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Article

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Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) – A novel approach to investigate the wettability of pharmaceutical powder blends

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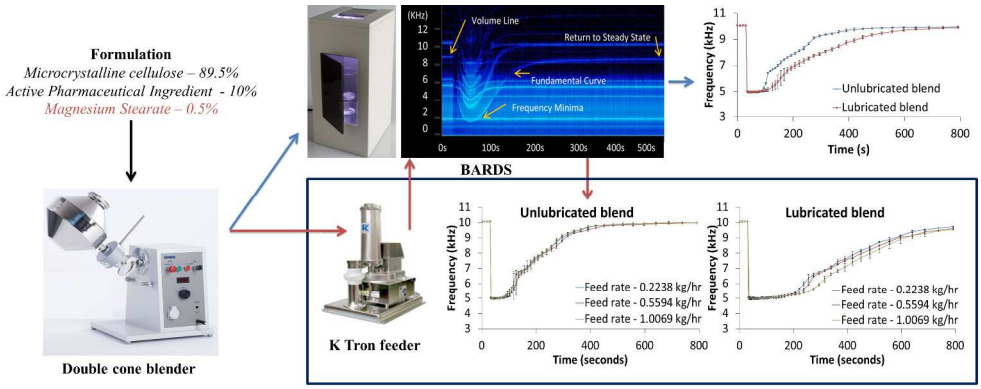
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Abstract

The ability of Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) to assess the wettability of powder blends is investigated. BARDS is a novel analytical technology developed based on the change in acoustic phenomenon observed when material is added into a solvent under resonance. Addition of solid material to the solvent results in the introduction of gas (air) into the solvent, changing the compressibility of the solvent system and reducing the velocity of sound in the solvent. As a material is wetted and dissolved, the gas is released from the solvent and resonance frequency is altered. The main purpose of this work is to demonstrate the ability of BARDS to assess differences in the wetting behaviour of tablet excipients (microcrystalline cellulose (MCC) and magnesium stearate (MgSt)) and a model drug (metoclopramide hydrochloride) as single component powders and multi-component powder blends. BARDS acoustic responses showed a prolonged release of gas for the powdered blends with lubricant compared to un-lubricated blends. As the elimination of gas from the solvent was assumed to follow first order elimination kinetics, a compressible gas elimination rate constant was calculated from the log plots of the gas volume profiles. The gas elimination rate constant was used as a parameter to compare the release of gas from the powder introduced to the solvent and hence the powder wetting behavior. A lower gas elimination rate constant was measured for lubricated blends compared to non-lubricated blends, suggesting the prolonged hydration of lubricated blends. Standard wetting techniques such as contact angle measurements and wetting time analysis were also used to analyze the blends and confirmed differences in wetting behavior determined by BARDS. The study results demonstrate the capability of BARDS as a rapid, analytical tool to determine the wetting behavior of the pharmaceutical powder blends and the potential of BARDS as a process analytical technology (PAT) tool.



Introduction

Wettability of a powder is an important parameter to consider, as it can be used to predict the dispersion, disintegration and dissolution of powders in fine chemical, pharmaceutical, food and ceramics industries[1–4]. Wettability of powders is commonly determined by measuring the contact angle of a liquid on solid surface at the three-phase interface of solid, liquid and vapour. Powder wettability can also be assessed by measuring different processes such as spread wetting, capillary wetting, condensational wetting and immersional wetting[2,5]. Different techniques routinely used to evaluate the wettability of the powders are numerous, these include sessile drop,[2,5,6] Wilhelmy plate,[1,4,7,8] Washburn capillary rise,[2,9] thin-layer wicking,[2,4,10] capillary pressure,[4,11] drop penetration,[4,12] dynamic contact angle,[4,13] atomic force microscopy[4,8,14] and environmental scanning electron microscopy[2,4]. A review by Alghunaim *et al.,* provides an excellent overview of a number of these techniques[4].

Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) is a novel technique that can be used to analyze the wetting behavior of powders. A recent study by Vos *et al.,* showed the potentiality of BARDS to detect the transfer of water into milk protein concentrate (MPC) powder particles with different rehydration characteristics[15]. BARDS works on the principle of frequency change of acoustic resonances that are mechanically provoked in a solvent using a stirrer bar when a solute is added[16]. The acoustic resonances correlate with the compressibility of the solvent system with or without solute. When a powder is introduced into a solvent it introduces gas (air) into the solvent, which changes the compressibility of the solvent. As the powder is wetted or dissolved, the associated gas is eliminated and solvent compressibility returns to a steady state. The acoustic resonance generated depends on different physical and chemical parameters of the powder that is added into the solvent. BARDS monitors the acoustic profile of solvent as a powder disperses and dissolves. It correlates the acoustic profile of the solvent to changes in the compressibility of the solvent as a result of powder dispersion and dissolution within the solvent[16,17].

The work presented demonstrates the ability of the BARDS technique to detect differences in the wetting behavior of commonly used tablet excipients microcrystalline cellulose (MCC), magnesium stearate (MgSt) and a model drug (metoclopramide hydrochloride) as single component and multicomponent powder blends. It was anticipated the presence and distribution of the hydrophobic lubricant, MgSt, in the blend would alter the wetting behavior of MCC and drug within the blend. The re-

sults presented demonstrate the ability of BARDS to detect differences in the wetting behavior of blends due the presence and distribution of the lubricant. These differences in wetting behavior were also assessed using the more widely reported wetting measurement techniques of contact angle and wetting time.

Working principles of BARDS

The velocity (v) of sound in a medium whether air or liquid medium is determined by equation 1

$$V_{(sound)} = \sqrt{\frac{1}{K.\rho}} \qquad \text{Equation 1}$$

where ρ is mass density (kg m^{-3}) and K is compressibility (which is the inverse of bulk modulus) of the medium (Pa^{-1}). Generation of micro bubbles in a liquid decreases the density in a negligible way in comparison to a large increase in compressibility. The net effect is a significant reduction of the sound velocity in the liquid. The following relationship between the fractional bubble volume and the sound velocity in water was derived by Frank S. Crawford, as given in equation 2[18].

$$\frac{v_w}{v} = \sqrt{1 + 1.49 \times 10^4 . f_a} \qquad \text{Equation 2}$$

Where v_w and v are velocities of sound (m s^{-1}) in pure and bubble filled water respectively, and f_a is the fractional volume occupied by air bubbles. The factor 1.49×10^4 in the formula was calculated as shown in equation 3.

$$(v_w)^2 \, \rho_w \frac{1}{\gamma p} = 1.49 \times 10^4 \qquad \text{Equation 3}$$

Where ρ_w is the density of water, γ is the ratio of specific heats for dry air and p is the atmospheric pressure. Equation 2 is based on the approximation presented originally by Wood *et al.*, [19].

