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Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS): A Rapid Test for Enteric Coating Thickness and Integrity of Controlled Release Pellet Formulations.

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Abstract:

There are no rapid dissolution based tests for determining coating thickness, integrity and drug concentration in controlled release pellets either during production or post-production. The manufacture of pellets requires several coating steps depending on the formulation. The sub-coating and enteric coating steps typically take up to six hours each followed by additional drying steps. Post production regulatory dissolution testing also takes up to six hours to determine if the batch can be released for commercial sale. The thickness of the enteric coating is a key factor that determines the release rate of the drug in the gastro-intestinal tract. Also, the amount of drug per unit mass decreases with increasing thickness of the enteric coating. In this study, the coating process is tracked from start to finish on an hourly basis by taking samples of pellets during production and testing those using BARDS (Broadband Acoustic Resonance Dissolution Spectroscopy). BARDS offers a rapid approach to characterising enteric coatings with measurements based on reproducible changes in the compressibility of a solvent due to the evolution of air during dissolution. This is monitored acoustically via associated changes in the frequency of induced acoustic resonances. A steady state acoustic lag time is associated with the disintegration of the enteric coatings in basic solution. This lag time is pH dependent and is indicative of the rate at which the coating layer dissolves. BARDS represents a possible future surrogate test for conventional USP dissolution testing as its data correlates directly with the thickness of the enteric coating, its integrity and also with the drug loading as validated by HPLC.

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Keywords: Hypromellose, Enteric Coated Pellets, Dissolution, BARDS,

Abbreviations: BARDS; Broadband Acoustic Resonance Dissolution Spectroscopy

Introduction:

Omeprazole is a popular over the counter medicine used to reduce indigestion and heartburn. Its mode of action is as a proton pump inhibitor (PPI). It is preferentially delivered to the lower intestine to avoid first pass degradation in the stomach[1]. Therefore, enteric coatings are used to protect the drug and to provide a controlled release formulation[2]. A common formulation in the market are capsules containing enteric coated pellets [3]. The pellet contains the API as the core of the sphere followed by a layer of sub-coating and enteric coating.

The sub coating is added to protect the API from interacting with the enteric-coating. Ideally, the addition of the sub coating should have no impact on the dissolution of the pellets once the enteric coating has eroded[4]. The thickness of the enteric coating determines the controlled delivery of the drug in gastrointestinal track.

The grade of polymer used as the enteric coating also determines the timing of release of the drug in the gastro-intestinal tract. There are several commonly used enteric coatings with the most common being cellulose esters, polyvinyl derivatives and polymethacrylates.

In this study, we investigate the thickness and the integrity of the enteric coating during and post manufacture of omeprazole pellets, using a novel technology called

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broad band acoustic resonance dissolution spectroscopy (BARDS). The use of BARDS provides an analytical tool with reliable and reproducible data in a time efficient manner. It also provides an assay for the drug concentration in the pellets by default.

In previous studies it has been shown how BARDS produces unique spectra for differing size distributions of non-coated pellets. Once the pellets are coated they display a lag time during dissolution associated specifically with the thickness of the exterior coating. The length of the lag time was shown to be dependent on the sodium hydroxide concentration of the dissolution medium [5]. Also, bio-relevant solution can be used for *in-vitro* BARDS experiments such as artificial saliva.

Changes in the compressibility of a solvent during dissolution produces the BARDS signal. The speed of inducted sound in the vessel is reduced resulting in frequency changes within the solution.

The speed of sound (v) in a solvent is determined by Equation 1.

$$v_{(sound)} = \sqrt{\frac{1}{K\rho}} \qquad (1)$$

Where ρ = mass density and K = compressibility, which is the inverse of the bulk modulus, of the medium. Generation of micro gas bubbles in a liquid decreases the density in a negligible way in comparison to the large increase in compressibility. The net effect is a significant reduction of the sound velocity in the dissolution medium. Equation 2 demonstrates the relationship between the fractional gas volume and the speed of sound in water as derived by Frank Crawford [6].

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$$\frac{v_w}{v} = \sqrt{(1 + 1.49x10^4 f_a)} \qquad (2)$$

where v_w and v are the sound velocities in pure and bubble-filled water, respectively. f_a = the fractional volume occupied by air bubbles. The factor 1.49 x 10^4 in Equation 2 was calculated as shown in Equation 3:

$$(v_w)^2 \rho_w \frac{1}{\gamma p} = 1.49x10^4 \qquad (3)$$

Where ρ_w = the density of water, γ = ratio of specific heats for dry air and p = atmospheric air pressure. Equation 2 was also independently derived as far back as 1930 by A.B. Wood[7].

The fundamental resonance mode, excited by tapping the stirrer bar against the inner wall of the dissolution vessel was measured using a microphone. The fundamental resonant 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. The resonant frequency response is explained as;

$$freq = \frac{freq_w}{\sqrt{1+1.49x10^4 f_a}} \qquad (4)$$

where freq and $freq_w$ are the resonance frequencies of the fundamental resonance modes in bubble-filled and pure water, respectively. The total volume of the gas is due to entrained gas, gas due to oversaturation, and gas escaping the solvent due to elimination at the surface or reabsorption. A comprehensive treatment of the principles involved in BARDS analysis is given in Fitzpatrick *et al.* [8] Travnicek *et al.*, have also demonstrated the reproducibility of the acoustic phenomenon used in

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BARDS. [9] Other references to the phenomenon have appeared repeatedly in the literature since 1930. [10-15]

Figure 1 shows the BARDS spectrogram of the dissolution of 0.3g of uncoated omeprazole pellets in 0.01 M NaOH (25 mL).

