The Sound of Tablets during Coating Erosion, Disintegration, Deaggregation and Dissolution.

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Abstract

This research aims to address a gap in our understanding of the mechanisms by which pharmaceutical tablets achieve highly reproducible and predictable drug release. The present industrial and regulatory practice is centred around tablet dissolution, i.e. what follows disintegration, yet the vast majority of problems that are found in formulation dissolution testing can be traced back to the erratic disintegration behaviour of the medicinal product. It is only due to the distinct lack of quantitative measurement techniques for disintegration analysis that this situation arises. Current methods involve costly, and time-consuming test equipment, resulting in a need for more simple, green and efficient methods which have the potential to enable rapid development and to accelerate routine solid drug formulation dissolution and disintegration testing. In this study, we present a novel approach to track several sequential tablet dissolution processes, including coating erosion, disintegration, deaggregation and dissolution using Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS). BARDS, in combination with minimal usage of UV spectroscopy, can effectively track these processes. The data also show that a solid oral dose formulation has an intrinsic acoustic signature which is specific to the method of manufacture and excipient composition.

1. Introduction

Standard dissolution testing is a familiar, routine and regulatory test for product release for a wide range of formulations. Typical apparatus consists of ~6 stirred dissolution vessels which are sampled periodically either manually or automatically in order for drug concentration to be determined. The apparatus has been standardised and in use by the pharmaceutical industry for decades with little adaptation. The methodology of tablet disintegration and hardness testing are also rudimentary in design and operation. Traditional approaches to characterising tablets include visual observations of disintegration, tablet hardness testing and dissolution testing where the concentration of drug in solution is used to determine an endpoint *via* Ultra Violet-Visible Spectroscopy (UV-Vis) and/or High-Performance Liquid Chromatography (HPLC) measurements. There have been few if any disruptive technologies in this pharmaceutical *physical testing* space for many years, most likely due to regulatory protocols[1] and this is likely to remain the status quo in the long term. However, given the time and expense of standard dissolution testing and associated delays with batch release, there is an onus on the industry to explore faster, greener and more data-rich complimentary dissolution methods to statistically and scientifically support current testing methods.

Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) is one such approach which offers a complimentary and possible surrogate to standard dissolution testing based on the speed of real-time data acquisition and how the data can be extrapolated to match standard regulatory methods. BARDS is based on an acoustic phenomenon first described by A.B. Wood (1930) .[2] It was most notably characterised by Frank S. Crawford in a series of papers published during the early 1980s, giving the phenomenon the title of the 'hot chocolate effect'. [2, 3] Since its discovery, the effect has been intermittently discussed in the literature. [4-9] However, it was not until 2012 that its significance as an investigative tool for the analysis of powders, tablets and compounds, in general, was realised with the development of BARDS. [10, 11]

The underlying principles of BARDS have been reported extensively in the literature summary, a BARDS signal results from reproducible changes in the compressibility of a solvent during the dissolution of a compound. The compressibility change alters the speed of sound, resulting in

frequency changes within the solution. The sound velocity *(v)* in a medium, whether in air or a liquid phase, is determined by eqn (1).

$$v_{(sound)} = \sqrt{\frac{1}{K_p}} \qquad \text{Equation 1}$$

where ρ = mass density in kg/m^3 and K = compressibility, 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 significant increase in compressibility. The net effect is a substantial reduction of the sound velocity in the liquid. The relationship between the fractional bubble volume and sound velocity in water is given in eqn (2).[15]

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

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

$$(v_a)^2 p_a \frac{1}{\gamma\rho} = 1.49 \times 10^4 \qquad \text{Equation 3}$$

where ρ_w = the density of water, γ = the ratio of specific heats for dry air and ρ = the atmospheric air pressure. Eqn (2) is based on the approximation, which was initially presented by A. B. Wood[12]. BARDS analysis of an induced acoustic excitation of the containing vessel is focused on the lowest variable frequency-time course, i.e., the fundamental resonance mode of the liquid. 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 frequency response is described as;

$$freq = \frac{freq_w}{\sqrt{1+1.49x10^4.f_a}} \qquad \text{Equation 4}$$

where $freq_w$ and freq are the resonance frequencies of the fundamental resonance modes in pure and bubble-filled water, respectively. The transient total volume of the gas bubbles is determined by introduced entrained gas bubbles, bubbles evolving due to gas oversaturation, and bubbles disappearing due to elimination at the surface. A detailed and comprehensive outline of the principles and underlying processes involved in BARDS analysis is given by Fitzpatrick *et al.* .[10]

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. As an example, Figure 1 shows a typical BARDS spectrum of the dissolution of sodium carbonate in 25 mL of deionised water. Note the overtones and harmonics also changing above the fundamental curve.