BARDS analysis of an induced acoustic excitation of the containing vessel is focused on the lowest variable frequency time course, i.e. fundamental resonance mode of the liquid. The fundamental reso-

nance frequency is determined by the sound velocity in the liquid and the approximate but fixed height of the liquid level, which corresponds to one quarter of its wavelength[18]. The frequency response is described by Equation 4.

$$freq = \frac{freq_w}{\sqrt{1+1.49\times10^4 f_a}} \qquad \text{Equation 4}$$

Where $freq$ and $freq_w$ are the resonance frequencies of the bubbled filled water and fundamental resonance modes in pure water, respectively. Complete outline of working principles and theory of BARDS was described by Fitzpatrick *et al*.,[16].

Materials and methods

Materials

Microcrystalline Cellulose (Avicel PH200) was kindly donated from FMC International, Cork, Ireland. Metoclopramide HCl was obtained from Kemprotec Ltd, Cumbria, United Kingdom and Magnesium Stearate was obtained from Alfa Aesar, Manchester, United Kingdom.

Methods

Blends for preliminary proof of concept testing

Small blends of 10 g with active pharmaceutical ingredient (API) (10%), MCC (89.5%) and magnesium stearate (0.5%) were prepared in triplicate in 50 ml falcon tubes. Samples of 250mg were collected after 5 manual rotations and 100 manual rotations and analyzed using BARDS.

Preparation of blended formulations

Formulation 1 (unlubricated) and Formulation 2 (lubricated) with a total blend size of 2 kg were blended in a stainless steel double cone blender (DKM) with a 11.9 liter volume operated with ERWEKA AR402 drive unit at angle of 90^0. The blender rotated for 30 minutes at 30 rpm with microcrystalline

cellulose (90%w/w) and metoclopramide hydrochloride (10%w/w). Magnesium stearate (0.5%) was added to the formulation 2 and blended for a further minute at 30 rpm. Six blend samples (three samples from the top and three from the bottom of the blender) were collected for each blend and analyzed using BARDS. Amendments have been inserted into the revised manuscript in red font to facilitate identification of additions.

Feeding of Blends

Formulation 1 and formulation 2 were each fed with a K-TRON MT-12 twin screw microfeeder (COPERION K-TRON, Niederlenz, Switzerland) to achieve different levels of power lubricant (MgSt) distribution within blends in a controlled manner. K-TRON MT12 feeder was supplied with a range of different twin screw designs, for example coarse concave (CCS), coarse auger (CAS), fine concave (FCS), and fine auger (FAS). Coarse concave screws have a self-cleaning function suitable for cohesive materials and the auger screws do not have this self-cleaning ability but have the advantage of higher feeding capacity[20,21]. The feeder was also supplied with different designs of screens, for example coarse square screen (CSqS), fine square screen (FSqS), coarse slotted screen (CSlS) and fine slotted screen (FSlS). In feeder set different screw designs can be paired with different screw designs. The function of the screen is to break up clumps of cohesive powders and can also be used to create back pressure to prevent very free flowing powders from flowing uncontrollably from the feeder[20,21]. The feeder set up used in this study comprised of a fine concave screw (FCS) and fine square discharge screen (FSqS), with the objective of minimizing MgSt build-up on screws and feeding rate and promote overlubrication of blends. The feed factor is the theoretical 100% feed rate that can be achieved with a given set of tooling and material and was determined through equipment calibration. The feed rates set points were set at 0.2238, 0.5594 and 1.0069 kg/hr for 20%, 50% and 90% of the feed factor for formulation 1. The same feed rates were used for formulation 2 for direct comparison. The hopper was filled to the same level for all feeding runs. The feeder performance was evaluated using an independent catch scale using the K-Sampler Test System (COPERION K-TRON, Niederlenz, Switzerland). Blend samples were collected and analyzed using BARDS.

Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS)

Instrumentation

BARDS Spectrometer consists of a dissolution vessel equipped with a magnetic stirrer and a microphone set above the dissolution vessel, which receives and records the responses from the vessel. There is access at the front of the dissolution vessel and a tripper motor with a weighing boat on it to introduce the sample into the dissolution medium. The glass tumbler containing 25ml of deionised water is placed on the stirrer plate. The stirrer motor underneath is positioned so as to allow the magnetic stirrer bar to gently tap the inner glass wall, which will act as the source of broadband acoustic excitation. This will induce various acoustic resonances in the glass, liquid and the air column above the liquid. The audio is sampled at a rate of 44.1 kHz. The resonances of the liquid vessel are recorded in a frequency band of 0-20 kHz. A frequency time course is generated as shown in Figure 1

Experimental procedure

The BARDS spectrometer records the initial steady state resonances of the vessel containing solvent, deionised water, as a reference for 30 seconds once the stirrer is set in motion. Following addition of the sample the pitch of the resonance modes in the deionised water decrease giving rise to a frequency minimum *(f_{min})* by effecting the change in the velocity of the sound, before gradually returning to steady state over several minutes. The amount of blend sample analysed was 250 mg, which was equivalent to that of the intended formulation tablet weight. Spectra were recorded for a total of 800-1200 seconds which is dictated by the rate of return of the fundamental frequency to steady state. All experiments were performed in duplicate and an average reading and spread of two analyses is presented. The time courses of the observed acoustic profiles were measured under standardized conditions of constant volume, concentration, temperature and stirring rate.

Spectral Information

Acoustic spectra are characterized by specific nomenclature. The first 30 seconds of the spectrum corresponds to steady state resonances of vessel 10 kHz as shown as volume line in Figure **1**. Sample was tipped into the deionized water at the 30 second time point, resulting in a decrease of resonance frequencies due to a change in the velocity of sound. This resonance line is called the fundamental curve[16]. The time taken to reach the frequency minimum (f_{min}) is designated as *Δt.* The time for which

the response holds on f_{min} is known as the lag phase. The approximate time taken for the fundamental curve to progress from f_{min} to steady state is designated as ΔT. In this study all the time points shown are specific to each phase of the acoustic response. Lag phase and ΔT are used to identify the degree of wetting of the individual powders and blends.

Contact angles by spread wetting

Optical tensiometer (Attension Theta, Biolin Scientific Ltd., Espoo, Finland) was used to measure the contact angle (θ). A 5µl deionized water droplet was placed on the 250 mg blend compacted to a porosity of 12.3% ± 0.7, by sessile drop technique with dynamic live measurements at a temperature of 20^0C. All measurements were recorded in triplicates and the average value and standard deviation was determined.

Wetting time

The wetting time of the blends compacted to a porosity of 23.6% ± 1.3 was measured using the following procedure[22,23]. Two Whatman filter papers were placed in a petri dish of 10 cm in diameter. A small volume (8 ml) of red amaranth solution was added into the petri dish. A tablet was placed carefully on the surface of the filter paper. The time required for the red solution to reach the upper surface of the tablet was noted as the wetting time. All the measurements were made in triplicate and the average value and standard deviation was determined.

