



## Small volume method for drug release screening using ultrasonic agitation

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3 **Small volume method for drug release screening using ultrasonic agitation**  
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## Abstract

Drug release testing plays a major role along all parts of the dosage form development and manufacturing process. However, official methods to perform this type of testing are often resource intensive and require highly specialized facilities. Affordable and accessible methods for studying drug release behavior are currently lacking. This work presents a small volume approach to solid dissolution and drug release testing of solid dosage forms using ultrasonic agitation. Cavitation and acoustic streaming were generated by a microprobe horn delivering a 40 kHz acoustic signal into a 50 mL test vessel. These two phenomena resulted in breakdown of and release of drug from tablet samples. Prednisone Performance Verification Tablets were used as model tablets to study the effect of system parameters on the drug release process. The effects of these parameters on the acousto-hydrodynamic environment were studied using streak photography and hydrophone measurements. Drug release behavior showed a slow/fast threshold transition separated by a highly variable regime as a function of the system parameters. Observations from drug release experiments and results from acousto-hydrodynamic characterization experiments suggested that this transition is dominated by acoustic streaming. This method represents a screening method to probe relative differences in dosage form composition and acts as a complimentary approach to official testing methods. The small volume format of this test has potential applications in the study of drug release properties from low-dose and novel solid dosage forms as well as reduced cost and increased accessibility of release testing for post-manufacturing tablet quality screening, a current need in low- and middle-income countries.

**Keywords:** dissolution; drug release; ultrasound; streaming; cavitation; prednisone

## Introduction

Drug release testing methods have been developed for the characterization of active pharmaceutical ingredient and dosage form during the drug discovery and formulation development phases,<sup>1-3</sup> the prediction of *in vivo* performance and the development of *in vitro-in vivo* correlations,<sup>4-6</sup> and quality control during and after dosage form manufacturing.<sup>6-10</sup> The ability to determine *in vivo* performance from an *in vitro* test is based on the assumption that the hydrodynamic environment of the test method is comparable to the underlying physiology experienced *in vivo*. The most widely used methods for dissolution testing, the colloquial name of drug release testing in the pharmaceutical and regulatory space, are the United States Pharmacopeia (USP) apparatus 1 and 2 – the rotating basket or paddle, respectively, in a 1 L tank. These apparatuses, and a few others, have been adopted by pharmacopeias globally to standardize conditions for regulatory testing<sup>11</sup>. Despite the fact that USP makes no explicit claim that the design of these apparatuses is linked to or mimics *in vivo* dissolution conditions, these apparatuses are the only widely accepted tools to assess *in vivo* dissolution performance; numerous independent studies on the hydrodynamic environment of these instruments have focused on retroactively justifying this similarity between apparatus and physiological dissolution conditions<sup>7,12,13</sup>.

New drug release testing methods for testing novel dosage forms have been described in the literature<sup>14-17</sup>. Reducing the media volume required per test is another focus of new methods. In particular, several studies have demonstrated small volume drug release tests as an alternative to USP dissolution tests for quality control analysis.<sup>18-20</sup> However, most of these new drug release testing methods represent variations on traditional approaches, and they all appear to be partially influenced by the underlying assumption that the method must be linked to physiological conditions in order to provide useful information on dosage form properties.

Drug release data collected from any well characterized and discriminatory methods can provide fundamental information on dosage form composition. This underlying assumption that *in vitro* conditions must be linked to *in vivo* conditions imposes a strict and unnecessary constraint on the design space of new drug release testing methods. While the tests that do allow for the prediction of *in vivo* dissolution behavior will always be necessary, the current methods to achieve this come with a high resource cost, both in terms of amount of media and dosage form sample needed, which places a large burden on tests that don't need to meet this standard. Rapid and accessible methods of obtaining information about dosage form composition would add value at multiple stages of the dosage form development and quality control pathways; however, few, if any, new methods focus on these properties. Screening methods to assess relative differences in dosage form composition could provide this information at increased throughput and reduced costs relative to current and traditional methods, and this information can be used to better allocate resources for traditional methods if and when further testing is required.

Ultrasonic agitation as a mechanism to achieve convection has not been explored in the drug release testing literature despite demonstrated benefits in solid dissolution processes; ultrasonic agitation increases the surface area of the dissolving species and the mass transfer coefficient of the overall process.<sup>21</sup> The application of ultrasound, acoustic waves with frequencies greater than 20 kHz, to liquid media produces two unique phenomena: ultrasonic cavitation and acoustic streaming. Ultrasonic cavitation refers to the formation, growth, and collapse of gas- or vapor-filled microbubbles in response to pressure fluctuations of the acoustic wave. These bubbles are either pre-existing or generated by the tensile rarefaction phase of the acoustic wave interacting with micro- or nanoscale impurities. The often violent collapse of these microbubbles results in local fluid pressures in the GPa regime,<sup>22</sup> and collapse near solid surfaces results in a reentrant jet which can damage and erode soft ceramics<sup>23</sup> and even