Figure 1

In general, entrained gas, between and within particles, are introduced into the solution, when a compound/sample is wetting and/or dispersing in an aqueous solvent. Also, a reduction in the solubility of gases in solution will take place during dissolution, resulting in gas oversaturation. This oversaturation is partly removed by the generation of gas bubbles where nucleation sites are available. The entrainment and liberation of gas bubbles and their subsequent escape from the solution causes a transient yet reproducible change in the compressibility of the solution which can be monitored acoustically, under standardised conditions.[13]

BARDS is also applied initially in this study to give an indication of tablet coating thickness and consistency. The use of BARDS as an in-process technique to track coating thickness in real-time has been previously reported [13-16]. Current methods of monitoring coating thickness include scanning electron microscopy (SEM)[17] energy dispersive X-ray imaging (EDX), [18] fluorescence microscopy [19], confocal laser scanning microscopy (CLSM) [20], atomic force microscopy (AFM), confocal Raman micro-imaging [21, 22] air-coupled acoustics [23], direct/contact ultrasonic methods[24] and Optical Coherence Tomography (OCT). The ability of terahertz pulsed imaging to analyse coatings have also been reported with the capability to interrogate single drug-containing pellets, yielding quantitative measurements [25].

Pantoprazole is among the top twenty selling drugs in the world under various trade names[26]. It is an over the counter and prescription medication used in the treatment of symptomatic gastro-oesophageal reflux disease, prophylaxis and treatment of gastroduodenal ulcers. It is administered as a racemic mixture of *R*- (+)- pantoprazole and *S*- (–)- pantoprazole[27] with weakly basic and acidic properties. Pantoprazole is one of several approved irreversible proton pump inhibitors (PPIs) which have been used worldwide over the past 25+ years. PPIs suppress

gastric acid secretion through the irreversible inhibition of H^+ /K^+ - ATPase on the cell membranes of gastric parietal cells[28].

Pantoprazole is commercially available as an oral suspension and as enteric-coated tablets[29]. The stability of the drug in aqueous solution is pH-dependent, where the rate of degradation increases with decreasing pH. Pantoprazole is preferably absorbed in the small intestine[30]. Therefore, an enteric coating is utilised in formulations of the drug to prevent drug degradation in the stomach before its systemic absorption.

Functional enteric coatings control the location of drug release within the digestive system from solid oral dosage forms[31]. The most commonly used enteric coating polymer classes are the poly(meth)acrylates known in general as Eudragit®, manufactured by Evonik ®. These polymers are chemically designed to target drug release within the gut depending on the pH environment. Tablets coated with enteric coating polymeric excipients are typically designed to dissolve to allow subsequent drug release in the small intestine which has an enteral alkaline pH of about 7-9. The majority of currently used enteric coating polymers are weak acids (pKa typically ~5) which remain un-dissociated in the low pH environment of the stomach, depending on their pKa, but readily ionise in pH environments above their pKa.[32] The polymer may be applied at very thin coating thicknesses to tablet or pellet surfaces.

The pharmaceutical industry uses enteric coating for a variety of reasons including protecting both the stomach from the drug and the drug from the stomach, allowing the safe release of the drug further along the intestinal tract, protecting acid-liable drugs from gastric fluid and to impart a delayed-release effect to the formulation. It also protects formulations against light and oxidation, thus improving product stability. In this study, most of the tablets under investigation are coated with the 1:1 methacrylic acid-ethyl acrylate anionic copolymer Eudragit® L30 D-55, available commercially as a 30% aqueous dispersion and used to impart enteric protection to the surfaces of solid oral dosage forms.

Several coated pantoprazole-containing branded formulations were procured, which were produced by the same manufacturer (product license holder). These medicinal products were also chosen due to their inclusion of the polymer coating excipient Eudragit L30 D-55. BARDS is employed in experiments throughout this study to demonstrate how the copolymer loading and the processes of disintegration, deaggregation and dissolution can be tracked for tablets produced

by three different companies but sold under six different brand names. The concept of an Erosion, Disintegration, Deaggreation, Dissolution and coating Integrity (EDDDI) Plot to track all these processes is also introduced. BARDS, in combination with minimal usage of UV spectroscopy, can effectively track EDDDI processes of the tablets understudy while also providing a new measure of medicinal product integrity. The data also shows that a solid oral dose formulation has an intrinsic acoustic signature which is specific to the method of manufacture and excipient composition. BARDS represents a possible future surrogate / orthogonal quality control and presumptive test for tablet dissolution mapping and fingerprinting prior to product market release. BARDS data correlate directly with the integrity of formulation enteric coating and also with drug release as validated by UV-Vis spectroscopy.

2. Experimental

2.1 Materials

Sodium hydroxide of analar grade was purchased from Sigma Aldrich and Riedel-de Haën, Lot number STBG9017. Doubly distilled water was used for all experiments. Pantoprazole-containing tablets were purchased from a local pharmacy as outlined in Table 1

Table 1:

2.2 Instrumentation

A BARDS spectrometer acquired from BARDS Acoustic Science Labs (BASL) was used to analyse all samples. The spectrometer consists of a chamber containing a glass dissolution vessel, stir bar, a magnetic stirrer and microphone. There is access at the front for the dissolution vessel and at the top to allow a sample in a weighing boat to be placed on a tipper motor for the introduction of the solute. The resonances of the liquid vessel are recorded in a frequency band of 0-20 kHz. The glass vessel containing 25 mL of 0.06 M aq. sodium hydroxide (NaOH) is placed on the stirrer plate. The stirrer motor is located underneath this plate and allows the stir bar to tap the side of the vessel gently. The stirrer rate is set to 500 rpm. The follower acts as a source of broadband acoustic excitation, thereby inducing various acoustic resonances in the glass, the liquid and the air column above the liquid. The induced acoustic resonances are registered by the microphone and converted to a spectrum using a computer with a sound card and generic software, as seen in Figure 3.