RESULTS

Preliminary BARDS studies –proof of concept

The BARDS acoustic spectra of the individual blend components (25mg of metoclopramide HCl and 225mg of MCC) and 250 mg of a metoclopramide HCl/MCC blend are shown in Figure 2. Table 1 details the lag times and steady state time points for the individual components and blends. All samples were added to 25ml water following the period (30s) of steady state resonance. The acoustic response generated for MgSt upon addition to water was a straight line without any frequency decrease (acoustic spectra not shown). The MgSt sample did not disperse in water due to its hydrophobic nature. Hence no air was introduced into the water and no change in resonance frequency was observed. There was

a slight frequency decrease of 0.3 kHz for metoclopramide HCl samples and gradual return to steady state after approx. 50 s as shown in Figure 2. The acoustic profile after addition of metoclopramide was a V-shaped response to f_{min}, which is a good indication of trapped and adhered gases that are introduced into the solvent with a fast gas release. The frequency change was sustained only for a short period of approx. 15 s due to the high solubility and rapid dissolution of metoclopramide hydrochloride in water.

In contrast, the frequency of MCC and metoclopramide/MCC blend was decreased to approx. 5 kHz and sustained a lag time up to approx. 80 s after sample addition was observed. Both the spectra gradually returned to steady state (ΔT) at approx. 310 s (Table 1), with a slight deflection of acoustic response for metoclopramide/MCC blend in the range of 190 – 270 s (Figure 2). The U-shaped acoustic response of the MCC and metoclopramide/MCC blend indicates the gas oversaturation in the solvent[16]. The greater frequency decrease of MCC, compared to metoclopramide, relates to the larger sample weight and and hence the volume of entrained gas introduced. MCC does not dissolve in water but hydrates in water resulting in the prolonged lag time.

Figure 3 shows the BARDS profiles of metoclopramide/MCC lubricated and unlubricated blends after varied degrees of rotation. The blend frequency decreases to an f_{min} of approx. 5kHz for all blends. The frequency is sustained at f_{min} for approx. 120 s and 145 s for the lubricated blends prepared at 5 rotations and 100 rotations respectively, which is designated as lag phase (start of f_{min} to finish of f_{min}). This differentiates the effect of lubricant, blending on the lag time. In contrast the unlubricated blend lag phase was sustained for approx. 80 s. Similarly the time taken to return to steady state resonance (ΔT) was approx. 600 s for the lubricated blend rotated 5 times and approx. 800 s for 100 times rotated blend Figure 3. The notable shift in the lag times and the time taken to return to steady state was attributed to the increased coating of metoclopramide and MCC with hydrophobic MgSt which delayed the wetting of the blend and hence displacement of gas from powder to water phase. This phenomenon of powder lubricants retarding the wetting and dissolution of blend components is a commonly observed effect of MgSt when over blended [24–26]. The end of lag time signifies the starting point of wetting of blends, which is similar to the results obtained by Hurson *et al.,* on enteric coated drug spheres[27]. Lag time can be potentially used to indicate the coating thickness or the degree of lubrication of the blends by hydrophobic MgSt and the start of return to steady state frequency can be related to the wetting of blend and outgassing of the oversaturated gases. The results of this preliminary proof

of concept study demonstrated the potential of BARDS to detect differences in the wetting of blends due to the presence of MgSt and the degree of blending of MgSt.

Comparison of unlubricated and lubricated formulations by BARDS

Following on from the preliminary proof of concept study, the ability of BARDS to detect differences in the wetting behavior of lubricated and unlubricated blends prepared using a lab scale double cone blender and subsequently fed at different feed rates through a screw feeder was assessed.

BARDS analysis of blends prior to feeding

Figure 4 shows the BARDS profiles of unlubricated and lubricated formulations, prior to feeding. Following addition of the sample to water there was a decrease to a plateau frequency of approx. 5 kHz after 30 s. Formulation 1 (unlubricated) showed a lag time of approx. 80s and formulation 2 (lubricated) showed a lag time of approx. 100 s. The lag phase indicates that the rate of gas evolution in the water phase is equal to the rate of gas loss from the water phase. The disappearance of gas from the solvent after f_{min} proceeded more slowly for formulation 2, which resulted in notable extension in time of approx. 640 s for acoustic resonance to return to steady state, whereas for formulation 1 it was found to be approx. 450 s. The differences in the acoustic responses between the formulations as shown in Figure 3 and Figure 4, is mainly due to the volume of gas introduced into solvent after powder sample addition, the amount of gas generated, the rate of gas released from the powders and the rate of gas eliminated from the solvent during the wetting of unlubricated and lubricated formulations. All these parameters were examined in depth by determining the changes in gas volumes using equation 4.

Equation 4 was applied to BARDS frequency data to analyze the fractional gas volume (f_a) occupied by compressible gas following the introduction of powder samples and during the wetting of the formulations. Both formulations quickly immersed when added into the water and reached a constant gas volume which lasted for a lag phase of approx. 45 s and 65 s for unlubricated and lubricated formulations respectively, Figure 5A. The curves represent an evolution and gas release from the water surface. No difference in the gas evolution following the addition of sample to the water was noted between the formulations. However, the release of gas from the water following sample addition was extended in

the lubricated blend data. The gas volume data (Figure 5A) is plotted in a logarithmic scale as shown in Figure 5B. The gas or air elimination rate constant (*k*) for the compressible gas in solution was assumed to be a first order process and was determined from the descending slope of the log plots shown in Figure 5B.

Table 2 shows the gas elimination rate constants (*k)* and the time range for which this constant is calculated. The gas elimination rate constants calculated for all samples of formulation 1 (unlubricated) were consistent ($k \approx 1 \times 10^{-5}\ s^{-1}$), whereas the presence of MgSt in formulation 2 resulted in a reduction in gas elimination constant ($k \approx 7 - 8 \times 10^{-6}\ s^{-1}$), and greater variability between samples. The slower gas escape for the lubricated blend suggests that hydration of MCC may have continued during the gas release phase, which is steady state attaining phase. This result is generally in agreement with the previous study on milk protein powder concentrates[15]. The slow gas generation of lubricated blends strongly inhibits hydration of the powder. In order to validate this hypothesis, these blends were fed through K-Tron MT12 loss in weight feeder, to obtain blends of varying degrees of lubrication to determine the influence of increased distribution of MgSt in blends on the BARDS acoustic response. These blends were also analyzed for their wetting time and contact angle measurements which are more recognized methods to determine blend hydration[22,23].

BARDS analysis of blends following to feeding

Slower gas elimination rate constants have been attributed to slower wetting of blends as previously discussed[15]. Here we demonstrate the differences in the wetting behavior of lubricated blends with equivalent composition but different degrees of controlled distribution of lubricant using a feeding system. The aim is to use the BARDS technique to obtain more reliable, mechanistic and kinetic information that relates to the degree of lubrication.

Formulation 1 (unlubricated) was unaffected by feed rate when analysed by BARDS as shown in Figure 6A. The lag phase lasted for approx. 90 s and the acoustic response reached steady state after approx. 420s as shown in Figure 6A. In contrast, formulation 2 (lubricated) showed a slight extension in the lag phase as the feed rate increased, Figure 6B. All the lubricated blends returned to steady state after approx.790s (Figure 6B). The extension in lag phase was attributed to increased coating of the MCC and

drug particles with MgSt due to increased feeding rate and hence prolonged wetting as discussed previously.