Figure 1

The acoustic profile of interest is called the fundamental curve. The frequency minimum (f_{min}) represents an equilibrium between the rate of formation of gas in solution and the rate of gas liberation at the surface. In BARDS analysis, the fundamental curve is used to make comparisons between individual experiments. Note the acoustic frequencies of the vessel remain steady for the first 30 s until the addition of the pellets. Thereafter, the resonant frequency at 10.0 kHz decrease to 4 kHz and gradually returns to steady state after ~200 s. The majority of disintegration and dissolution has taken place by f_{min}. However, dissolution and gas generation may still take place after f_{min} even though the rate of gas loss at the surface is greater than the rate of evolution. There is another frequency (8.2 kHz) of the vessel that is not dependent on the compressibility of the liquid and therefore remains unchanged. There are resonant frequencies of the vessel which resonate around the vessel only and not in solution. These frequencies remain unaffected by the dissolution event.

In general, gases trapped between and within particles are introduced with the sample when it is dissolved in any solvent. Another source of gas, due to

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dissolution, is the reduction in its solubility, of that which is already in solution, resulting in gas oversaturation. Oversaturation can only be removed through nucleation and generation of gas bubbles in the solution. Alternately, it is removed through a very slow return to equilibrium with the atmosphere which can take hours to days.

The entrainment of gas in a sample combined with the subsequent evolution of gas and its escape provokes reproducible change in the compressibility of the solution which is monitored acoustically, under set conditions.

Current state of the art for monitoring coating thickness include techniques such as scanning electron microscopy (SEM) [16], atomic force microscopy (AFM), confocal Raman micro-imaging [17], fluorescence microscopy [18] , energy dispersive X-ray imaging (EDX) [19], and confocal laser scanning microscopy (CLSM) [20]. The application of terahertz pulsed imaging to analyse film coatings has also been reported with the capability to interrogate individual pellets yielding quantitative measurements [21].

The objective of this study is to demonstrate the ability of BARDS as an analytical tool to rapidly determine the coating thickness, the coating integrity and drug assay of the pellets in just one measurement.

Experimental

Materials

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Omeprazole pellets and Omeprazole powdered API standard were received from Aenova Ireland Ltd. Samples from three individual batches harvested at hourly time points were supplied from the sub-coating and enteric coating manufacture lines. The Materials listed in Table 1 are based on a theoretical lacquered batch size of approximately 400kg pellets, allowing for 64.4% pellet core, 5.6% sub-coat and 30% enteric coat. However, the sub-coat and enteric coat may vary depending on equipment performance during processing. The ratio of the sub-coating components and enteric coat component must never change.

Sub-coating

Omeprazole Pls Temmler Unlacquered are maintained in a fluidised state in the Coater while atomised coating suspension is sprayed onto the pellets. The Unlacquered Pellets are charged into the preheated Coater. Spraying commences with the sub-coating suspension using the following conditions in the Coater. If necessary, the sub-coating suspension may be filtered.

- Spray air pressure : 2.0-2.5bar
- Product temperature : ≤ 40°C, target value 25-30°C
- Monobloc temperature : Maximum 7°C
- Process air flow : 4,500-6,000m^3/h Note 1
- Inlet air temperature : variable, to maintain product temperature
- Spray rate : 800-1500g/minute Note 2

Note 1: Process air flow maybe adjusted to maintain optimum fluidisation of product

Note 2: Spray rate may be adjusted to maintain the specified product temperature

Enteric coating

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Omeprazole Pls Temmler sub-coated are maintained in a fluidised state in the Coater while atomised enteric lacquer dispersion is sprayed onto the pellets. The lacquering conditions are to be adjusted during processing to achieve optimum performance of the coater. If necessary the enteric lacquer suspension may be filtered. For optimum processing, the processing conditions during lacquering should be as follows.

- Spray air pressure 2.0-2.5bar
- Product temperature 26-36°C, target value 28-32°C)
- Monobloc temperature Maximum 7°C
- Process air flow 4,500-6,000m^3/h Note 1
- Inlet air temperature variable, to maintain product temperature
- Spray rate 500-2000g/minute Note 2

Note 1: Process air flow maybe adjusted to maintain optimum fluidisation of product.

Note 2: Spray rate may be adjusted to maintain the specified product temperature.

Analytical grade sodium hydroxide and potassium phosphate monobasic were purchased from Sigma Aldrich.

HPLC grade methanol, acetonitrile and amber vials were purchased from Sigma Aldrich. All mobile phases were ultrasonically degassed and filtered prior to use. The 0.22µm filters were purchased from Alltech Associates Inc. Agilent Captiva premium syringe filters were purchased from Carl Stuart Limited (Ireland). Doubly distilled water (dH_2O) with a resistivity of 18 M Ω cm^{-1} was used for the preparation of all dissolution media.

