characterizing the cavitation behavior of 3 mL glass vials dropped by hand from 20 and 40 cm with water. Figures 2-13, 2-14 and 2-15 provide image sequences from those experiments. Each frame presented is 15 µs apart and the sequence begins at impact. And from the obtained data, it can be extracted that by increasing the solution volume, the duration of the greatest created bubbles increased.
Table 2-8. The data set for 3 ml vial filled with water and dropped from 20 and 40 cm using hand drop method

<table>
<thead>
<tr>
<th>Drop height</th>
<th>Fill volume (ml)</th>
<th>T (µs)</th>
<th>Frequency (KHz)</th>
<th>Cavitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 cm</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>20 cm</td>
<td>2</td>
<td>30</td>
<td>33.33</td>
<td>Yes</td>
</tr>
<tr>
<td>20 cm</td>
<td>Full (2.4)</td>
<td>60</td>
<td>16.6</td>
<td>Yes</td>
</tr>
<tr>
<td>40 cm</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>40 cm</td>
<td>2</td>
<td>45</td>
<td>22.2</td>
<td>Yes</td>
</tr>
<tr>
<td>40 cm</td>
<td>Full (2.4)</td>
<td>60</td>
<td>16.6</td>
<td>Yes</td>
</tr>
<tr>
<td>60 cm</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>60 cm</td>
<td>2</td>
<td>75</td>
<td>13.3</td>
<td>Yes</td>
</tr>
<tr>
<td>60 cm</td>
<td>Full (2.4)</td>
<td>75</td>
<td>13.3</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Figure 2-13. 3 ml glass vial dropped from 20 cm via hand and filled 1 ml by water

Figure 2-14. 3 ml glass vial dropped from 20 cm via hand and filled 2 ml by water
Figure 2-15. 3 ml glass vial dropped from 20 cm via hand and filled 2.4 ml by water

Hand Dropped Results – Influence of Potential Energy

Figures 2-12, 2-16 and 2-17 provide image sequences of the cavitation behavior of 5 mL plastic vial dropped by hand. Each frame presented is 30 µs apart and the sequence begins at impact. As it is obvious from Figures 2-12, 2-16 and 2-17, by increasing the height of drop, the intensity and the average duration of cavitation and size of created bubbles increased.

Figure 2-16. 5 ml plastic vial dropped from 20 cm via hand and filled 6 ml by water

Figure 2-12. 5 ml plastic vial dropped from 40 cm via hand and filled 6 ml by water

Figure 2-17. 5 ml plastic vial dropped from 60 cm via hand and filled 6 ml by water
And the last observations from the experiments show that the minimum height of drop for different cases was different. These values for water and buffer can be found in Tables 2-9 and 2-10 respectively. And it can be evaluated that buffer cavitated in smaller amount of drop height.

**Table 2-9. Minimum height of drop to have cavitation**

<table>
<thead>
<tr>
<th>Solution:</th>
<th>Water</th>
<th>5 ml vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial:</td>
<td>3 ml vial</td>
<td>5 ml vial</td>
</tr>
<tr>
<td>Materials:</td>
<td>Glass</td>
<td>Plastic</td>
</tr>
<tr>
<td>Fill volume:</td>
<td>Full</td>
<td>2 ml</td>
</tr>
<tr>
<td>Minimum height:</td>
<td>15 cm</td>
<td>20 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2-10. Minimum height of drop to have cavitation**

<table>
<thead>
<tr>
<th>Solution:</th>
<th>Buffer</th>
<th>5 ml vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial:</td>
<td>3 ml vial</td>
<td>5 ml vial</td>
</tr>
<tr>
<td>Materials:</td>
<td>Glass</td>
<td>Plastic</td>
</tr>
<tr>
<td>Fill volume:</td>
<td>Full</td>
<td>2 ml</td>
</tr>
<tr>
<td>Minimum height:</td>
<td>15 cm</td>
<td>20 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Discussion**

The original hypothesis of this work was that cavitation in drop shock cases was linked primarily to the energy per mass. The existence of a minimum height for cavitation supports this concept, but this is not so clear from the results of the fill volume studies. A more quantitative approach would be to observe the correlation of cavitation probability against the potential energy into the system as the mass of solution within the
vial. Figure 2-18 shows more of a scatter plot behavior rather than a strong correlation indicating that some other mechanisms have an equal or stronger influence over cavitation by mechanical shock. However from this figure no evaluation could be made that by changes in these parameters, the occurrence of cavitation does increase or not.