Formulation 1 when fed at different feed rates, showed constant gas volumes over the time period of approx. 60s, with a relatively rapid gas elimination rate constant thereafter ($k \approx 1.17 - 1.21 \times 10^{-5}\ s^{-1}$), Figure 7A and Table 3. Lubricated blends show an increase in constant gas volume with increase in formulation feed rate, Figure 7B. Slower gas elimination rate constants were observed for the lubricated blend ($k \approx 5.99 - 6.74 \times 10^{-6}\ s^{-1}$), Table 3.

Contact angle and wetting time of formulations before and after feeding

Contact angle is a commonly employed technique used to investigate the wetting of powders. When the surface of compacted powder is exposed to a liquid drop, the rate of change of the contact angle is monitored and recorded until the it reaches equilibrium[5]. In this study, the major diluent used in preparing blends was microcrystalline cellulose, which swells upon contact with water[28], so the initial point of contact between compacted powder and water droplet is reported, after the droplet is stabilized. Compacts with similar porosity were prepared for contact angle measurements. Contact angle results are shown in Figure 8(A). The compact from formulation 1 (unlubricated) showed a contact angle of approx. 10^0, and the compact from formulation 2 (lubricated) showed a 4 fold increase in the contact angle, which was attributed to the presence of MgSt. The feed rate did not show any effect on the contact angle measurements for compact from formulation 1 as anticipated. However compacts of formulation 2, as the feed rate increased the average contact angle increased, but it was not statistically significant, possibly due to variability in measurements. Similar to the BARDS technique, the contact angle method detected differences in wetting behavior between lubricated and unlubricated blends however but due to inherent test variability the technique was unable to detect differences between lubricated blends fed at different feed rates.

The wetting time method described above is an alternative method that can used to determine the wetting behavior of powders. Figure 8(B) shows the differences in the wetting time for the formulation 1 and formulation 2 compacts of equivalent porosities. An increase in the feed rate was expected to result in an increased degree of lubrication for formulation 2. However increased feed rate did not show significant differences in wetting times (54.6s ± 0.5 and 52s ± 2.6) between the blends fed at

0.2238 kg/hr and 0.5594 kg/hr respectively. However formulation 2 fed at 1.0069 kg/hr, showed an increased wetting time of 74.3s ± 10.96. These results support the attribution of differences in BARDS profiles to differences in blend wetting behavior. Compared to both techniques assessed, the BARDS method was easier to perform and analysed the blends in their powdered form without the need for compaction prior to analysis.

Discussion

It is important to understand the wetting behavior of pharmaceutical blends as wetting is the critical step in the dissolution and disintegration process of tablets[1,4]. MgSt is one of the most commonly used lubricants in tablet manufacturing and due to its hydrophobic nature, if not properly monitored during blending has the potential to overcoat powders in the blend thereby compromising the tablet quality[29,30]. This study demonstrated the capability of BARDS to identify differences in hydration behaviour of blends due to different degrees of MgSt distribution, at a fixed MgSt concentration (Figure 3). BARDS analysis generated reproducible, qualitative data that could be related to powder hydration in a timeframe suitable for its use as a process analytical technology (PAT) tool. Other PAT tools have successfully measured MgSt homogeneity within blends[31], in-line and at-line[32,33], with the objective of identifying differences in subsequent blend behaviour including hydration. Compared to these techniques, the BARDS method proposed studies blend hydration behaviour by immersion of powder in the liquid system of interest. Previous BARDS hydration studies focused mainly on single component milk protein powders[15] here we demonstrated the applicability of BARDS in multi-component pharmaceutical powder blends for the first time and specifically to the study of blend lubrication.

Individual components and blends yield significantly different acoustic profiles specific to the amount of sample and composition of blend as shown in Figure 2 and Figure 3. Compound solubility has an effect on the acoustic response[16]. The results demonstrated that a soluble API sustained a V- shaped frequency change for only very short duration compared to insoluble MCC, which wets but does not dissolve in water. Preliminary testing of blends prepared manually showed notable shift in the acoustic response for blends rotated 100 times compared to blends prepared with 5 rotations. This was further demonstrated by preparing lab scale blends in a controlled manner.

Equation 4 was used to convert the BARDS frequency data, to generate fractional gas volume (f_a) occupied by the compressible gas during wetting or dissolution of the powders. From this the log plots of gas volume were plotted to calculate the gas elimination rate constants to allow the quantitative comparison of the wetting behavior of powders. Formulation 1 (unlubricated) showed faster gas elimination rate constant compared to formulation 2 (lubricated) Table 2.

In this study, results generated by BARDS were also compared to more standard wetting techniques of contact angle and wetting time. However, there are some limitations to these techniques. For both methods the powder was compacted prior to analysis in order to achieve reproducible results. The nature of this formulation, in particular the hydrophilic and swelling behavior of MCC, undermines the reproducibility and accuracy of the contact angle technique. However despite these limitations, the contact angle results demonstrated a significant change in the measurements between lubricated and unlubricated formulations. Washburn capillary rise method, which is one of the most widely used wetting techniques was not evaluated in this study, however there are also a number of limitations associated with this technique such as layer swelling, difficulty in determining time zero, not suitable for powders with contact angle more than 90^0 and attaining consistent pore architecture will be challenging[2–4,10,11]. BARDS offers some key advantages compared to traditional techniques; powder can be directly analysed without packing or compacting and the acoustic profile is generated by dispersion of the blend in water, akin to disintegration and dissolution experiments. BARDS experiments require only 25ml of solvent with 10-300mg of sample, which greatly minimizes the quantities of powder required in comparison to comparable wetting tests[4]. BARDS is a highly reproducible method, when used under similar conditions and using similar amount of sample. Under these controlled condition BARDS provides a real time acoustic spectra reflecting the compressibility of the solution during the phase change of the solute.

This study highlights the ability of BARDS as a novel technique to identify over or under lubricated blends and potentially assists in predicting dissolution behavior of specific batches. BARDS can also be used to identify batch to batch variability[17]. BARDS can also be used to rapidly monitor the degree of lubrication and hydration behavior of pharmaceutical blends demonstrating its potential as an at-line process analytical technology (PAT) screening tool during development and routine pharmaceutical production for enhanced quality control and finished product quality.

Conclusion

The work presented demonstrates the ability of the BARDS to detect differences in the wetting behavior of commonly used tablet excipients microcrystalline cellulose (MCC), magnesium stearate (MgSt) and a model drug (metoclopramide hydrochloride) as single component and multi-component powder blends. BARDS detected differences in the wetting behavior of lubricated and unlubricated blends and was compared with the wetting measurement techniques of contact angle and wetting time. In comparison with these techniques, BARDS determined the wettability of powder by immersion and without the requirement for powder compaction. In addition BARDS was shown to be a more reproducible and rapid technique than the standard methods. The BARDS technique was also shown to be capable of detecting differences in the wetting behavior of lubricated blends, of equivalent composition, following different blending processes and feeding rates. The results of this study highlight the ability of the BARDS technique as a rapid, at-line technique for in-process analysis of pharmaceutical blend lubrication and potentially the wetting behaviour of pharmaceutical powders and blends.