Instrumentation

A BARDS spectrometer (BARDS Acoustic Science Labs (BASL)) was used to analyse all samples. It consists of a chamber with a glass dissolution vessel, a microphone, a

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magnetic stirrer and a stir bar. 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. All the experimental parameters are standardised as described by Fitzpatrick *et al*. [8] and the method is also scalable.

An Agilent HPLC series 1100 with Diode-Array Detector and heated column (40^0C) was used to analyse omeprazole. An Agilent Eclipse XDB C18 column 5µm particles, 4.6 x 150 mm was used throughout the study. An injection volume of 5 micro-litres was employed.

Methods

In a typical BARDS experiment, the spectrometer records the steady state resonances of the system as a reference for thirty seconds when the stirrer is set in motion. The pitch of the resonance modes in the solution changed significantly when the pellets are added before gradually returning to steady state over several minutes. Approximately 300 mgs of pellets were used in each experiment. Dissolution solvents were gas equilibrated immediately before use by shaking vigorously for 60 s and then to stand for 10 minutes [22]. The solvent used were buffer (PBS: Methanol 60:40 pH=11.4) or sodium hydroxide (pH=12).

The frequency resonance data is manually extracted from the acoustic spectra which were recorded for 1400 s typically. There is dedicated software used to click on defined time points along the fundamental curve, which is then automatically exported to an excel file. All experiments were performed in duplicate, and an average datum point and the data spread are presented. The time courses of the

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detected acoustic profiles were reproducible under standard conditions of volume, mass, temperature, and stirring rate. The steady-state frequency before addition of the sample is designated as the "volume line," due to its variance depending on the liquid volume in the vessel.

HPLC Procedure:

Samples were collected during BARDS runs at certain time points using 2 mL syringe and then filtered into the HPLC vials. The column was washed for 30 min with 70% Methanol: water before commencing the analysis. A gradient method was used for the analysis of the omeprazole. Mobile Phase A was buffer (IBPS, pH 5.8). Mobile phase B was Acetonitrile. The flow rate was 1.5 mL min^{-1}. The detection wavelength was 280 nm. A run time of 15 minutes was used. The retention time of Omeprazole was 9.5–10 minutes. The gradient elution parameters are given in Table 2.

SEM Analysis:

Samples were mounted onto aluminium stubs using double sided carbon tape. All samples were sputter coated with a 5nm layer of gold palladium (80:20) using a Quorum Q150 RES Sputter Coating System (Quorum Technologies, UK), before being examined using a JEOL JSM 5510 Scanning Electron Microscope (JEOL Ltd., Japan). Digital electron micrographs were obtained after multiple pellets were mounted at the same time to give the best chance of finding one with the correct

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orientation. A professional SEM technician carefully looked through the mounted samples to measure a pellet which was deemed parallel to the mount.

Results and Discussion

The initial coating step is to apply a sub-coat to protect the API from interacting with the enteric coating. Figure 2 shows the data for the sub-coating process for three individual batches. Note as the coating thickness increases there is a shift in the f_{min} to a lower frequency at a longer time period. The red profile represents an uncoated pellets and the black profiles represent the finished sub-coated pellets. This trend is similar for all three batches. The disintegration and dissolution of the pellets is instantaneous regardless of the level of sub-coating applied.

Figure 2

The reproducible data indicates that it is possible to track the sub-coating process at-line in real time.

The next step in the coating process is to apply the enteric coating (Eudragit L30 D-55). The concentration of the enteric coating solution is gradually increased during the early coating stages. Figure 3 (A-E) shows data associated with samples taken at hourly intervals during the coating process. The red profile in this instance represents that sub-coated microsphere. Figure 3 (A) shows that there is a slight shift in the BARDS dissolution profile after 60 minutes. It is possible to see the first indication of a lag time after 30 seconds before the decrease in resonant frequency.

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Figure 3 (B) shows a dissolution profile for the pellets after 120 minutes of coating. The lag time has now increased to 170 seconds (170 s – 30 s =140 s in total). This is due to the time taken for additional coating to erode under basic conditions. The erosion of the coating does not lead to gas evolution and therefore no BARDS response is obtained. Also note, experiments were performed using 0.1 M HCl as the dissolution media and no change in the resonant frequency was observed throughout the experiment and no drug was detected. The erosion of the coating is a chemical process due to the interaction of the hydroxide media and the carboxylic groups on the polymer. There is no gas evolution due to this process. This is always expected based on the chemistry of most enteric coating polymers. However, once the enteric coating has dissolved, the sub coated sphere is exposed which generates a BARDS response. Figures 3 (C-E) show the data for the additional hourly samples. An increase in the lag-time is evident for each hour of coating that passes until the process is finished with a lag-time of 700 seconds. Figure 3 (F) is a composite of all the data for samples taken throughout the process. There are also two additional profiles relating to the charging/introduction of the enteric coating at the start of the process. Note the f_{min} value is steadily increasing during the coating process and the value for the down slope is decreasing. Evans–Hurson *et al*. have shown that the lag time is directly proportional to the hydrogen ion concentration for a fixed coating thickness [5].

Figure 4

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In Figure 4 (A) data is shown for samples which were obtained at time points +/- 5 minutes during the enteric coating of three different batches. The inter-batch variability is shown to be insignificant for the time points tested. This demonstrates good process control.