2.3 Experimental Procedure

In a typical experiment, the spectrometer records the steady-state resonances of the system as a reference for 30 seconds (s) once the stirrer is set in motion. The pitch of the resonance modes in the solution change when each pantoprazole-containing tablet under investigation is added, before gradually returning to a steady-state over 3000 s (50 minutes). The frequency-time course of the fundamental resonance is presented, as manually extracted data from the total acoustic response. All experiments were performed in triplicate, and an average reading with error bars

representing the standard deviation is presented. The time courses of the observed acoustic profiles are shown to be reproducible under standardised conditions (constant volume, mass, temperature and stirring rate). The steady-state frequency before the addition of the solute is designated as the ‘volume

Figure 2

3. Results and Discussion

Pantoprazole tablets are commercially available in two typical dosage forms, containing either, 20 mg or 40 mg of active pharmaceutical ingredient (API) (equivalent to 22.6 mg and 45.2 mg pantoprazole sodium sesquihydrate respectively). EDDDI analysis of a variety of formulations from multiple manufacturers (Table 1) was performed and described below.

The analysis of Pantoprazole Mylan (40 mg) tablets was initially undertaken in various concentrations of aq. NaOH in order to investigate the effect of media concentration and pH on the erosion of the coating and the initial lag time in BARDS spectra. The lag time is the duration (in seconds) of the frequency-time course after the addition of the tablet, which remains unchanged as the coating erodes. Once the enteric coating has eroded, the tablet core begins to disintegrate, and there is a significant decrease in frequency due to evolution of entrained gas in the tablet and gas oversaturation of the dissolution medium as API and excipients dissolve. All experiments were carried out in triplicate.

Figure 3

Figure 3 shows the acoustic frequencies of the glass vessel remaining at steady state for all profiles for the first 30 s of the spectra until the addition of the sample. After that, the resonance frequency of all profiles at 9.4 kHz decreases insignificantly to 9.38 kHz after tablet addition due to the extra volume of the tablet, which increases the liquid level and so decreases the final volume line resonance frequency. The lag phase for the green profile (0.06 M aq. NaOH) continues until the enteric coating is eroded after 500 s, indicating a complete loss of the coating from the tablet surface, after which point a frequency minimum (f_{min}) of 8.4 kHz is reached due

to core disintegration. The curve then gradually returns to a steady state after approximately 2000 seconds.

A decreasing concentration of aq. NaOH causes the lag time to increase, i.e. the enteric coating erodes more slowly. Coating erosion is a chemical process due to the interaction of the basic media and the carboxylic acid groups on the polymer. The greater the rate at which the polymer carboxylic acid groups become deprotonated under the influence of base, the more highly ionised (and hydrophilic) the polymer becomes, thereby facilitating its dissolution into the basic medium and loss from the tablet surface. No gas evolution occurs due to this process but gas oversaturation increases. This can be tracked by dissolved oxygen measurement using a DO probe.[23] Once disintegration takes place, the overpressure at the electrode decreases due to the smaller particulates acting as nucleation points for gas to evolve.

Somac Control® and Pantoloc Control® are both manufactured by Takeda but marketed by Takeda and GlaxoSmithKline (GSK), respectively. The solvent used for the EDDDI BARDS analysis of these tablet formulations was 0.01 M aq. The time it takes for the enteric coating to erode is directly related to the hydroxide ion concentration in solution[15]. This relationship can be potentially used as a proxy to predict the erosion time, depending on the pH of the media.

Figure 4

Figure 4 (A) shows the two products, Somac Control® and Pantaloc Control®, producing identical EDDDI BARDS spectra. Both samples are the same formulation and contain the same excipients. Whereas GSK is the marketing authorisation holder in Ireland for the two products, the listed manufacturer of both is Takeda GmbH. An experiment where one or two tablets, of the same brand, were analysed simultaneously in 0.01 M aq. NaOH also yielded similar EDDDI profiles on a per tablet basis, as shown in Figures 4 (B) and (C).

The lag time of the black profile for the single tablet analysis of Pantoloc Control® can be seen in Figure 4 (B) and is approximately the same as that of the two tablet analysis (blue profile). This result mirrors a previous study which shows the lag time is independent of the number of microspheres dissolved in basic solution which have the same coating[14] The f_{min} is lower in the two tablet analysis due to the higher mass of API and excipients present in the dissolution media. However, the disintegration rate of both experiments appears the same as indicated by the

downward slope (~600 s) of the frequency spectra. No return to steady-state is observed for the two tablet experiment as the solution becomes saturated, resulting in a suspension of disintegrated tablet contents. At the endpoint of the single-tablet analysis, there was complete dissolution of the tablet, affording a clear, colourless solution.