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List of Tables

Table 1 BARDS profile lag times and time to return to steady state for metoclopramide, MCC, blend of metoclopramide-MCC and blend of metoclopramide-MCC-MgSt prepared by manual rotation.

Components	Approx. Lag time (s)	Approx. Time to return to steady state (s)
Metoclopramide	-	50
MCC	80	310
Metoclopramide/MCC 5 (rotations)	80	310
Metoclopramide/MCC/MgSt (5 rotations)	120	600
Metoclopramide/MCC/MgSt (100 rotations)	145	800

Table 2 Calculated gas volume elimination rate constant (*k*) and time ranges used for the calculation of the rate constant for samples of formulation 1 and formulation 2. Samples were taken from various locations in the lab scale blender. Formulation 1 (metoclopramide 10% w/w and MCC 90% w/w) and formulation 2 (metoclopramide 10% w/w, MCC 89.5% w/w and 0.5% w/w MgSt).

Blend Location	Formulation 1		Formulation 2	
	Time range (s)	*k* (s^{-1})	Time range (s)	*k* (s^{-1})
Top – 1	95-390	1.00E-05	109-556	8.00E-06
Top – 2	95-390	1.00E-05	167-556	7.00E-06
Top – 3	95-390	1.00E-05	109-556	8.00E-06
Bottom – 1	95-390	1.00E-05	109-556	8.00E-06
Bottom – 2	95-390	1.00E-05	156-556	7.00E-06
Bottom – 3	95-390	1.00E-05	126-556	8.00E-06

Table 3 Lag time, time to return to steady state, calculated gas volume elimination rate constant (*k*) and time ranges used for calculation of the constant for samples of formulation 1 and formulation 2. Blends were prepared using lab scale blender and fed at different rates through a screw feeder. Formulation 1 (metoclopramide 10% w/w and MCC 90% w/w) and formulation 2 (metoclopramide 10% w/w, MCC 89.5% w/w and 0.5% w/w MgSt).

Feed rate (kg/hr)	Formulation 1				Formulation 2			
	Approx. Lag time (s)	Approx. time to return to steady (s)	*k* (s^{-1})	Time range (s)	Approx. Lag time (s)	Approx. time to return to steady (s)	*k* (s^{-1})	Time range (s)
0.2238	90	420	1.17E-05	95-419	210	790	5.99E-06	207-792
0.5594	90	420	1.19E-05	95-419	220	790	6.02E-06	222-792
1.0069	90	420	1.21E-05	95-419	240	790	6.74E-06	255-792

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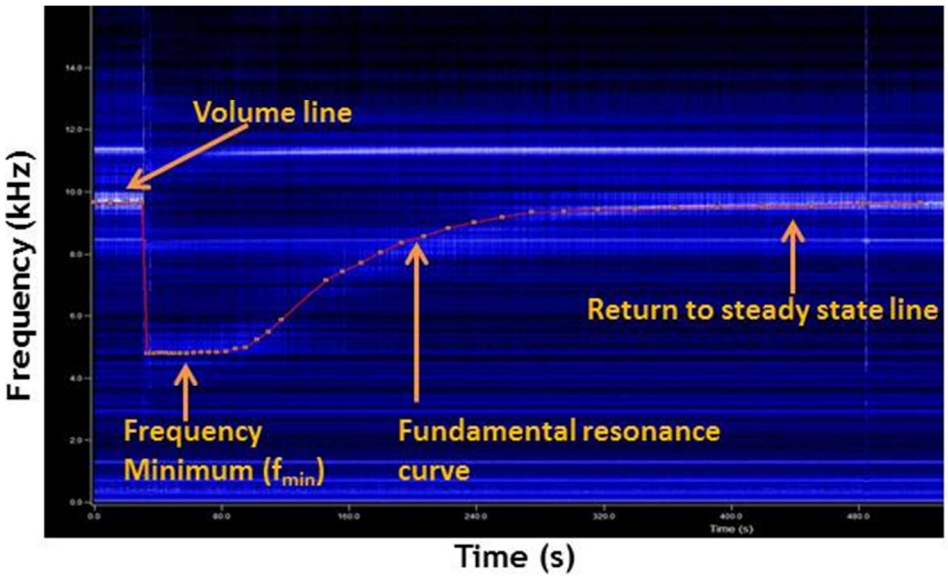


Figure **1** Representative BARDS raw spectrum of 250 mg microcrystalline cellulose (MCC) in 25 ml water.

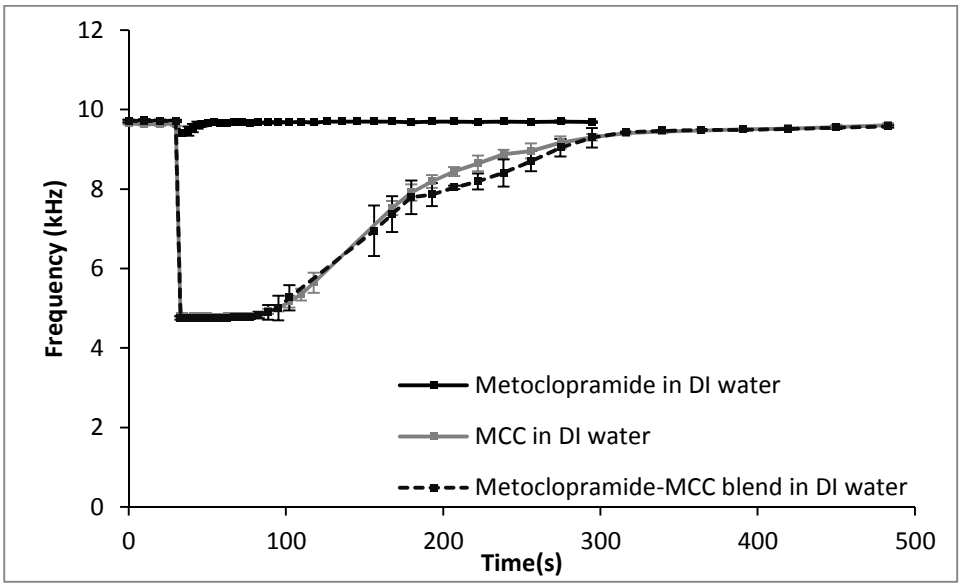


Figure 2 BARDS acoustic response in 25ml deionised water (DI). Metoclopramide (25mg) black line, microcrystalline cellulose (225mg) grey line and blend of metoclopramide (10% w/w) and MCC (90% w/w) (250mg) dashed line. Average values shown, n =3, y error bars indicate standard deviation.