Figure 4 (B) illustrates that the dissolution of the enteric coating strongly depends on the concentration of the base. This is useful to determine the rate of the dissolution of the enteric coating in a controlled pH environment and it will differ in bio-relevant media.

SEM was used to determine the coating thickness of the pellets which were sampled at hourly intervals during the coating process. An example of an SEM image is shown in Figure 4(C). The coating thickness as determined by SEM is plotted against the lag times taken from Figure 3. Figures 4 (D) shows direct correlation between the lag time and coating thickness with an r^2 value of 0.96. The last point is an outlier and when removed the r squared value increases to 0.99. The reason for the outlier we believe is due to the depletion of the basic media due to the increased thickness of the coating.

The lag time was further investigated by collecting 2 mL of the sample during a BARDS run every 100 seconds. These samples were analysed using HPLC in chronological order. Figure 5 (A) shows a typical BARDS spectra for coated pellets but in this example the HPLC samples were taken during the BARDS analysis resulting in small spikes in the spectrum. This is due to the syringe tip puncturing the surface of the solution which results in a frequency change the sample is

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removed and replaced. An equation was used to correct for the dilution factor after sampling which is given in Equation 5

$$Corr(n) = Corr(n-1) + Conc(n) - 23/25 \times Conc(n-1) \qquad \text{Equation (5)}$$

Where (n) = the sequence number in the sampling (data point n), Corr (n) = the corrected concentration and Conc (n) = the measured concentration. The resulting data in Figure 5 (B) and 5 (C) show a direct correlation between the drug concentration and the lag time of the BARDS experiment. There is no drug release during the lag time until all the coating is eroded and the drug containing sphere in the middle begins to disintegrate and dissolve.

Figure 5

The data shows the integrity of the polymer during the lag-time with zero drug release and once the coating has broken down there is rapid drug release. Note, the percentage release of drug detected at the frequency minimum is ~50% and increase towards 100% by the time the acoustic profile has returned to steady state frequency as shown in Figures 5 (B) and (C). This may indicate that disintegration results in the majority of gas evolution followed by continued dissolution of particulates in suspension resulting in greater drug release after f_{min}. Also note, the buffer:methanol dissolution media in Figure 5 (B) accelerates the dissolution of the polymer more quickly than hydroxide alone.

Figure 5 (D) and (E) show BARDS profiles of the Omeprazole pellets at different stages of coating and their HPLC results given as % release. The data show that when the lag time and the enteric coating increases, the amount of omeprazole in the

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sample decreases linearly. 100% release represents the desired drug loading following the coating process. Therefore, a samples of bare pellets after 40 mins of coating contains excess API (140%). As the coating thickness increases there is less drug per unit weight of sample. HPLC analysis of the finished pellets measure 95% of content. The remaining 5% is in particulate suspension which was removed by filtration before analysis. The release data has been normalised to 100% release for the finished product in Figure 5 for convenience. Figure 5 (E) demonstrates that 300 minutes of coating is the optimum time required to achieve the correct drug content and coating thickness.

Therefore, the lag time can be used to determine three key parameter which are (a) the coating thickness, (b) the integrity of the coating and (c) the amount of API in the sample provided the concentration is known before the coating process. Therefore, just one HPLC measurement is required to compliment the BARDS method, thus reducing very significantly the inputs such as the analyst time, solvents and expense.

The number of pellets per 300 mg sample mass was found to decrease from 444 for uncoated drug sphere to 386 for sub-coated pellets and 280 pellets when fully enteric coated. This represents a 37% decrease in the number of pellets per unit weight before and after the coatings process.

Finally, Figure 5 (F) shows the gas volume time courses derived from the BARDS data presented in Figure 3(F) using equation 4. There is a significant difference between the sub-coated spheres and the spheres collected thereafter during the final coat. This is indicative of reduced porosity of the surface of the sphere with the

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addition of the polymer leading to less surface gas present and a reduction in the compressibility of the solvent once the coating process begins. The lag time along the x-axis increases with coating time similarly to Figure 3. The slopes values of the disintegration and dissolution of the core spheres in Figure 5 (F) decrease with coating time. This indicates that the rate of disintegration is decreasing possibly due to the depletion of hydroxide in solution due to the erosion of the outer polymer layer. This has been noted previously by Fitzpatrick *et al*. [23].

Conclusions.

BARDS analysis of pellets during production has been shown to be highly beneficial for determining coating thickness, integrity and drug concentration. A single BARDS measurement can provide all three data requirements in a time efficient manner.

The layering of both the sub coat and the enteric coating can be tracked using BARDS. The sub coat was found not to influence the rate of dissolution. BARDS measurements have been cross validated by conventional techniques including SEM and HPLC.

The data represents a potential new regulatory method for the quality assurance of microsphere formulations.

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DISCLOSURES

Both Seán McSweeney and Dara Fitzpatrick are directors of the spin out company BARDS Acoustic Science Labs.