Figure 2-18. A scatter plot showing the cavitation and non-cavitation cases in all experiments, Energy per mass (J-kg\(^{-1}\)) and Mass of solution (kg)

It is possible that the differences in vial properties alter the amount of energy transmitted to the solution via energy absorption or dissipation, but due to experiments, as the potential energy transmits to kinetic energy, some portion of that was absorbed by the vial and dissipated by the solution. Hence by changing the drop height which leads to change in potential energy, that would be figured out that the absorption of energy by solid, would be neglected in comparison with dissipation of energy in fluid.
There are a number of factors driving energy transfer and nucleation that might also be contributing to the phenomena. One likely candidate is the surface roughness of the interior vial surfaces. Values of surface roughness were evaluated to be 1.5, 1 and 15 µm for 5 ml glass, 3 ml glass and 5 ml plastic vial [22]. It is difficult to determine if surface roughness has a significant impact or if simply the sharper curvature of the smaller vial drives additional cavitation, but from the high speed images so that cavitation occurs in the bulk as much or more than at the walls of the vials suggesting that surface roughness is not a primary mechanism.

Another contributing candidate is the cross sectional area of the impact area over which a large fraction of impact kinetic energy is transmitted to the solution for dissipation. Figure 2-19 contains a plot of a data set as a function of energy per mass (as defined above) and cross sectional area of the vial impact surface. As it can be seen in Figure 2-15, the observation shows conflict between cavitation and non-cavitation and probable cavitation cases, which could not be divided into two regions of cavitation and non-cavitation definitely.
Somehow accounting for the degree of which the fluid is compressed during impact may also be relevant to the driving mechanisms for cavitation. The degree the fluid will compress during impact will largely depend on the height of the fluid column when all other solution properties are held constant. Figures 2-20 and 2-21 attempt to explore this effect by observing the probability of cavitation as a function of fluid height per cross sectional area and energy per mass. From these figures, the separation of cavitation and non-cavitation regions can be easily determined, and so that trends of correlation appear, by increasing the drop height and height of solution the probability of cavitation increased in both water and buffer.
Figure 2-20. The cavitation and non-cavitation regions in all experiments tested by water, Energy per mass (J-kg\(^{-1}\)) and Height of solution to surface area of solution filled in vial (m\(^{-1}\))

Figure 2-21. A scatter plot showing the cavitation and non-cavitation regions in all experiments tested by buffer, Energy per mass (J-kg\(^{-1}\)) and Cross section area of vial (m\(^2\))
Summary

From the data collected it can generally be stated that water has a lower probability for cavitation as compared to buffer and protein solutions. Moreover the use of a drop tower alters the intensity of cavitation observed over all conditions as compared to those dropped by hand on to comparable steel surface. Cavitation appears to occur more often and throughout the solution as compared to hand dropped vials under the same or similar conditions. Furthermore the use of plastic vials in comparison with glass vials leads to more cavitation. In all cases if the solutions cavitate, the cavitation duration of the greatest bubbles in glass vials was greater in comparison with those of the plastic vials. Moreover cavitation may be directly correlated to the concept that large masses dropped input more energy for cavitation. So this could be directly related to the fill volume of vials dropped in the tower and by hand. In all cases this results in more intense cavitation with more nucleation events, longer duration of cavitation and greater size of bubbles for the greatest created bubbles.

Although the angle of impact could not be methodically adjusted, several hand dropped experiments were recorded from the same drop height to gain insight into the impact angle on cavitation. From this data set no statistically significant variation could be observed. And finally two other parameters that would dramatically change the occurrence of cavitation are the solution and drop height. So it can be illustrated that by increasing the height of drop, the size and number of bubbles created significantly rose. Moreover by changing the solution, noticeable differences would be obvious.
CHAPTER 3: COMPUTATIONAL METHODS