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3 hardened steel.<sup>24</sup> Taken in aggregate, the effects of many tiny cavitation events have been shown to  
4 increase reaction rates, open unique reaction pathways compared to traditional means of mechanical  
5 agitation, and fracture and ablate solids; the field of Sonochemistry is dedicated to studying these  
6 effects.<sup>25</sup>  
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8 Primary acoustic streaming occurs because a propagating acoustic wave generates a body force  
9 owing to viscous absorption in the bulk fluid,<sup>26–28</sup> one manifestation of what is generally referred to as  
10 the acoustic radiation force.<sup>29–32</sup> The resulting macro-scale fluid flow can further be enhanced by  
11 scattering of particles and bubbles in the host fluid, a second manifestation of the acoustic radiation  
12 force. Depending on the intensity of the ultrasonic field and the geometry of the test chamber, fluid flow  
13 can be laminar, vortical, or turbulent. At the microscale, a second boundary-layer streaming flow, often  
14 referred to as “micro-streaming”, will result directly from oscillations of the cavitation bubbles.<sup>33,34</sup>  
15 Transport is accelerated by high flow shearing rates occurring at micron-sized scales compared to  
16 primary acoustic streaming.  
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18 Various experimental techniques and measurement tools have been employed to characterize  
19 the fluid flow and acoustic properties of ultrasonic horn reactors. Techniques such as streak  
20 photography, particle image velocimetry, and laser Doppler anemometry have been used to explore  
21 fluid flow in these systems.<sup>35–38</sup> Computational techniques have been used to model these multiphase  
22 flows in the parameter regimes of certain applications.<sup>39–41</sup> The flow generated from the horn is directed  
23 downwards from the radiating surface. The velocity profile generated resembles a conical jet whose  
24 radius increases with distance from the tip of the horn. A large cloud of cavitation bubbles forms directly  
25 underneath the horn, and these bubbles can be scattered into the liquid. The macro-scale flow is  
26 enhanced by the scattering of these bubbles and of bubbles located away from the horn. The conical jet  
27 produced by the horn continues traveling away from the horn tip until it reaches a boundary. The  
28 boundary causes recirculation of the flow upwards into the bulk resulting in vortical structures  
29 throughout the bulk.  
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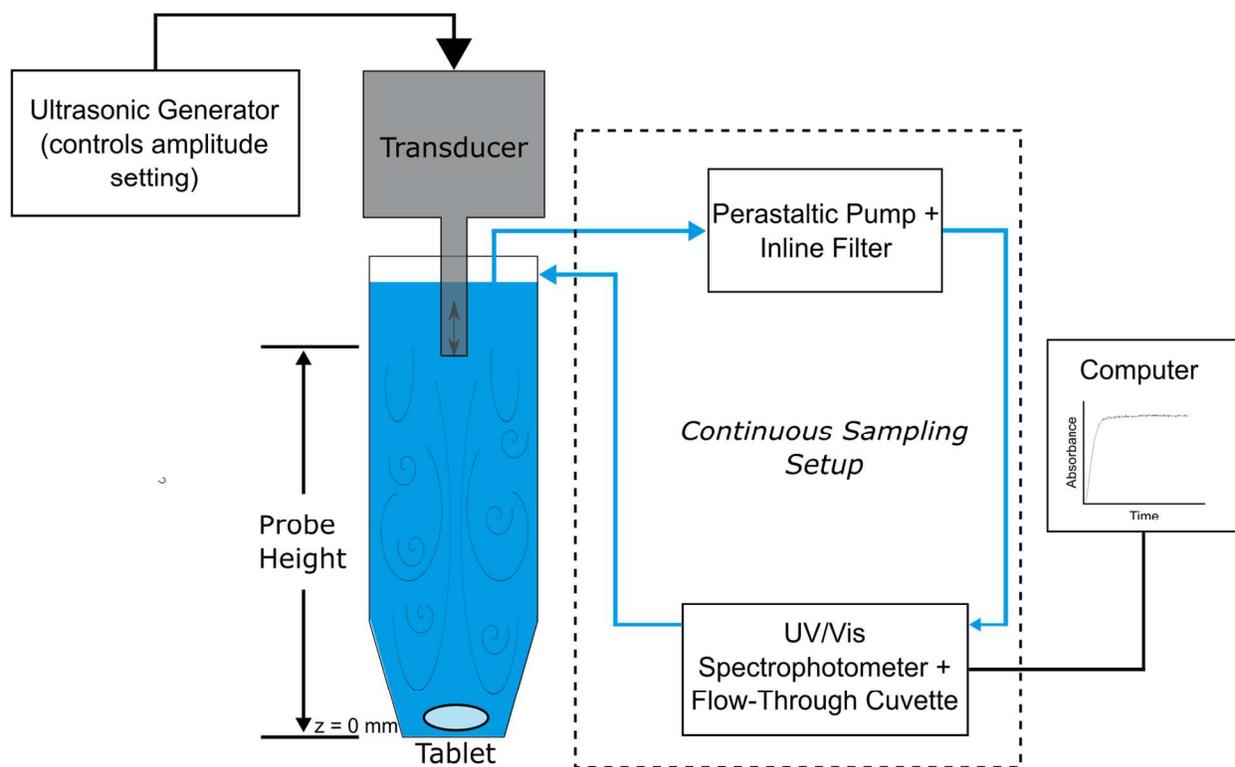
31 The study of drug release from solid dosage forms provides important information along the  
32 entire drug and formulation development and manufacturing process. Traditional methods of  
33 performing this testing are resource intensive and are not accessible outside of specialized lab  
34 environments, however. Affordable and accessible methods have great potential to expand the use and  
35 reach of drug release testing, but these qualities are rarely the focus of new methods described in the  
36 literature. We seek to address this gap by employing ultrasonic agitation, with resultant cavitation and  
37 acoustic streaming, as a novel means to perform drug release testing of tablets in a small volume  
38 format. An automated, continuous, closed-loop sampling system was designed to measure drug release  
39 from prednisone tablets. Drug release behavior was studied as a function of critical system parameters.  
40 The effect of these parameters on the acoustic-hydrodynamic environment was studied using streak  
41 photography methods and local pressure measurements recorded by a hydrophone.  
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## 45 **Experimental**