The data in Figure 4(C) for Somac Control® 20 mg tablets are also dose-related. Simultaneous disintegration of two tablets occurs at a similar rate to that of a single tablet. The f_{min} value is reached at the same time point (1200 s) irrespective of the number of tablets. However, the f_{min} value is sustained for longer with two tablets due to more disintegration and deaggregation taking place in solution. The lag time does not differ and is 600 s for both analyses.

Figure 5

Pantoprazole Bluefish 20 mg and 40 mg tablet formulations were also comparatively analysed to determine their respective EDDDI profiles by BARDS, as shown in Figure 5(A). Tablets were added after 30 s of initiating the acquisition of acoustic data. The lag time is similar for both the 20 mg and 40 mg tablets indicating the same enteric coating thickness has been applied to both formulations. Figure 5 (B) compares the simultaneous addition of one (black profile), two (red profile) or three (blue profile) 20 mg tablets to the dissolution vessel. The lag time of 270 s indicates that tablet erosion time remains the same irrespective of the tablet number. This observation is also true of enteric-coated microspheres and is only expected as long as the basic solution is not the limiting reagent of the enteric polymer carboxylic acid deprotination.[22] There is no buffer capacity available to maintain this trend with an increasing number of tablets.

Similar trends can be seen in Figure 5 (C) for tablets with a higher content of pantoprazole (Pantoprazole Bluefish 40 mg tablets). The rate of gas evolution, denoted by the negative slopes post-coating erosion, increases with a greater number of tablets due to a greater amount of disintegrant present in solution. This trend is evident for all products tested. However, the standard deviation also increases with a greater tablet number. Three times the amount of coating is eroding in a three tablet experiment. This also has the effect of increasing the oversaturation of gas in solution threefold. The surface area for gas nucleation also increases three-fold in the

presence of three tablets. This allows for the nucleation of the increased gas concentration on surfaces sooner than a single tablet experiment as amplified in Figure 5 (D). This theory is reinforced by the data for a two tablet experiment which forms part of a trend in shorter lag time with increasing tablet number.[15]

Figure 6

Fig 6 (A) shows the analysis of Protium® 20 mg and 40 mg tablets (black and red profiles, respectively). The lag time of both formulations are the same (220 s). A similar assumption can be made to that observed for Pantoprazole Bluefish (Figure 5) – the loading of the functional enteric polymer is the same for both dosage forms. The 20 mg Protium® tablet reaches a minimum acoustic frequency at 542 s, sooner than the 40 mg tablet which reaches the frequency minimum at 662 s; indicating a shorter disintegration time. This may be due to a reduced amount of disintegrant in the 40 mg tablet relative to the amount of API present. There is a prolonged frequency plateau at 8.3 kHz for the 40 mg tablet evident in Figure 7A and is likely a result of the gas evolution rate being in equilibrium with the rate of gas loss at the surface, indicating a longer disintegration period of 600 s. The return to baseline steady state is not achieved for either tablet due to insoluble excipients retaining gas and oversaturation of the solution, and is more evident for the 40 mg tablet.

Fig 6 (B) compares the spectrum of the two Takeda-manufactured formulations analysed – Protium® 20 mg and Somac Control® 20 mg tablets. The lag times are approximately the same for both formulations, indicating little or no difference in polymer thickness. Their f_{min} also differ statistically. However, a difference of ~300 Hz relates to a very small difference in the gas volume produced by the two formulations.

Figure 7

Figure 7 (A) compares the BARDS spectra of all four 20 mg pantoprazole formulations under investigation. Pantoprazole Bluefish 20 mg (black profile) has the longest lag time, indicating the thickest polymer loading of all four formulations. In general, the lag time is the same for the other three formulations made by Takeda. The Bluefish tablet exhibits a slower disintegration rate but faster deaggregation as it returns to steady-state by 1250 s. The other three profiles for the Takeda-manufactured products (red, green and blue profiles) are very similar apart from the

frequency minima (f_{min}) value. The small differences in this value may be interpreted as inter-batch variability.

In comparison, the acoustic profiles of 40 mg pantoprazole-containing tablets from three different manufacturers are concurrently shown in Figure 7 (B). Their lag times, frequency minima and return to steady-state times are significantly different for all three formulations. Pantoprazole Mylan 40 mg tablets (black profile) have the thickest enteric coating as indicated by the longest lag time of 336 seconds. Protium® 40 mg (red profile) has the thinnest enteric coating corresponding with the shortest coating erosion time. Meanwhile, Pantoprazole Bluefish 40 mg tablets (blue profile) exhibited the fastest rate of disintegration and also the lowest f_{min} of the 40 mg formulations studied.

Note Pantaloc 20 mg (Figure 7 A, green profile) and Protium® 40 mg (Figure 7 B, red profile) both display a plateau at the f_{min}. The plateau represents an equilibrium between the rate of gas evolution in solution and the rate of loss at the surface according to Henry's law and does not represent a frequency cut-off.