Introduction

In this chapter the computational approaches were applied to model the free-fall of vial and compared the obtained results with those of experiments. Computational models are dependent to the algorithms and boundary conditions to reach convergence, so validation or calibration of the methodology is required to physically prove the accuracy and reliability of the simulated models for application over a diverse set of conditions. As time propagates, the actions on the solid part affect the internal fluid flow, and the fluid flow influences the vial. So the interaction between these two parts requires a two-way coupled interaction. Research in the field of Fluid and Solid Interface (FSI) area has been considerable over the last two decades with the greatest advances in numerical stability over the last ten years. FSI is the computational coupling of structural and a fluid behavior enabling material shape to effect fluid flow and fluid flow to alter material shape. Both the action and reaction of the solid material to the fluid flow (and vice versa) are enabled through the transition of forces at interfaces and tracking of the resulting deformation. [23]. Coupling of fluid and solid behavior can be accomplished through partitioned or monolithic approaches. The monolithic approach builds a single set of dependent equations while the partitioned approaches allow information from separate solid and fluid solvers to talk at the interface.
Partitioned approaches are easier to implement and allow the use of commercial software. A partitioned approach can either be weakly or strongly coupled. Weakly coupled approaches pass information at each time step with strongly coupled approaches pass information along within the iterations of each time step. Neither approach is perfect because numerical instability would be created by applying an elastic solid material and an inelastic fluid. Taking smaller time steps to reduce the movement of the solid material seems like a smart approach but can amplify this problem by increasing the number of opportunities a perturbation from the deformed material and inelastic fluid is presented to the solution. Highly deforming thus thin structural elements suffer from these complications the most. Unfortunately partitioned FSI simulations are frequently unstable and many published results from early efforts simply demonstrate the outcomes of these instabilities rather than physical phenomena. Until recently, it was thought that monolithic approaches might be the only stable approach. However, adding elasticity to the fluid through the use of minor compressibility or under relaxing the coupling helps alleviate the problem for most cases.

The FSI algorithm is based on solving the fluid or solid equations and transferring data to the other part before each time step, and each time step includes some coupling iterations to increase the accuracy and stability of numerical solution, Figure 3-1. This coupling iteration may take as much time while relating to the convergence of the obtained results and the duration of time steps or a determined number [24]. The number of coupling is considered up to seven times between the solid and fluid parts in each time
Although 7 times coupling iteration is enough for convergence of a stable situation, the results converge in fewer steps, so less coupling iteration is needed.

**Methods**

ANSYS Workbench housing ANSYS Fluent (fluid solver), ANSYS Mechanical - transient structural (solid solver), and multi-physics system coupling was used to compute the vial drop simulation.

**Geometry**

The vial geometry was constructed in Design Modeler. The geometry was chosen to reflect the shape and dimensions of 5 mL glass vial. As such the total height of the vial...
is 40 mm and the diameter is 20 mm as shown in Figure 3-2. The wall thickness is 2 mm having the same properties as glass, Table 3-1. To simplify the validation studies the vial was filled completely with fluid (water at 20 °C and 1 Atm: reference density= 998.2 kg/m³, reference bulk modulus= 2.2E9 Pa and viscosity= 1.003E-3 kg/m-s). The initial mesh was created from tetrahedral cells with 47,276 cells in the solid geometry and 109,537 cells in the fluid domain. The average size of a cell edge in solid and fluid domains were 7E-4 m and 4E-4 m, Figure 3-3 and 3-4 respectively.

![Figure 3-2. A schematic geometry of vial](image)

**Table 3-1. Solid properties**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial size</td>
<td>5 ml</td>
</tr>
<tr>
<td>Material</td>
<td>Glass</td>
</tr>
<tr>
<td>Density (Kg/m³)</td>
<td>4500</td>
</tr>
<tr>
<td>Young’s Modulus (GPa)</td>
<td>70.0</td>
</tr>
<tr>
<td>Poissons ratio</td>
<td>0.22</td>
</tr>
</tbody>
</table>
Fluid System