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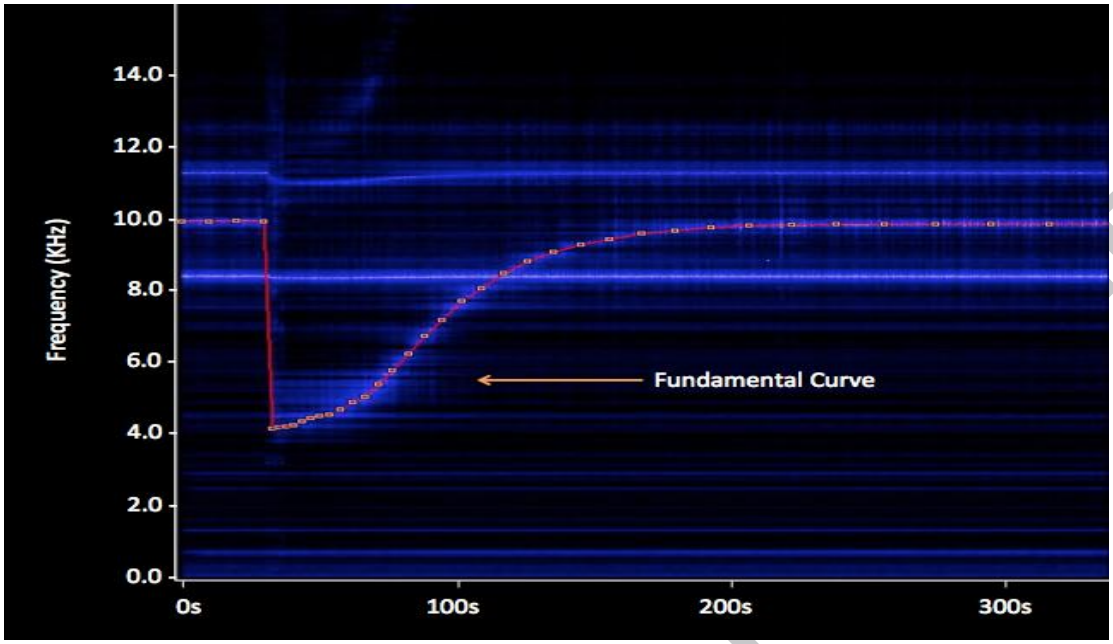
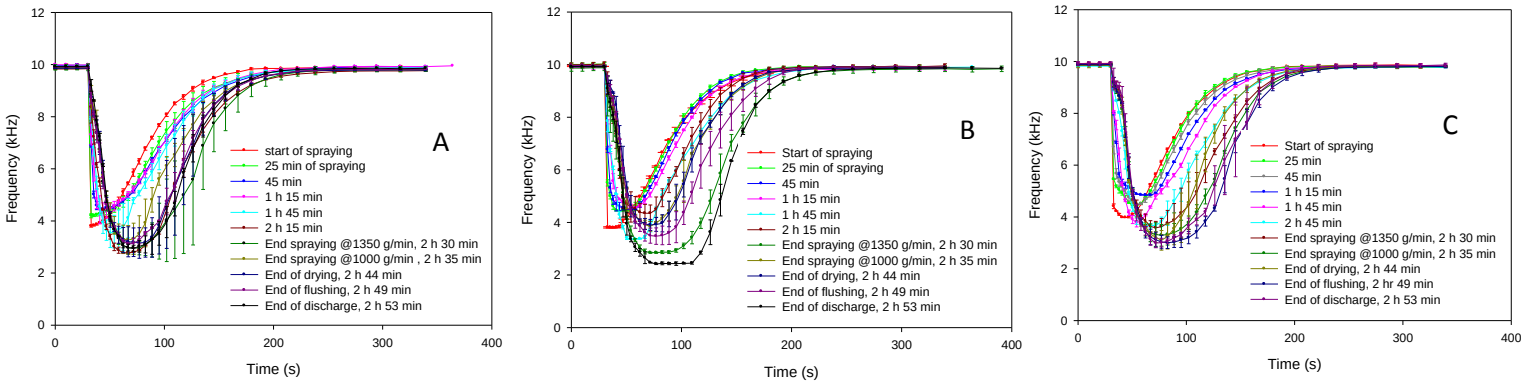


Figure 1: BARDS spectrum of 0.3 g of uncoated omeprazole spheres dissolving in 25 mL 0.01 M NaOH. The spheres are added at the 30 s time point.



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Figure 2: BARDS dissolution profiles of pellet samples from the sub-coating process for three individual batches of Omeprazole pellets, A, B and C. 300 mg of pellets were dissolved in 0.01 M NaOH for each experiment. All profiles were measured in duplicate.