BARDS can be used to track the individual processes associated with dissolution. BARDS spectra of enteric-coated tablet and microsphere drug formulations may be mapped using an Erosion, Disintegration, Deaggreation, Dissolution and coating Integrity (EDDDI) Plot. These plots can also be used to track the dissolution of tablet formulations in general. Figure 8 shows an EDDDI plot for the Bluefish 20 mg formulation. The red profile represents the UV-Vis analysis during the BARDS experiment. The UV-Vis profile measures the concentration of dissolved pantoprazole released from the tablet.

Figure 8

Sample addition occurs at 30 s post start of acoustic data acquisition. The initial decrease in the fundamental curve is due to entrained gas in the outer functional tablet polymer coating, followed by a subsequent return to a depressed frequency plateau (lagtime) during the erosion of the polymer. Note there is no pantoprazole released during the lag time (the first 300 s) as demonstrated by the UV-Vis data (red profile). Once the coating erodes, and the inner tablet core disintegrates, there is an immediate increase in the concentration of API in solution as indicated by the downward slope of the BARDS spectra. The $f_{\min}$ indicates an approximate end of

disintegration with ~ 50 % pantoprazole release correlated by the UV-Vis data. The end of the disintegration process is followed by continuing deaggregation of tablet components to release the remainder of the API. The frequency profile is gradually returning to steady-state in the BARDS spectrum during the deaggregation phase. Technically, the dissolution bracket seen in the EDDDI plot could also encompass the erosion process but has been used to cover the disintegration and deaggregation steps only to reflect API release.

Figure 7

In Figure 9 (A) the f_{min} of a Bluefish 20 mg tablet correlates with ~ 50 % pantoprazole release. This is also exhibited in Fig 10 (B-E). However, the Pantoprazole Mylan 40 mg tablet EDDDI plot (F) shows a pantoprazole percentage release of 100% at the $f_{min,}$ indicating a more rapid release of the drug. This leads to the hypothesis that the API of this formulation may be located in the outer section of the tablet and less so in the tablet core, i.e. the concentration of pantoprazole is greater away from the core. For the remaining formulations (A – E), deaggregation of tablet particles allows remaining pantoprazole to be released over a more extended time period relative to Pantoprazole Mylan.

5. Conclusion

In summary, BARDS analysis of tablets is of significant benefit for determining coating integrity, tablet disintegration,break-up and indicating drug release. A single BARDS measurement can provide data relevant to dissolution processesall data requirements in a time-efficient manner. BARDS measurements have been cross-validated usingby the conventional technique UV-Vis Spectrometry, allowing for the plotting of the method of trackingcorrelation of all dissolution processes intoknow as an EDDDI plot. BARDS data has shown a correlation between the lag time for the erosion of the tablet coatings with the basicity of the solvent used. Similarities between different brands but made by the same manufacturer, were apparent when tested using BARDS, e.g., Somac and Pantaloc which are both made by Takeda. The erosion time was found to be independent of the number of tablets dissolved for small tablets with a small surface area. However, a slight reduction in the erosion time was noted for multiple tablets with a relatively larger surface area due to conditions favouring greater gas nucleation (Figure 5

C). A different BARDS response is evident when a different formulation is used for pantoprazole, as shown in Figure 6 (B) even though the same manufacturer makes the tablets. Figure 7 shows that BARDS can qualitatively discriminate between pantoprazole formulations.

The data represents a potential new regulatory method for the quality assurance of tablet formulations and product performance. It is therefore highly relevant to the topical discussion surrounding the quality of medicines and specifically what constitutes so-called 'critical quality attributes'.

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

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Figure(s)