A transient fluid simulation was employed using ANSYS Fluent 15. A fully 3-D geometry was solved with no symmetry invoked. A standard k-epsilon closure model was used to describe turbulence because this model would be suitable for complex flows including abrupt pressure changes. A pressure-velocity simple algorithm was used to calculate the flow field with a second order discretization for momentum, and a first order discretization for turbulence equation. The wall boundaries were modeled with no-slip conditions using standard wall function to account for the viscous boundary layer at the surface of the vial. The temperatures for all the boundary conditions were set to 20 C. the fluid properties used to compare to experimental results were water at standard
temperature and pressure. To simplify the solution vials were filled to the top allowing standard k-epsilon model to capture liquid behavior without a Volume of Fluid technique. The compressibility of the water was a function of pressure’s changes. That is by increasing pressure, the density of water increases. Also a sliding wall mesh, defined by zero velocity relative to the cell motion, was utilized to simulate the fall and rebound of the vial. Initial conditions for the fluid domain were 0.2 m/s velocity downward to the ground, 1 Atm gauge pressure, 1 m2/s2 turbulent kinetic energy and 1 m2/s3 turbulent dissipation rate.

A total of 109537 elements were used to model the fluid system. The maximum cell skewness was 0.89 and the minimum orthogonal quality was 1.97E-1. Convergences for the computational domains were met when the residuals for all parameters were 1E-3. And Fluent looks at the flow throughout a particular time step. By dividing the smallest cell size by the velocity in the flow, the time step would be calculated and that would be less than this value. But in this case to investigate the pressure distribution during the cavitation, the time step is set to 2E-6s, this amount is calculated by considering the speed of sound in water. The operating pressure was set to zero Pascal at the top of the cap of vial. And increase of the height of drop was evaluated. Also the dynamic mesh utilized smoothing and remeshing capabilities. This was necessary because as the vial hits the ground, cell volumes needed to be deformed at the interface. Finally an initial velocity downwards to the ground was set for the simulations as inlet condition. To investigate the phase change in the simulation, a mixture phase change model was enabled. And no significant changes were made, so simulation was run without the phase
change model. The interface for transferring pressure information to the solid model is the exterior fluid boundary, as can be seen in Figure 3-5.

![Figure 3-5.Fluid interface](image)

**Solid System**

The solid system consists of the solid vial dropping from a prescribed height onto an anchored plate. This is defined by using the Transient Structural component of ANSYS Mechanical. To avoid long simulation, the vial was dropped from a smaller height, and an initial velocity, calculated by the equations of motion, was added to the initial conditions. The height was selected to be long enough for the transient solution to settle out from numerical oscillations from initial conditions as well as short enough to eliminate unnecessary computations, Figure 3-6. A ramping function was used to define a controlled increase and change in applied force by dividing this force from liquid to solid into number of the coupling iteration at each time step. The impact plate was modeled using shell elements as a rigid surface to eliminate the computations in that region and
element distortion on the surface because of the impact. The vial was modeled as a flexible material with the properties from Table 3-1. The vial had an initial downward velocity of 0.2 m/s but was not constrained in any degrees of freedom after impact, so the initial height of drop in the model would be 10 mm. Contact between the vial and plate was frictionless with a fixed joint defined around the edge of the upper plane of the impact plate. The body force applied to the vial was standard earth gravity (9.8066m/s²). And to make it more accurate, the interface treatment in contact of the vial and ground was adjusted to add offset with no ramping, while the offset was set to zero. This feature can be used whenever the contact is defined as one of the types of Frictionless, Rough or Frictional, and when the force of impact needed to be ramped. The interface upon which deformation and pressure were transferred to the fluid model was located on the inner wall of the vial surface, Figure 3-7.

![Figure 3-6. Initial condition of the vial, a gap of 10 mm between the vial and ground](image-url)
System Coupling

The solution method employed is a partitioned approach with weak coupling between the solid and fluid solutions along the specified interface. Specifically the transient mechanical model receives pressure or force nodal information along the interior boundary of the vial and utilizes this information to determine material deformation. Nodal deformation is then transferred back to the fluid solution.

The transfer of information occurs at maximum number of 7 times per time step. And 300 and 25 iterations for fluid and solid will be completed before transferring information to the other system respectively. A time step of 2 µs is used to ensure the capture of the pressure wave that will travel at the speed of sound within the vial after impacting the surface. The total time for the simulation is 0.07 second.
Simulation Sequence

The data transferred sketch and modeling flowchart are shown in Figure 3-8.