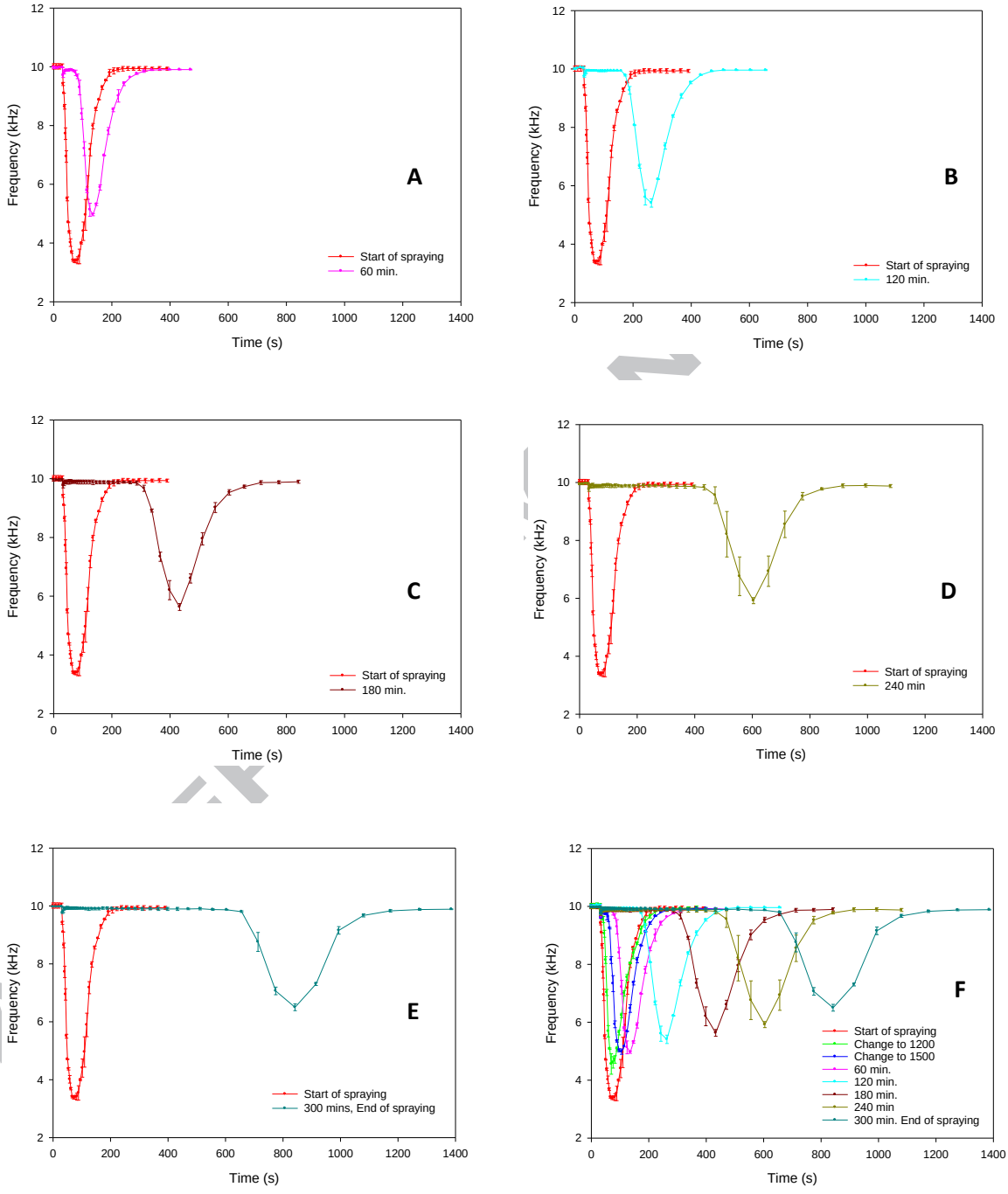


Figure 3: (A) BARDS profile of sub-coated pellets (red) and profile of pellets after one hour of enteric coating (pink) dissolved in 0.01M NaOH. (B) after 2 hours of enteric coating, (C) after 3 hours of

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coating, (D) after 4 hours of coating, (E) after 5 hours of enteric coating, (F) Composite of BARDS profiles of the pellets during the coating process.