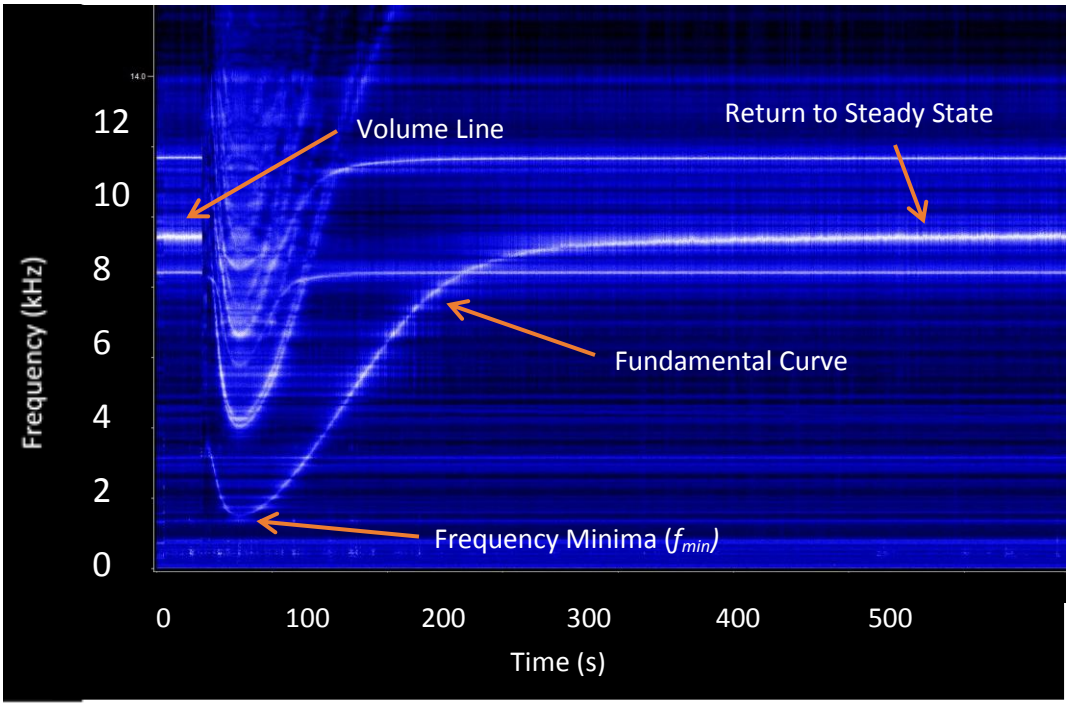


Figure 1: BARDS spectrum of the dissolution of Sodium Carbonate in 25 mL of Deionised water. Note the sample addition at the 30 s time point.

Figure 2 (A) Top view schematic diagram representing the contents of the dissolution chamber. (B) Top view photograph of the BARDS dissolution chamber. (C) External view of the instrument. (D) Tipper motor with a tablet sample of pantoprazole in a weighing boat ready for addition to the stirred solution below.

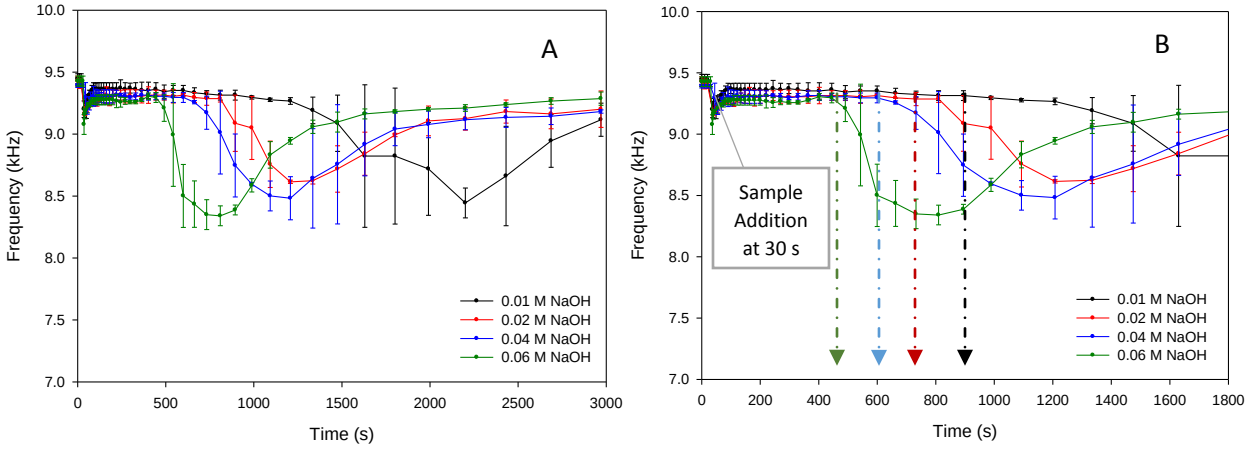


Figure 3 (A) BARDS analysis of a Pantoprazole Mylan 40 mg tablet in various concentrations of aq. NaOH (B) Labelled and the adjusted x-axis of BARDS spectra Pantoprazole Mylan 40 mg tablet in various concentrations of aq. NaOH. The vertical lines indicate the end of the lag time for each concentration of NaOH. The black vertical line represents the time point of sample addition on the spectra (30 seconds)