![Diagram Showing Computational Simulation Sequence](image)

a) Linked parts in the model  

b) Data transfer between parts after each time step

Figure 3-8. Showing the computational simulation sequence

Results and Discussion

Validation of the transient mechanical

The first step in validation was to ensure that the solid solution function correctly. The solid simulation was initially run without interaction with the fluid domain. The time of flight from time zero to impact was equal to data obtained via modeling, 0.0198 seconds using equations of motion. Previously Ted Randolph’s group attached accelerometers to vials and recorded the max g-forces of 1000 g (g-force) [19]. To utilize the obtained data in a comparison, a new model applying time step of 1E-7 s was investigated with similar conditions of those experiments, and the calculated g-force at
the time of impact, approximately 7500 g (g-force), does not match with that range of acceleration. This issue might be due to the restrictions of the high speed camera and the shock tower. Because the smallest time step that the camera records at the highest picture per second (pps) and the maximum g-force that the shock tower applies are 1E-5s and 2000 g (g-force) respectively [25]. Final the vial trajectory and behavior was compared to images recorded with the high speed camera for empty vials. Figure 3-9 shows the comparison between the time propagation and approximate location of vial. This figure provides confidence that the mechanical simulation is physically correct and could be within expected ranges.

Figure 3-9. A solid part comparison of vial drop in simulations and experiments, from the left to the right the time of the images are 0, 4E-3, 5.5E-3 and 7E-3s
**Fluid simulation validation**

Obtaining some degree of validation for the fluid domain simulation is more difficult than the solid. A few key parameters were observed. First, shortly after time zero the pressure distribution within the fluid should be high pressure at the bottom with slightly lower pressure at the top, Figure 3-10. The range in that pressure should be consisted with hydrostatic pressure changes and the mean should be approximately 1 atmosphere. Second, the time of impact was observed to be equal to the time in ANSYS Mechanical and the amounts obtained via equations of motion. As it can be seen in Figure 3-10, the pressure distribution of the fluid in the XY plane is shown while the time step of this model and initial velocity of drop were set as 2E-6 s and 0.5 m/s respectively. In this case the vial was cut in half and middle of the fluid became visible.

![Figure 3-10. The pressure distribution before and after of impact](image)

a) Before the impact  b) After the impact
FSI simulation validation

In this part the validation could be made by comparing the velocity of the vial in solid part of coupled model and the pressure distribution in the fluid part with that of model run separately and experiments respectively. Some preliminary results are obtained and for more investigation this part could be one main purpose of future research and work.

Summary

Generally it can be stated that modeling the solid part in ANSYS Mechanical results in a good comparison with experiments. This model can be validated with both physical evidence and calculations from the equations of motion. Also the fluid features like pressure distribution and velocity of the fluid in the model of fluid part using ANSYS Fluent can perfectly be compared with those of experiments. Additionally in the future FSI simulation by considering the low pressure regions created after the impact and comparing the results with observations from the experiments, an accurate validation can be made. However this comparison can be totally done working on the FSI part in a future work.
CHAPTER 4: CONCLUSION AND FUTURE WORK

Experimental and computational investigations of vial drop were conducted to assess the probability of cavitation under typical conditions of delivery of pharmaceutical products. An evaluation of more than 282 vial material, solution, drop method, drop height and fill volume conditions was assayed, and the probability of cavitation in vial delivery was determined. A simple method was developed to simulate the results obtained in experiments that could be helpful in mitigating cavitating systems for manufacturer. We distinguished that cavitation more likely is related to the parameters of the solution, fill volume and drop height. Those are, by increasing the height of drop and fill volume, the intensity of cavitation significantly rose, and by changing the solution, noticeable differences would be apparent. Furthermore the computational analysis was assessed by applying the 5 ml glass vial fully filled with water and dropped from small amounts of height, less than 1 cm. The comparison made between the results from solid and fluid modeling and experiments showed a promising validation. We determined that solid part in the tests was perfectly modeled for the conducted conditions and this matches to the results from experiments dropped from the same height. Also pressure distribution in the fluid part also matches with the observations in the experiments. To complete this exploration a FSI computational investigation should be carried out to verify cavitation’s occurrence.
Future work is needed on the computational side to validate the fluid and solid interface FSI model by studying similar drop heights and additionally other fluids, vial materials, fill volume, and vial size.
Reference