### 46 **Experimental Setup for Ultrasonic Agitation Mediated Drug Release Testing**

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49 Figure 1 displays a schematic of the experimental setup used for drug release testing of tablet  
50 samples. The ultrasonic cavitation mediated release test employed a 40 kHz ultrasonic generator  
51 (Vibracell VCX134FSJ; Sonics, Newtown, CT). The generator was connected to a transducer fitted with a  
52 stepped microprobe horn with a tip diameter of 3.18 mm. The microprobe horn was made from  
53 titanium Ti-6Al-4V and rated to have a peak vibrational amplitude of 180  $\mu\text{m}$ . The horn amplitude was  
54 set by the ultrasonic generator. This parameter is subsequently referred to as amplitude setting and  
55 could be adjusted between 20-100% in 1% increments. A custom stand was designed and built to ensure  
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consistent radial placement of the ultrasonic transducer and glass vessel. The stand also allowed for the distance between the bottom of the horn and the bottom of the test vessel to be adjusted. This distance is subsequently referred to as probe height, and the upper and lower limits of the probe height were dictated by the vessel geometry and the media volume; for this system the probe height can be adjusted between 35-55 mm. The media volume for each test was set to 50 mL. A 70 mL plastic, round-bottom test tube (BRAND<sup>®</sup>, Sigma-Aldrich, St. Louis, MO) was used as the test vessel. Ultrasound was administered to the test media via the microprobe horn at 1 Hz pulse repetition frequency and 50% duty cycle. The test media was sampled continuously via a closed loop system controlled by a peristaltic pump (CP 78023-12; Ismatec, Vernon Hills, IL) operated at a flowrate of 0.85 mL/min. Sampled media was first passed through a 1  $\mu$ m cannula filter (QLA, Telford, PA) submerged in the test vessel. The pre-filtered media was then passed through a 0.22  $\mu$ m pore size inline filter (.25 mm diameter, FLL/MLS CA; GVS Life Sciences, Sanford, Maine) before being sent to a flow-through cuvette (0.39 mL, 10 mm path length; FireFly Sci, Staten Island, NY). The cuvette is placed in a UV-Vis spectrophotometer (SpectraMax M5; Molecular Devices, San Jose, CA), and absorbance of the sampled media was measured at 285 nm. Test media was then pumped back to the test vessel. Total system dead-volume was determined to be 2.80 mL.



**Fig 1.** Schematic of experimental setup used for ultrasonic mediated drug release testing.

## Materials

Glass spheres (10  $\mu$ m average diameter, 10g) and Ethanol (200 proof) were obtained from Sigma Aldrich (St. Louis, MO). USP Prednisone reference powder (Lot: OOG356) and USP Prednisone Lot P Performance Verification Tablets (Lot: R031Y1) were obtained from Fisher Scientific.

## Ultrasonic Agitation Mediated Drug Release Test

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3 Drug release testing of tablet samples was performed using the experimental setup described  
4 above. Prednisone tablets dissolved in 20% ethanol solution were used as a model system. 53 mL 20%  
5 ethanol solution was dispensed into the test vessel. The system was primed with media for 5 min. After  
6 priming, absorbance measurements were taken for 80 sec to establish a baseline. A prednisone tablet  
7 was then inserted into the vessel and the horn was turned on. Ultrasonic agitation was applied to the  
8 test media for up to 3600 sec. At the end of the test, ultrasonic agitation was applied to the dissolved  
9 tablet solution for 5 min at 50% amplitude setting to ensure complete drug release. The horn was shut  
10 off, and absorbance measurements continued for 6 minutes. The system was flushed with fresh 20%  
11 ethanol solution for 10 min and dried out using air after each test. Three tablets were tested at each  
12 parameter configuration. Drug release testing was performed for amplitude settings of 30%, 35%, 40%,  
13 and 45% at probe heights of 35 mm, 45 mm, and 55 mm.  
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### 16 **Streak Photography Measurements**