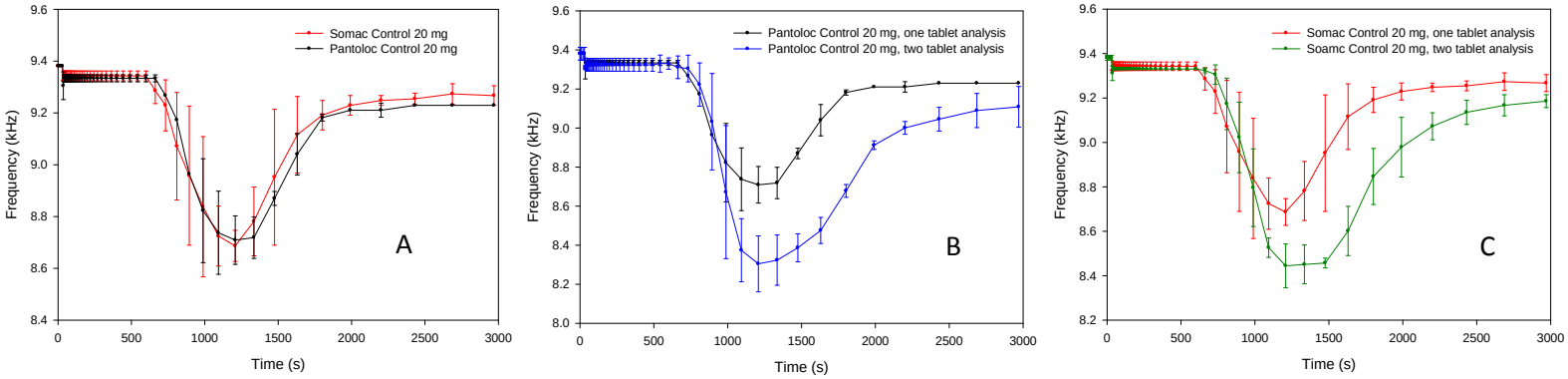


Figure 4 (A) BARDS analysis of Somac Control® (red) and Pantoloc Control® (black) 20 mg tablets in 0.01 M aq. NaOH, (B) BARDS multi-tablet analysis of Pantoloc Control® 20 mg tablets in 0.01 M aq. NaOH (one tablet – black; two tablets – blue) (C) BARDS multi-tablet analysis of Somac Control® 20 mg tablets in 0.01 aq. M NaOH (one tablet – red; two tablets – green).