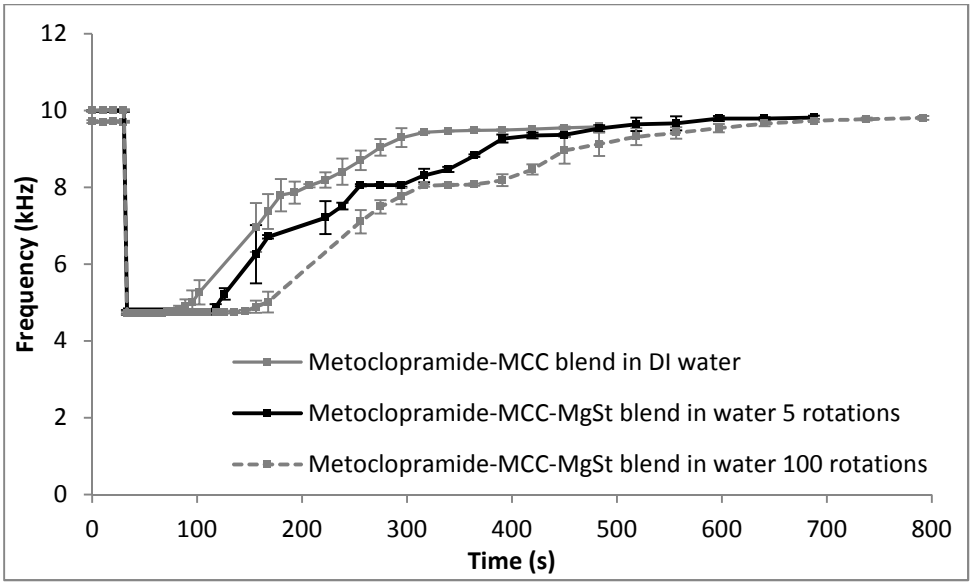


Figure 3 BARDS acoustic response for blends manually blended in 25ml deionised water. Metoclopramide 10% w/w and MCC 90% w/w (250mg) after 5 rotations (grey line), metoclopramide 10% w/w, MCC 89.5% w/w and 0.5% w/w MgSt (250mg) after 5 rotations (black line) and metoclopramide 10% w/w, MCC 89.5% w/w and 0.5% w/w MgSt (250mg) after 100 rotations (dashed grey line). Average values shown, n =3, y error bars indicate standard deviation.

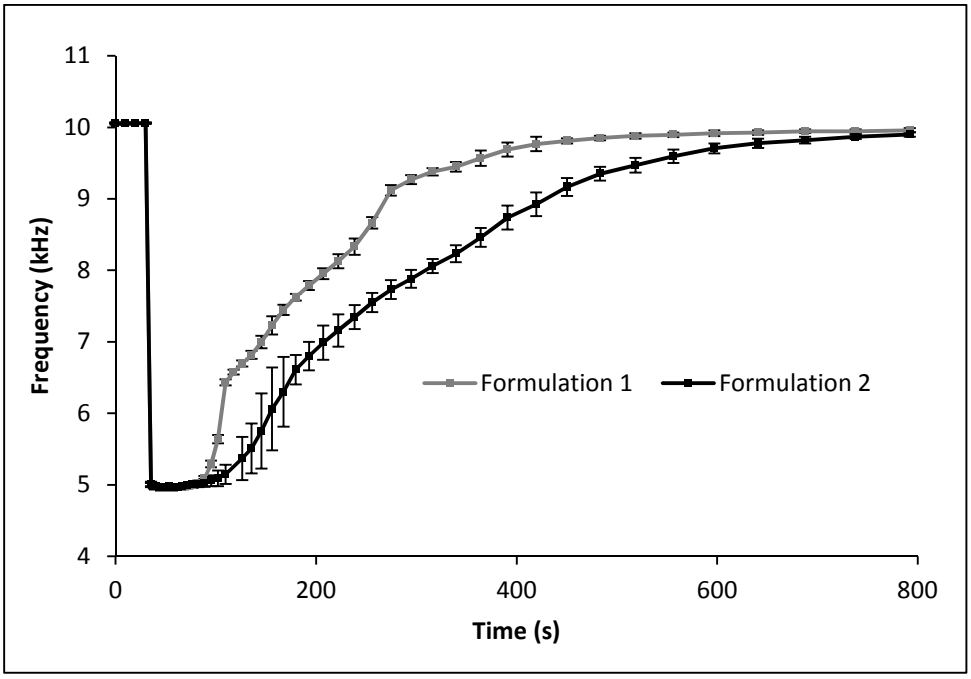


Figure 4 BARDS acoustic response for blends prepared using lab scale blender in 25ml deionised water. Formulation 1 (metoclopramide 10% w/w and MCC 90% w/w) (250mg) grey line and formulation 2 (metoclopramide 10% w/w, MCC 89.5% w/w and 0.5% w/w MgSt) (250mg) black line. Samples analysed were collected from 6 different locations in the blender and analysed in duplicate. Average values shown, n =12, y error bars indicate standard deviation.