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19 A cross section of a glass test tube (ChemGlass, Vineland, NJ) filled with 50 mL Milli-Q filtered water  
20 was illuminated by a sheet of light produced by a He-Ne laser (1135P; Uniphase, Manteca, CA) fitted  
21 with a cylindrical lens. A camera (Grasshopper3; FLiR, Billerica, MA) with a 35 mm lens (Fujifilm, Tokyo,  
22 Japan) was set up perpendicularly to the illuminated plane at a distance of 250 mm; a schematic of this  
23 setup is displayed in Figure 4A. Images captured were 960 x 600 pixels, and the field of view was 30.0  
24 mm x 18.8 mm. Neutrally buoyant, glass microspheres of 10  $\mu\text{m}$  average diameter were seeded at 0.1%  
25 w/V in the test vessel. Ultrasound was administered to the test media via the microprobe horn at 1 Hz  
26 pulse repetition frequency and 50% duty cycle for amplitude settings of 45%, 50%, and 60% and probe  
27 heights of 40 mm, 50 mm, and 60 mm. Images were taken every 100 ms for 10 sec during horn  
28 operation at each parameter configuration tested. The camera shutter speed and gain were set at 40 ms  
29 and 26.0 dB, respectively. The test media and tracer particles were replaced after all amplitude settings  
30 were tested at each probe height. Image processing and analysis were performed using MatLab  
31 (MathWorks, Natick, MA); images were sharpened with a Laplacian filter, converted to binary, and  
32 filtered to remove objects less than 8 pixels long. The length of all streak lines in pixels was determined,  
33 and each pixel value in an object was replaced by the length of the object. The weighted values in a 200  
34 x 200 pixel ROI centered above the bottom of the test vessel were summed, and this sum was divided by  
35 the total number of pixels in the ROI to provide a weighted density in the ROI, subsequently referred to  
36 as a flow score. An average flow score over 10 sec was calculated for each condition.  
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### 40 **Hydrophone Measurements**

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43 A needle hydrophone was submerged in a glass test tube filled with 50 mL Milli-Q filtered water  
44 degassed overnight in a vacuum chamber. The radial position of the hydrophone was approximately  
45 halfway between the centerline of the vessel and the vessel wall, in order to minimize cavitation  
46 damage to the hydrophone. The height of the hydrophone along the z-axis was controlled by an  
47 adjustable mount. The hydrophone was connected to an oscilloscope (DSO1012A, Agilent Technologies,  
48 Santa Clara, CA). The ultrasonic horn was operated at 20% amplitude setting at pulses of 500 ms; the  
49 probe height was set at 60 mm. Waveform data for horn pulses were recorded along the z-axis of the  
50 vessel at 2 mm increments from 0-30 mm, with 0 mm being the bottom of the vessel. Pressure  
51 magnitudes were calculated as running averages of peak-to-peak voltages ( $V_{pp}$ ) from the waveform data.  
52  $V_{pp}$  measurements were taken for two different test tube boundary conditions: (1) vessel exposed to air  
53 and (2) vessel exposed to large water bath.  $V_{pp}$  measurements for each condition were normalized by  
54 the highest value at that condition to calculate a relative pressure amplitude at each height along the  
55 vessel.  
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3 Drug release testing was performed as described in section 2.4. The experimental setup  
4 consisted of a glass test tube exposed to the two boundary conditions described above, but was  
5 otherwise identical to the setup described in section 2.1. Drug release tests were performed at an  
6 amplitude setting and probe height of 30% and 60 mm, respectively. Three prednisone tablets were  
7 dissolved at each boundary condition.  
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## 10 Data Processing and Analysis of Drug Release Curves

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12 Absorbance data from drug release testing was processed in MatLab (MathWorks, Natick, MA)  
13 prior to data analysis. Background absorbance of each test was calculated by averaging the first 80 sec  
14 of absorbance measurements from a test. Absorbance at complete tablet dissolution was calculated by  
15 averaging the last 80 sec of absorbance measurements from a test. The system dead-volume and  
16 flowrate were used to calculate residence time of sampled media in the sampling system. The residence  
17 time was used to identify the range of time over corresponding to ultrasonic agitation. Absorbance  
18 values for a test were background subtracted and normalized to absorbance at complete dissolution to  
19 yield fraction dissolved.  
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21 Dissolution efficiency (DE) was used as a general rate parameter to compare drug release curves  
22 across critical system parameters. Dissolution efficiency is defined as the area under the drug release  
23 curve divided by the total area of the plot bounded by the maximum achievable fraction dissolved and  
24 the length of the test and is given by Equation 1,<sup>42</sup>  
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$$26 \quad DE = \frac{\int_0^t (f(t)) * dt}{f_{max} * t} \quad (Eq. 1)$$

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28 where  $f(t)$  is the fraction dissolved at time  $t$ ,  $f_{max}$  is the maximum achievable fraction dissolved, and  $t$  is  
29 the total length of the drug release test in sec. Variability between dissolution efficiencies at the same  
30 system parameters are represented as percent coefficient of variation.  
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## 35 Results