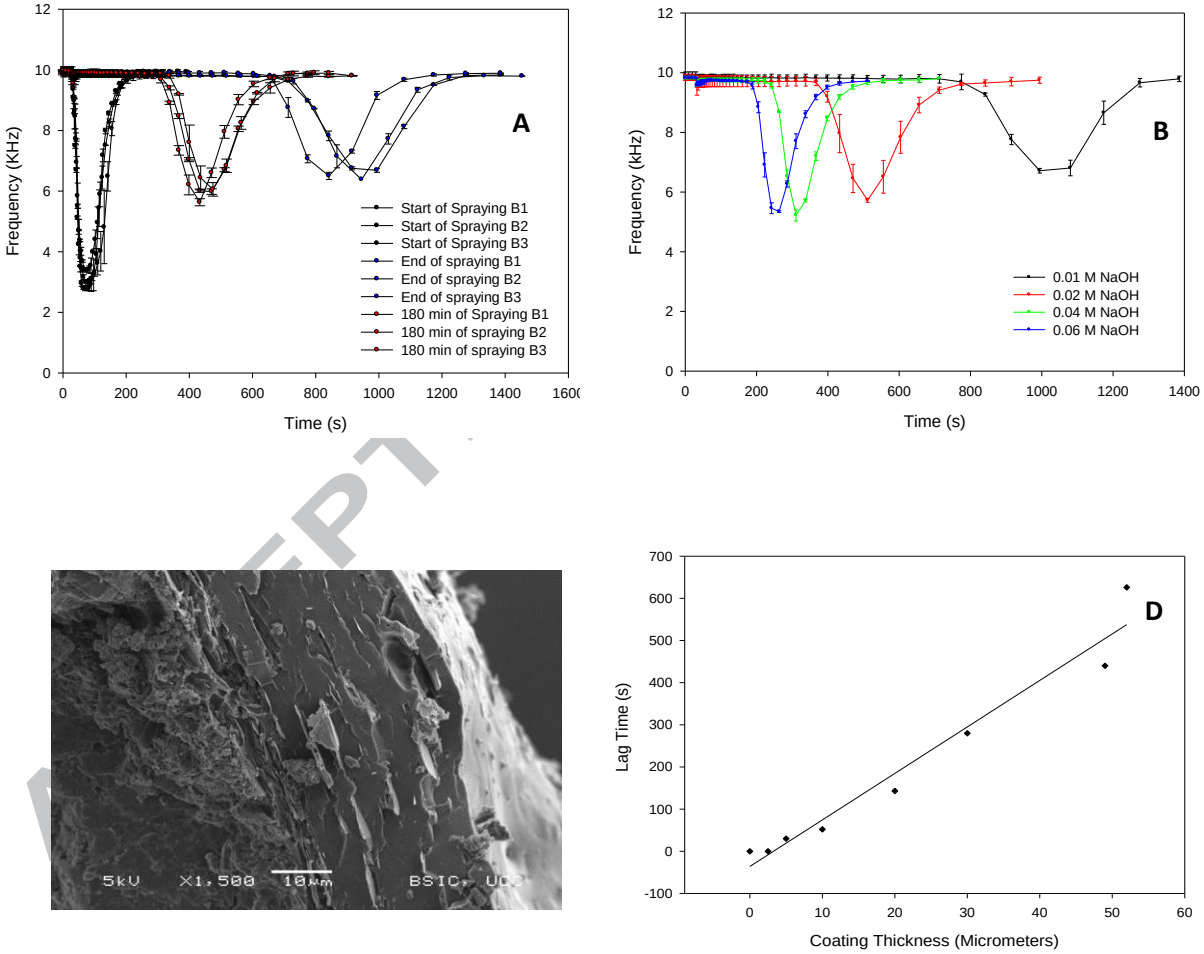
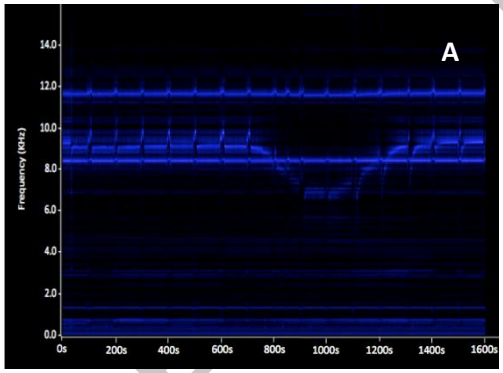
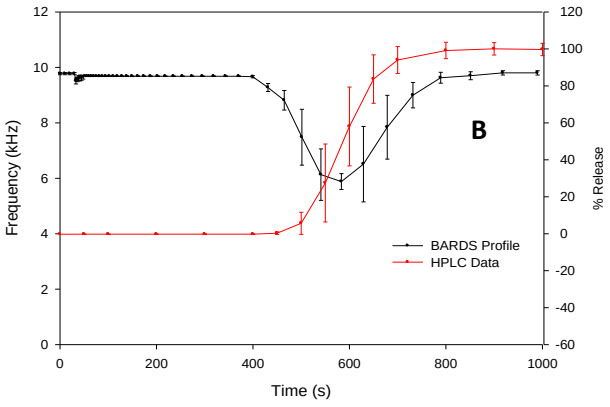


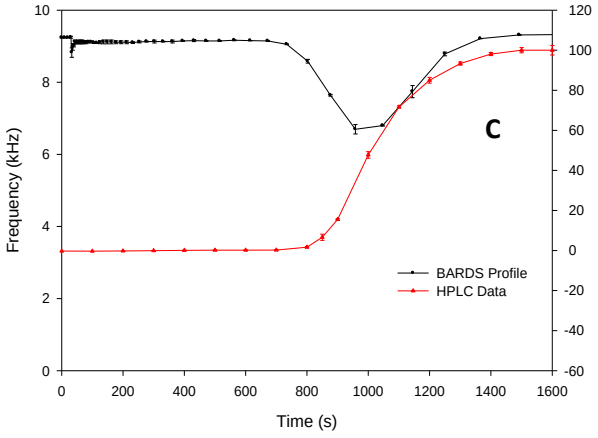
Figure 4: (A) BARDS dissolution data for three individual batches dissolved in 0.01M NaOH, where the pellets were sampled at fixed time points +/- 5 mins during the enteric coating process. (B) The dissolution of fully coated pellets at different NaOH concentrations. (C) SEM Photo of enteric coated