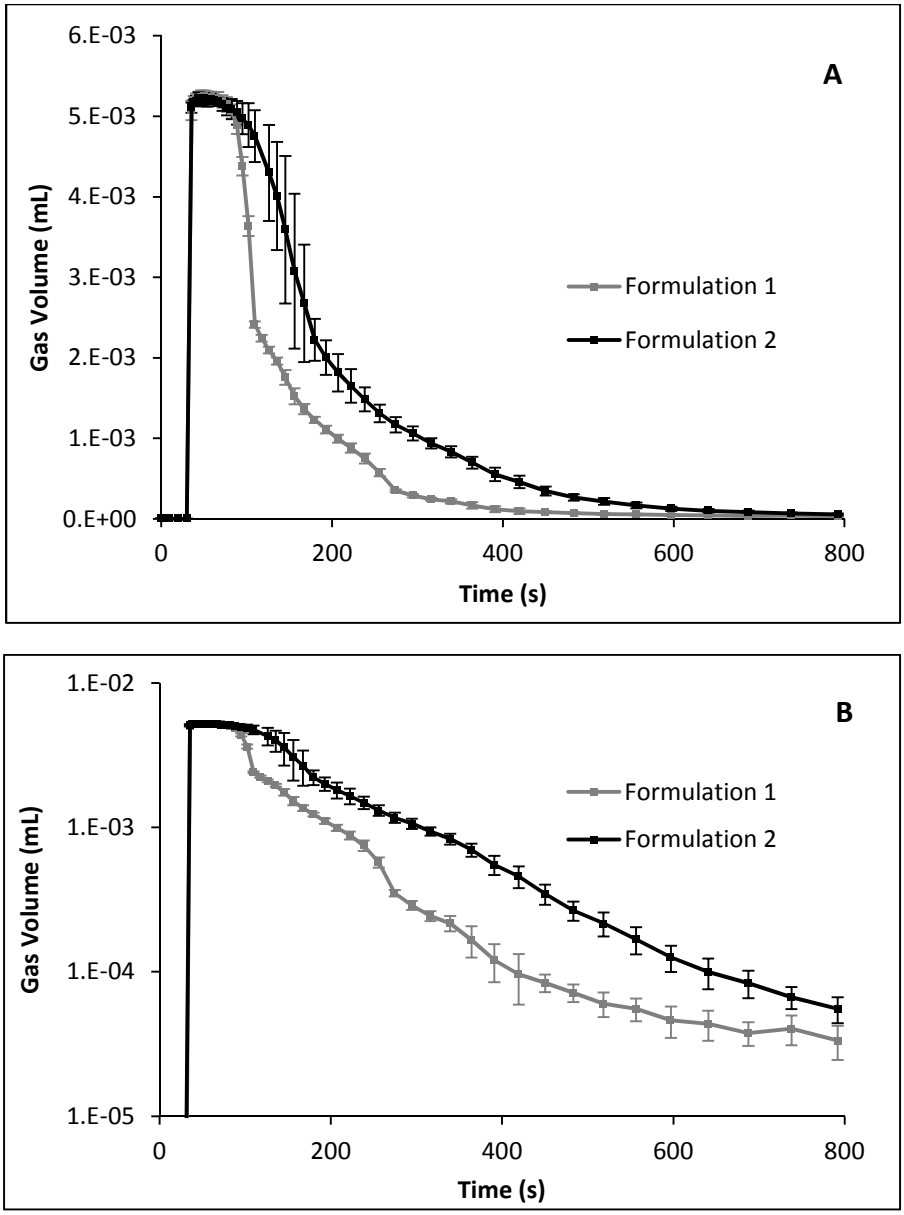
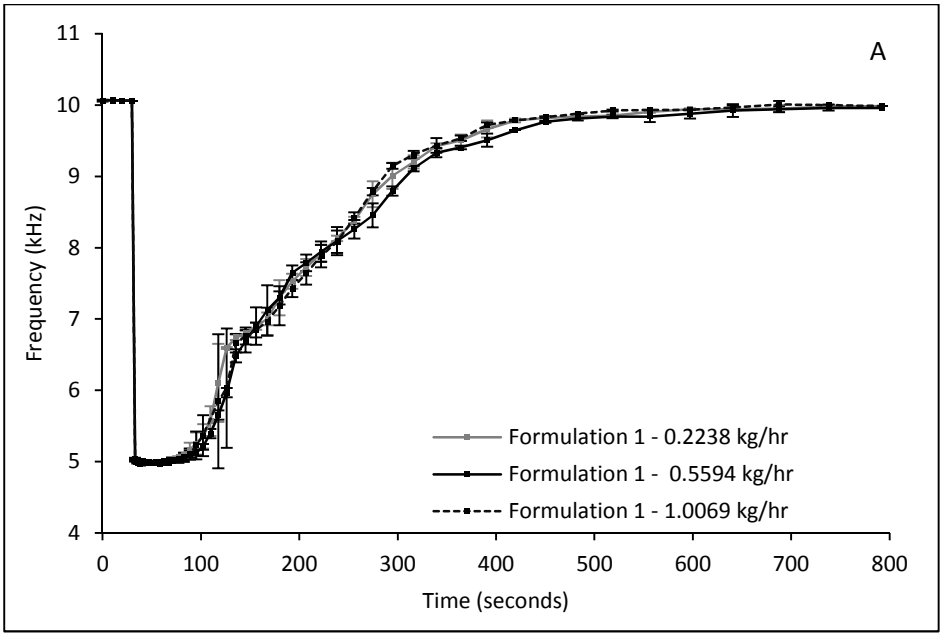


Figure 5 Gas volume plots for blends prepared using lab scale blender in 25ml deionised water. **A.** Plot of calculated gas volume versus time and **B.** Plot of log of calculated gas volume versus time. Formulation 1 (metoclopramide 10% w/w and MCC 90% w/w) (250mg) grey line and formulation 2 (metoclopramide 10% w/w, MCC 89.5% w/w and 0.5% w/w MgSt) (250mg) black line. Samples analysed were collected from 6 different locations in the blender and analysed in duplicate. Average values shown, n =12, y error bars indicate standard deviation.



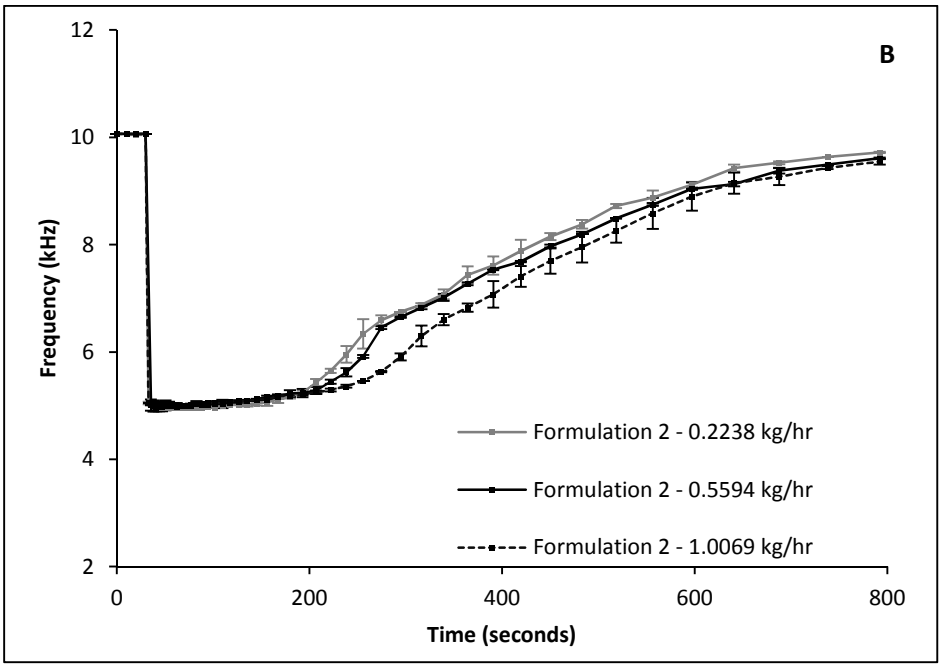


Figure 6 BARDS acoustic response for blend samples in 25ml deionised water. Blends were prepared using lab scale blender and fed at different rates through a screw feeder. Feed rate 0.2238 kg/hr (grey line), 0.5594 kg/hr (black line) and 1.0069 kg/hr (dashed black line). **A.** Formulation 1 (metoclopramide 10% w/w and MCC 90% w/w) (250mg) and **B.** Formulation 2 (metoclopramide 10% w/w, MCC 89.5% w/w and 0.5% w/w MgSt) (250mg). Average values shown, n =2, y error bars indicate max and min values.