### 36 Ultrasonic Agitation Mediated drug Release Test

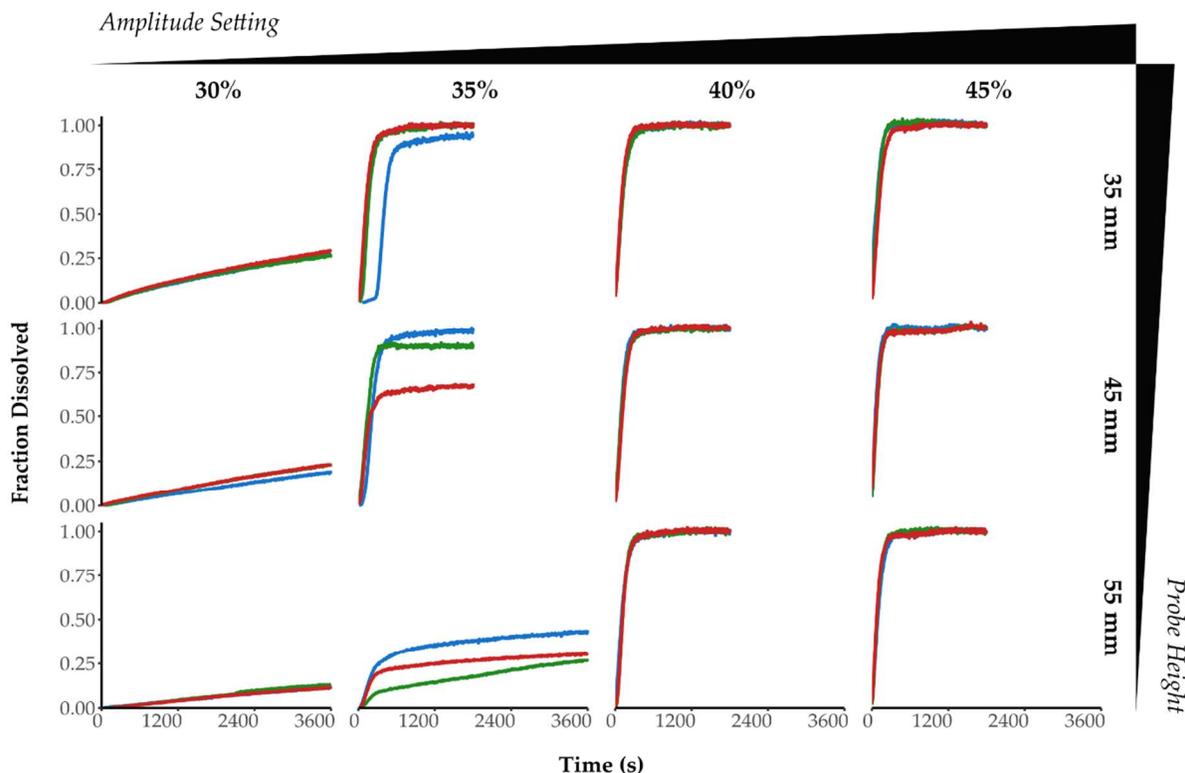
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38 Figure 4 displays drug release profiles of USP PVT prednisone tablets in 20% ethanol solution  
39 dissolved via ultrasonic agitation at 12 different combinations of amplitude setting and probe height.  
40 Drug release fell into three unique regimes dependent of amplitude setting and probe height. At an  
41 amplitude setting of 30%, fraction dissolved at all probe heights steadily increased over 3600 sec, and  
42 the maximum fraction dissolved after 3600 sec was 0.25 at a probe height of 35 mm. At amplitude  
43 settings of 40% and greater, fraction dissolved at all probe heights rapidly increased and approached 1.0  
44 within 600 sec after the onset of ultrasonic agitation. At an amplitude setting of 35%, fraction dissolved  
45 after 3600 sec and the shape of drug release profiles strongly varied with probe height.  
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49 A dissolution efficiency was calculated for drug release profiles generated at each parameter set  
50 tested; this data is shown in Figure 5. Dissolution efficiency increased with increasing amplitude setting  
51 and decreasing probe height. At an amplitude setting of 30%, dissolution efficiencies were less than  
52 12%. At amplitude settings of 40% and higher, dissolution efficiencies were all greater than 85%.  
53 Achievable dissolution efficiencies widely varied at 35% amplitude setting for all probe heights. Percent  
54 coefficient of variations between trials at each probe height at  $\leq 30\%$  amplitude setting and  $\geq 40\%$   
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amplitude setting were as low as 4.5% and 0.3%, respectively. Percent coefficient of variation between trials for each probe height at 35% amplitude setting were greater than 15%.