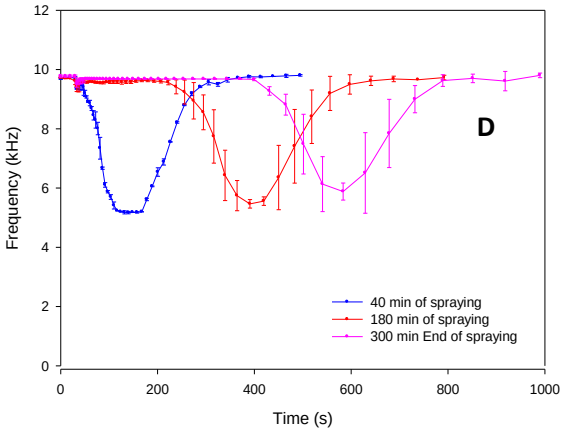
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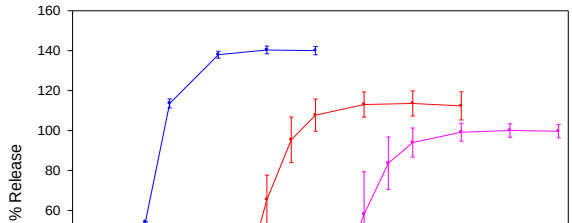
pellets after 3 hours of coating. (D) Enteric coating thickness, as measured by SEM v lag time. An r^2 value of 0.96 is obtained for the regression line.

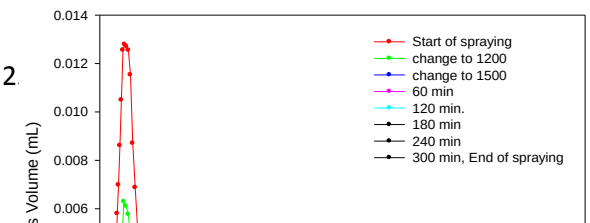












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Figure 5: (A) BARDS spectrogram of the dissolution of 300 mg of fully coated omeprazole in 0.01M NaOH with 2mL sampling taken every 100 seconds. Note the sampling action perturbs the acoustic profile at defined time points (B) BARDS dissolution profile of 300 mg of omeprazole pellets after 5 hours of enteric coating. The dissolution media is (60:40) pH 11 phosphate buffer and methanol with HPLC % release of the same sample also shown. (C) BARDS profile of 300 mg fully coated omeprazole sample dissolved in 0.01 M NaOH dissolution media and also showing the % drug release measure by HPLC. (D) BARDS data for pellets of varying coating thickness dissolved in (60:40) pH 11 phosphate buffer and methanol. (E) HPLC data of the percentage release of omeprazole for the data in (D). The 300 min profile represents the target formulation of 100% release of omeprazole. (F) Gas volume profiles derived from the BARDS data presented in Figure 3(F) using equation 4.

Table 1: Material Inputs into the coating processes.

Material Code	Material Description	Quantity (kg) [Note 4]	
OMT01	Omeprazole Pls Temmler Unlacquered	257.6 ±1%	
ZP606	Pharmacoat 606 (HPMC 6cP)	11.2	Sub-Coat
ZT133	Talcum	11.2	
N/A	Purified water [Note 1]	164 ±5 [Note 3]	
ZE104	Eudragit L30 D-55 [Note 2]	266.7	Enteric-Coat
ZT270	Triethyl Citrate	8.0	
ZT133	Talcum	32.0	
N/A	Purified water [Note 1]	173 ±5	

[Note 1:] Excluding purified water used for flushing of lines

[Note 2]: Expressed as weight of 30% dispersion, solid content approx. 80kg

[Note 3]: The water content of the sub-coating suspension: 88%, but may vary between 80 -90%.

[Note 4]: Overages to compensate for manufacturing losses may be added.

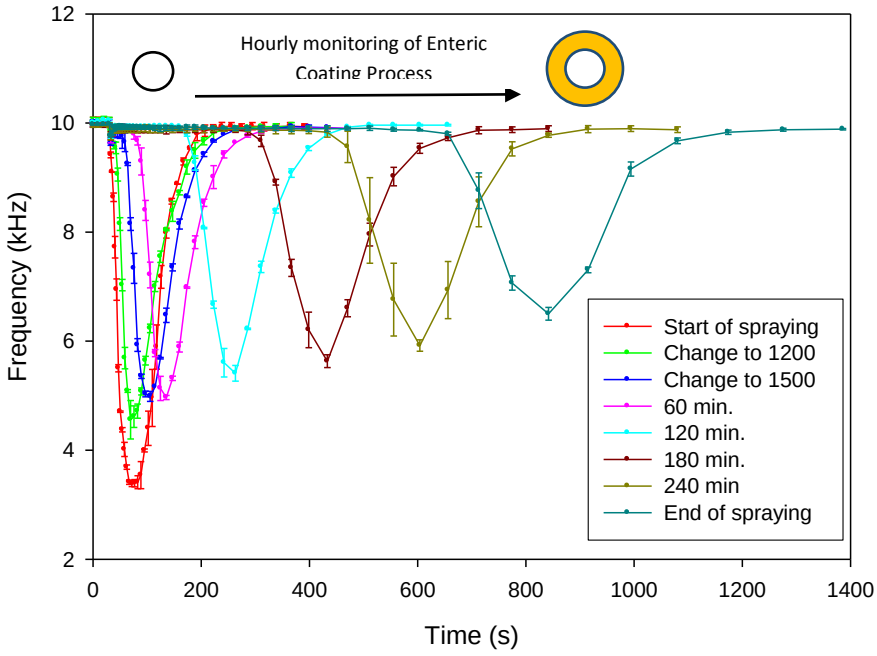
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Table 2: Gradient elution parameters

Time (mins)	% Mobile Phase A	% Mobile Phase B
0	80	20
13	70	30
14	80	20

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