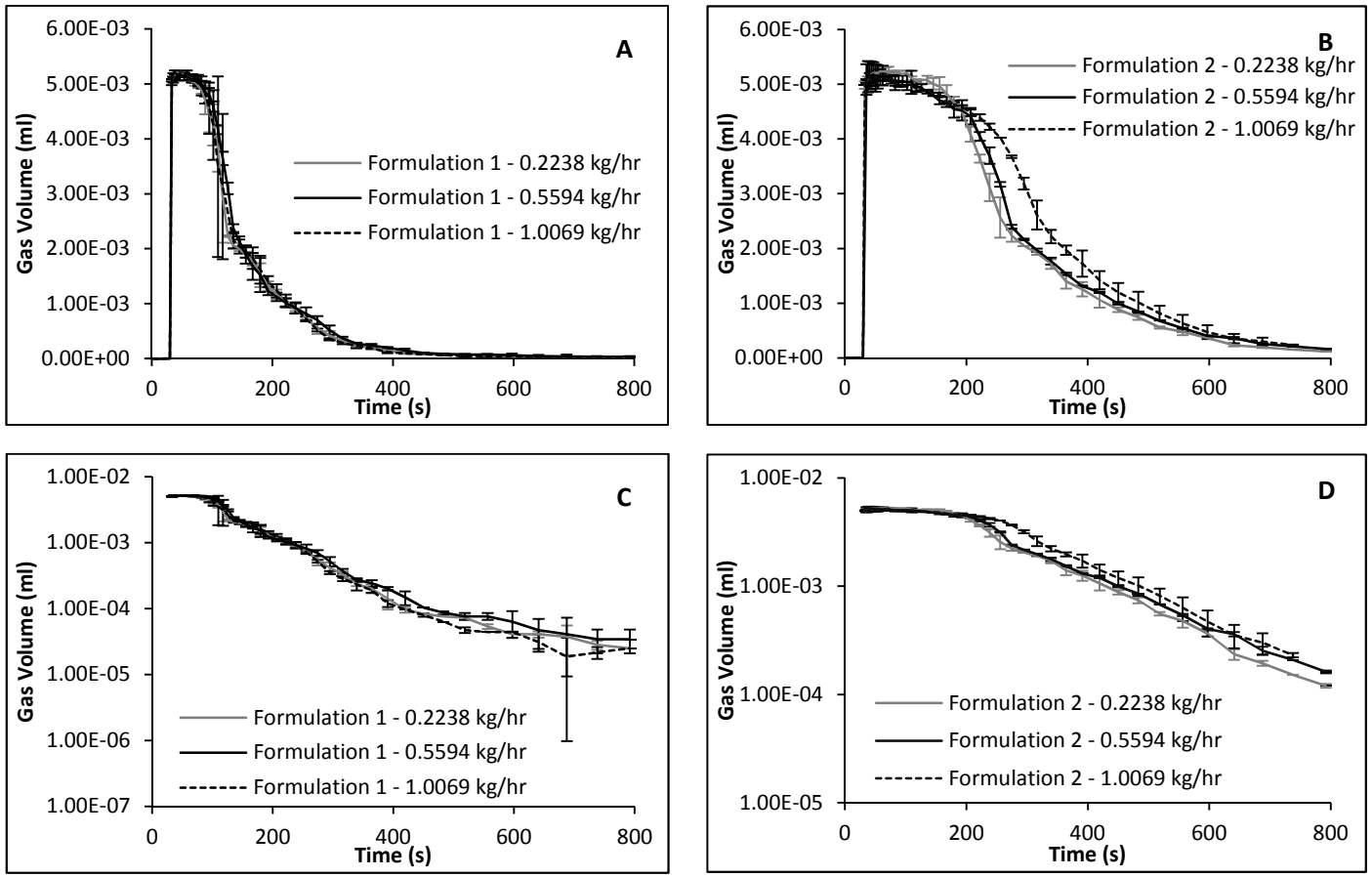


Figure 7 Gas volume plots for blends in 25ml deionised water. Blends were prepared using lab scale blender- and fed at different rates through a screw feeder. Feed rate 0.2238 kg/hr (grey line), 0.5594 kg/hr (black line) and 1.0069 kg/hr (dashed black line). **A.** Formulation 1 plot of calculated gas volume versus time, **B.** Formulation 2 plot of calculated gas volume versus time, **C.** Formulation 1 plot of log of calculated gas volume versus time and **D.** Formulation 2 plot of log of calculated gas volume versus time. Formulation 1 (metoclopramide 10% w/w and MCC 90% w/w) (250mg) and Formulation 2 (metoclopramide 10% w/w, MCC 89.5% w/w and 0.5% w/w MgSt) (250mg). Average values shown, n =2, y error bars indicate max and min values.

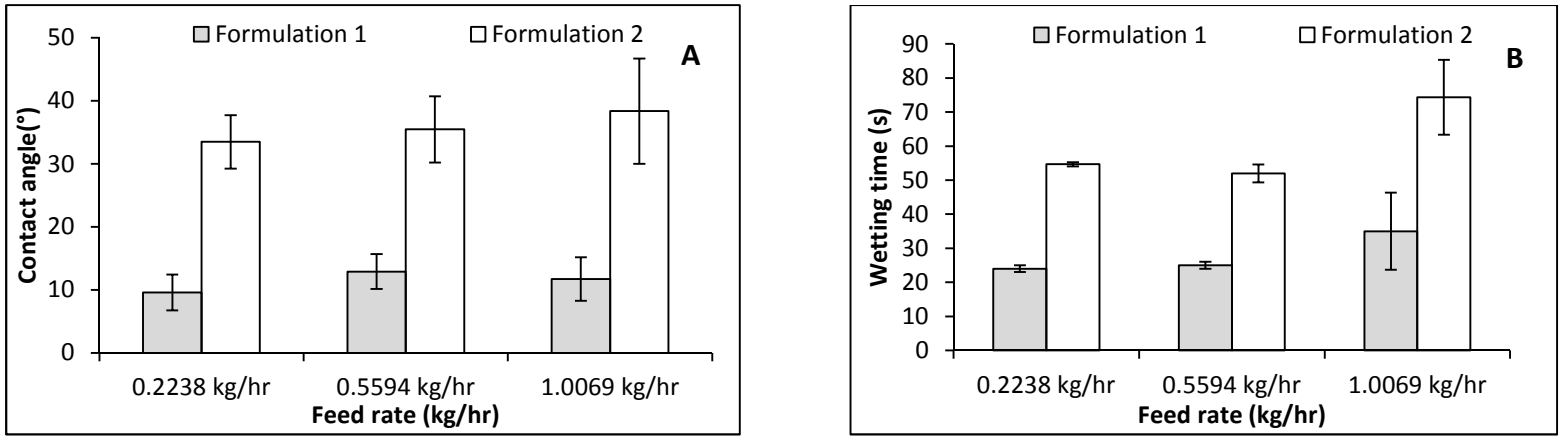


Figure 8 A. Contact angle (^{0}) of deionized water on blend compacts **B.** Wetting time of blend compacts with aqueous amaranth solution. Formulation 1 (metoclopramide 10% w/w and MCC 90% w/w) and Formulation 2 (metoclopramide 10% w/w, MCC 89.5% w/w and 0.5% w/w MgSt). Average values shown, n =3, y error bars indicate standard deviation.