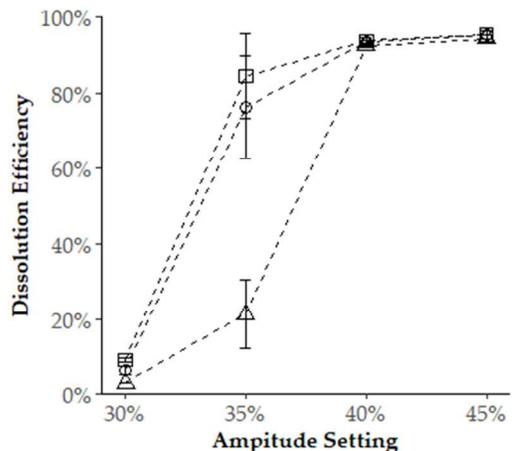
## Flow Characterization

Figure 4B displays representative images of flow behavior in the ROI over one pulse cycle as well as the pulse waveform and the flow score of each image. These images reveal that acoustic streaming



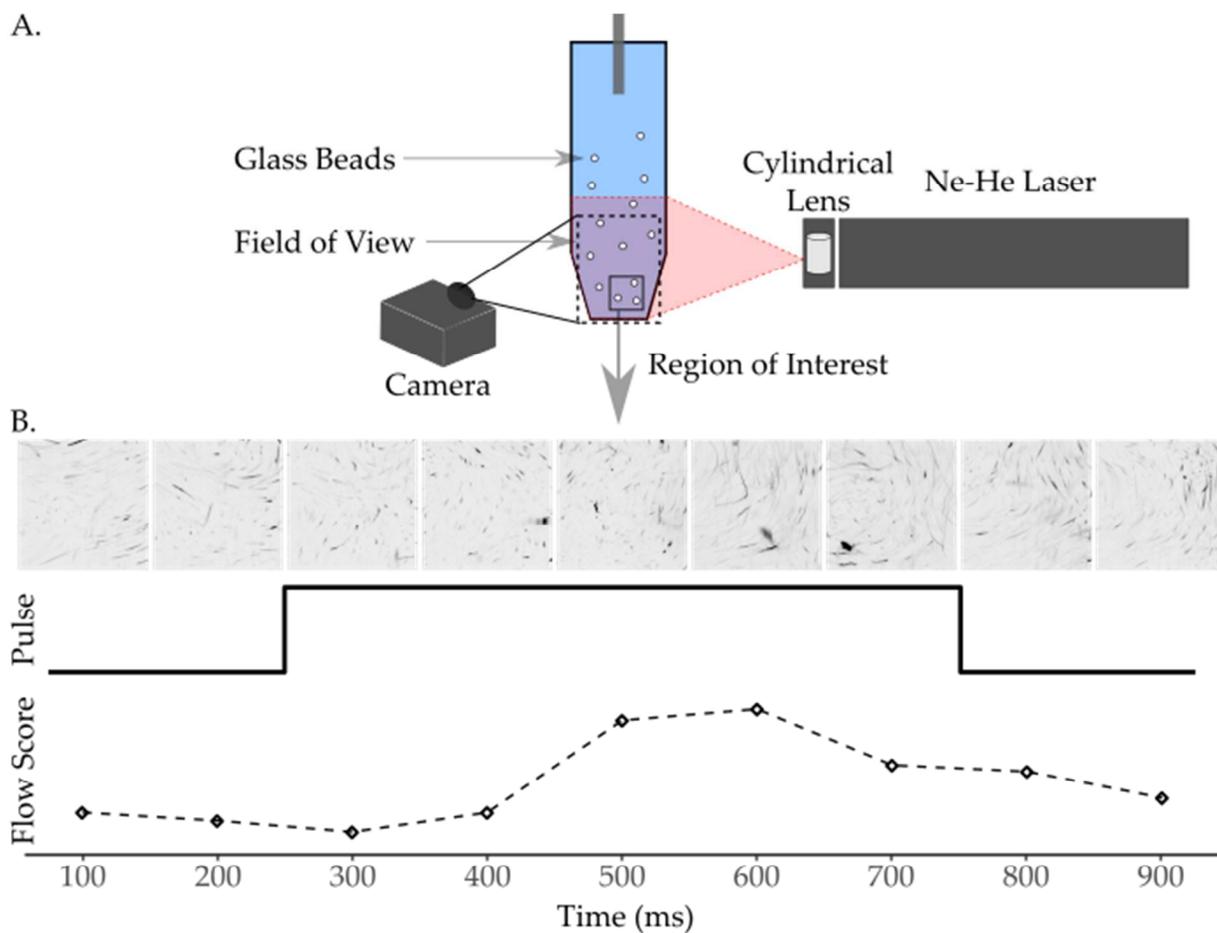
**Fig 2.** Drug release curves from prednisone tablets at different combinations of amplitude setting and probe height for a fixed acoustic dosage (1 Hz, 50% duty cycle). Three tablets were dissolved at each combination of amplitude setting and probe height.

generated by the ultrasonic horn results in coherent, vortical structures that are punctuated by regions of apparently turbulent behavior. Flow structures are similar from pulse to pulse. Fluid flow is generated from the tip of the horn, downwards towards the bottom of the vessel. When the flowing fluid reaches the bottom of the vessel, the fluid is redirected along the bottom and up the side walls, resulting in recirculation into the bulk of the liquid. These observations are consistent with flow patterns observed in other ultrasonic horn systems. Flow score slightly lags the pulse waveform; the horn needs to overcome inertial and viscous forces before axial streaming velocity reaches a maximum.



**Fig 3.** Dissolution efficiency as a function of amplitude setting at probe heights of 35 mm (squares), 45 mm (circles), and 55 mm (triangles). Data plotted as mean  $\pm$  standard deviation (n=3).

Figure 5 displays the average flow score in the ROI over 10 sec of ultrasound dosage calculated at each combination of pulse height and amplitude setting. Flow score increases non-linearly with increasing amplitude setting and decreasing probe height. Amplitude setting is related to acoustic power, with a higher amplitude setting resulting in higher applied acoustic power. As probe height decreases, the distance between the streaming source and the ROI decreases. The increase in flow score observed for lower probe heights indicates that the magnitude of streaming effects is higher closer to the acoustic source and attenuates as the distance from the source is increased.



**Fig 4.** (A) Schematic of experimental setup used for streak photography experiments. Please note that the camera is positioned perpendicularly to the illuminated plain; the image is not to scale. (B) Streak photography images over 1 pulse cycle. The pulse waveform and flow score is displayed for each image over the pulse cycle.

### Acoustic Characterization

Pressure amplitudes along the height of the test vessel at 2 different probe heights are displayed in Figure 6A for a test vessel with walls exposed to air and with walls submerged in a large water bath. In all cases, standing waves are observed with nodal spacing of about 17 mm consistent with the expected wavelength of 40 kHz in bubbly water of modest gas volume fraction. The spatial distribution of the sound field varies with boundary condition and horn height. The behavior of the pressure amplitude between  $z = 0-5$  mm, where the tablet initially resides differs for the two cases. When the vessel walls are submerged in a water bath, the pressure amplitude in the boundary/tablet region is lower than the pressure amplitude in the air surround condition. Pressure amplitudes showed a

strong variation with probe height as resonances are achieved at periodic values of probe height. The bottom of the vessel in the air surround condition, for both probe heights, acted as an active surface with high acoustic pressure.

Dissolution efficiencies for tablets dissolved in vessels with walls exposed to air and submerged in water are displayed in Figure 6B. The difference in dissolution efficiencies calculated for each boundary condition was not statistically significant.

## Discussion

The ultrasonic agitation mediated test does not aim to replicate or mimic the physiological environment experienced by tablets, a key consideration of all traditionally defined and official dissolution apparatuses. In light of this, this method is not presented as a replacement to official dissolution testing. Drug release data collected from any well characterized and discriminatory methods can provide fundamental information on dosage form composition. By removing the constraint of *in vivo* predictability, new approaches to drug release testing can be designed to meet specific needs that current methods do not accommodate well. The method presented here can serve as a complimentary approach to traditional tests to provide rapid and low-cost screening of relative differences in dosage form composition. For example, a small volume test using commercially available equipment has potential applications in the study of drug release properties from low-dose and novel solid dosage forms as well as reduced cost and portable release testing for post-manufacturing tablet quality screening, a current need in low- and middle-income countries.

Prednisone tablets were chosen for this study because they are used as Performance Verification testing tablets for USP apparatuses; they're drug release behavior in those systems is very well characterized. Prednisone tablets are immediate release, disintegrating, and effervescent. These types of tablets swell and break apart into smaller granules when exposed to aqueous media. In traditional dissolution apparatus, drug release occurs primarily from these granules in the presence of convective flow. Ultrasonic agitation can enhance the drug release process by intensifying tablet disintegration by two potential mechanisms. First, inertial and stable cavitation events occurring near the outer surface of the tablet result in microjetting that can break-apart fragments from the tablet surface. Second, ultrasonic agitation can result in cavitation events owing to the gas trapped in the tablets, breaking the tablet into smaller fragments from the inside-out near the surface.

Drug release behavior from prednisone tablets in 20% ethanol solution was observed to fall into three different regimes that were dependent on amplitude setting and probe height. Each regime is characterized by a unique interplay between the tablet disintegration process and the convective fluid flow in the test vessel. In the fast regime, the tablet is rapidly disintegrated into smaller fragments over approximately the first 30 sec of ultrasonic agitation. The convective fluid flow in this regime is strong enough to cause circulation of tablet fragments throughout the vessel. All tablet fragments undergo diffusive mass removal by convective flow and further fragmentation by inertial cavitation events. In the slow regime, tablet disintegration occurs over approximately 200 sec of ultrasonic agitation; this process is dominated by modest fluid penetration into the tablet and cavitation. The convective flow in this regime is not strong enough to cause circulation of tablet fragments throughout the vessel, and tablet

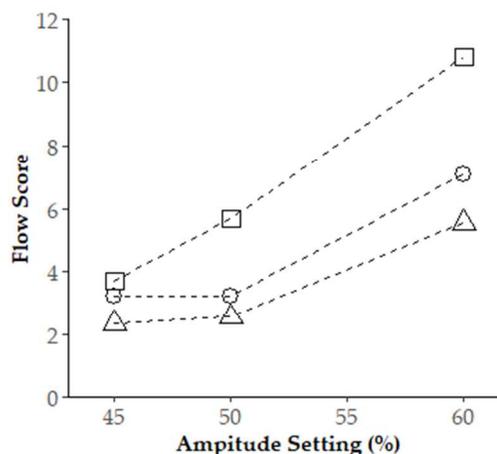
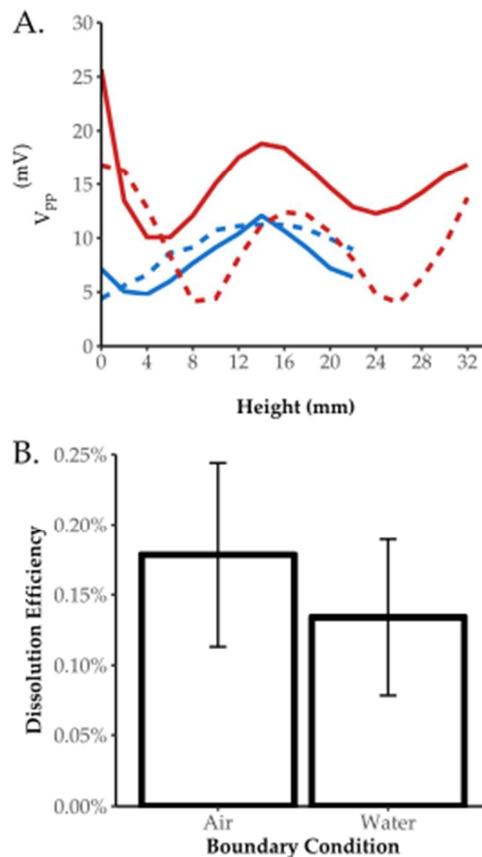


Fig 5. Flow Score as a function of amplitude setting for probe heights of 40 mm (squares), 50 mm (circles), and 60 mm (triangles).

fragments end up spread out along the bottom of the vessel. Undissolved fragments on the top layer are the only fragments to undergo diffusive mass removal due to convective fluid flow and inertial cavitation events. In the transition regime, tablet disintegration occurs between 30-200 sec depending on the flow and cavitation behavior. The onset, extent, and duration of circulation of tablet fragments in this regime is stochastic, so the amount of fragments exposed to convective flow and inertial cavitation differs from run-to-run for a given parameter set. The dissolution efficiencies produced in each regime reflect these observations. For the slow and fast regimes, dissolution efficiencies fall in distinct ranges, and variability between trials is low. In the transition regime, the range of achievable dissolution efficiencies is much wider, and variability between trials is high.

The most striking feature of the measurements presented is the threshold dependent behavior characterizing the transition from slow to fast release. A traditional acoustic interpretation would indicate that threshold is primarily dominated by the onset of inertial cavitation; however, the described observations are more complicated. In particular, visual observations reveal the primary difference between slow and fast release regimes to be the rapid, near-turbulent convective transport of fragments away from the bottom of the vessel into the bulk of the container. This behavior and the similar increases in dissolution efficiency (Fig. 3) and flow score (Fig. 5) with amplitude setting and probe height suggest that acoustic streaming velocity mainly controls the slow-fast transition – axial velocity in the tablet region of the vessel as measured from the horn tip directly interacting with the cavitation-fragmented tablet, at a given combination of amplitude setting and probe height, can result in advection of fragments up into the volume of the vessel exposing fragments to higher levels of cavitation and flow. This proposed mechanism is the most comprehensive assessment that can be made with the experimental results and observations presented in this work. Quantitative and spatial measurements of cavitation and axial streaming are needed to further elucidate the mechanism of the slow/fast threshold release behavior.

Interactions between drug, tablet formulation, and test media also determine drug release behavior by affecting the rate and extent of tablet disintegration and drug diffusion. The reduced volume nature of the ultrasonic agitation drug release method may necessitate the use of non-aqueous media to ensure complete solubility; in these tests, a 20% ethanol solution was needed for complete solubility of prednisone. Full characterization of the ultrasonic agitation mediated drug release test will involve further interrogation of both the acoustic properties of the system and the chemical properties of the dissolving species on the tablet disintegration and drug diffusion processes.



**Fig 6.** (A) Peak-to-peak voltage measured as a function of height from the bottom of the vessel at 50 mm (blue) and 60 mm (red) probe heights for 2 different boundary conditions: air (solid lines), water (dashed lines). (B) Dissolution efficiency at 60 mm probe height and 30% amplitude setting for air and water boundary conditions.

## Conclusion

A small volume, screening method for drug release behavior from solid dosage forms using ultrasonic agitation was explored. Ultrasonic agitation, with resultant cavitation and acoustic streaming, delivered via microprobe horn was used to facilitate tablet breakdown and drug release into solution. Drug release behavior displayed a highly repeatable and controllable transition between a slow and fast regime dependent on the acousto-hydrodynamic environment; the combination of cavitation and acoustic streaming controls and accelerates the release process. The method can serve as a complimentary approach to traditional tests where the rapid and low-cost screening of relative differences in dosage form composition is required. The lower volume increases the analytical sensitivity which allows for reduction in amount of drug required for testing, a potential boon for drug release testing at the early stages of drug and dosage form development where available quantities of drug product are typically low. On the regulatory side, the focus on relative differences in dosage form concentration and the decrease in test volume could allow for new, more accessible ways to screen for poor quality tablets and pills, an issue that currently plagues low and middle income countries.

## Conflicts of Interest

There are no conflicts of interest to declare.

## Acknowledgements

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