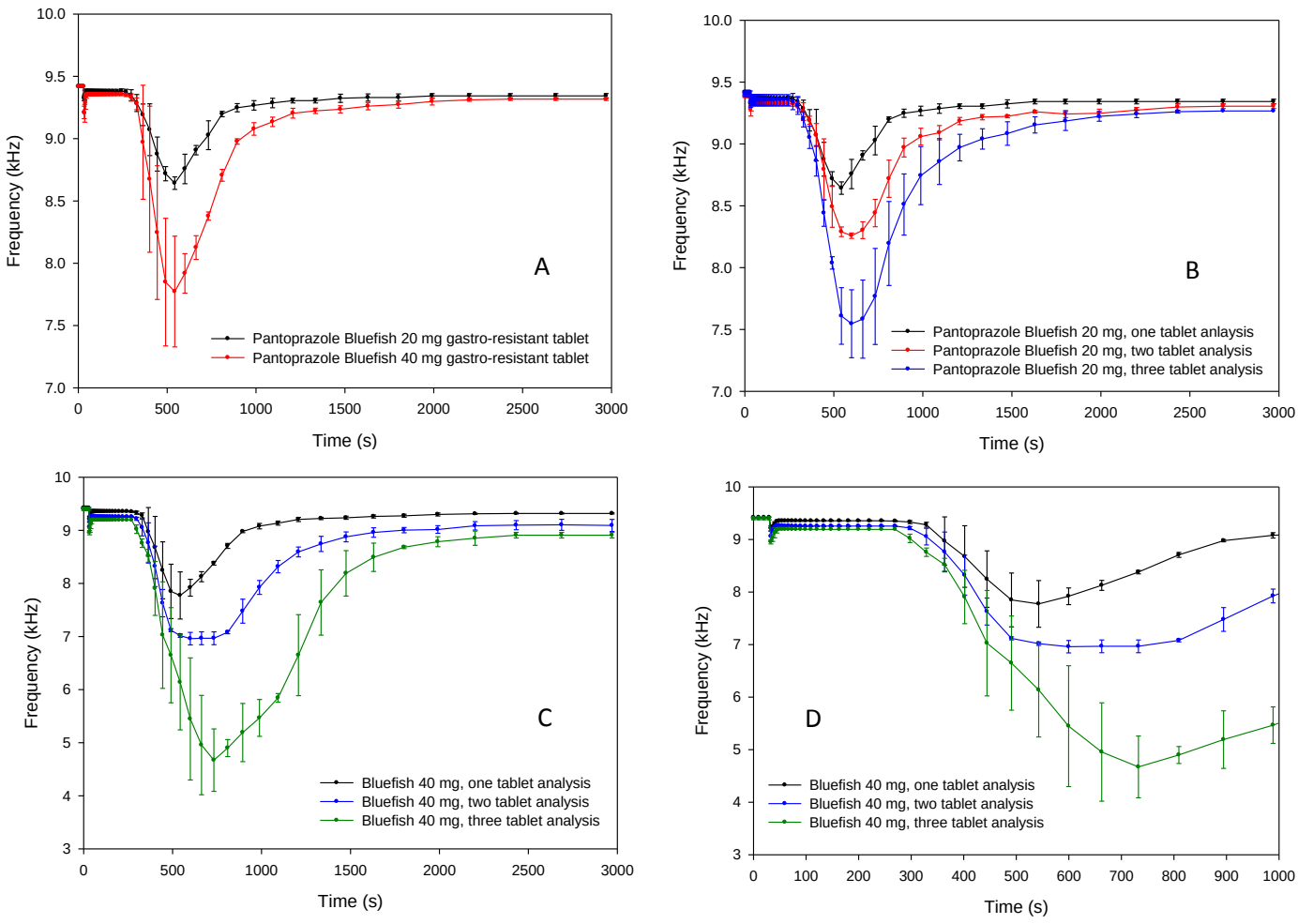


Figure 5 (A) BARDS EDDDI analysis of Pantoprazole Bluefish 20 mg (black) and 40 mg (red) tablet formulations in 0.06 M aq. NaOH (B) BARDS multi-tablet analysis of Pantoprazole Bluefish 20 mg tablets in 0.06 M aq. NaOH (C) BARDS multi-tablet analysis of Pantoprazole Bluefish 40 mg tablets in 0.06 M aq. NaOH (D) BARDS analysis of Pantoprazole Bluefish 40 mg tablets in 0.06 M aq. NaOH indicating the differences in the lag time for the multi-tablet analysis.

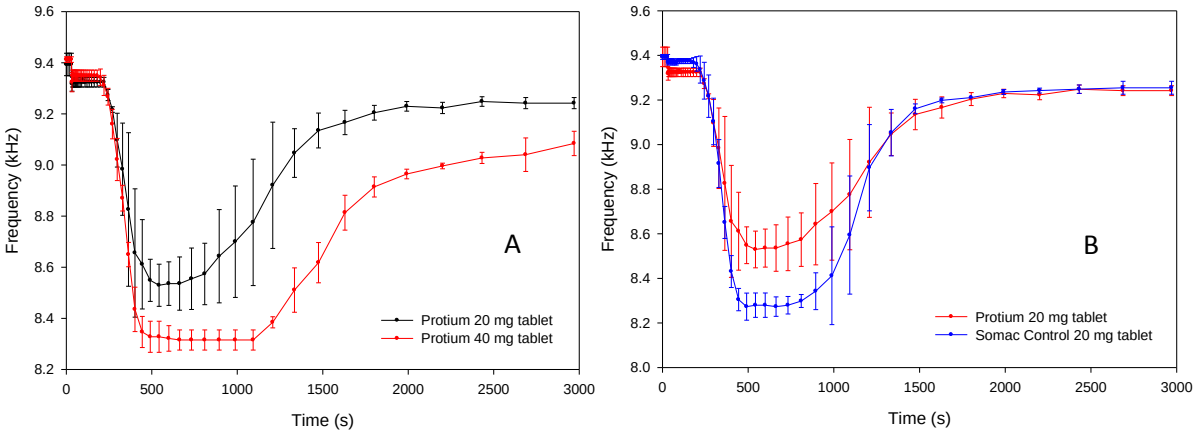


Figure 6 (A) BARDS EDDDI acoustic spectra of Protium® 20 mg (black) and 40 mg (red) gastro-resistant tablets in 25 mL of 0.06 aq M NaOH (B) BARDS acoustic spectra of Takeda-manufactured products, Protium® 20 mg (red) and Somac Control® 20 mg (blue) tablet analysis in 0.06 M aq. NaOH.

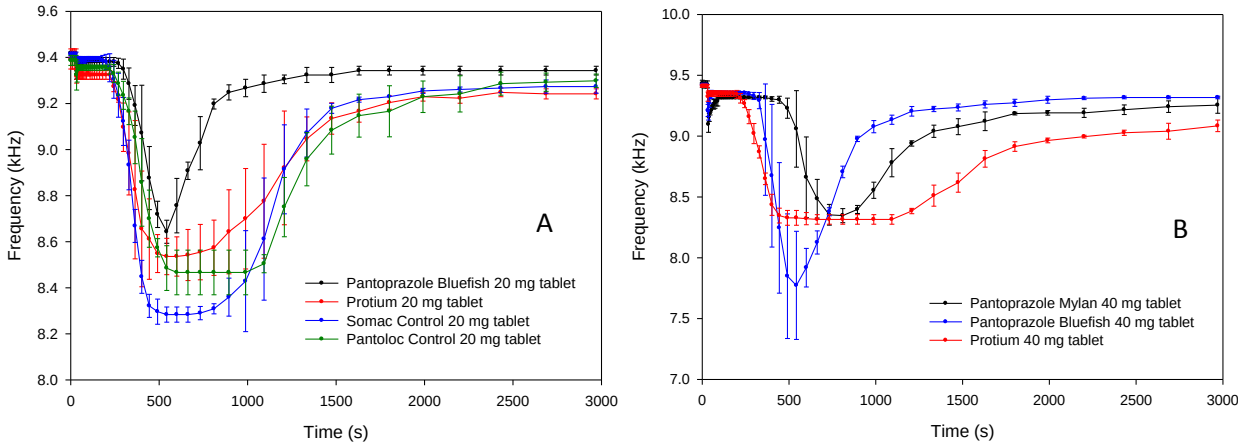


Figure 7 BARDS spectra of a selection of (A) 20 mg and (B) 40 mg pantoprazole-containing enteric-coated tablet formulations in 25 mL of 0.06 M aq. NaOH. Note that the NaOH concentration is different from Figure 5(A).

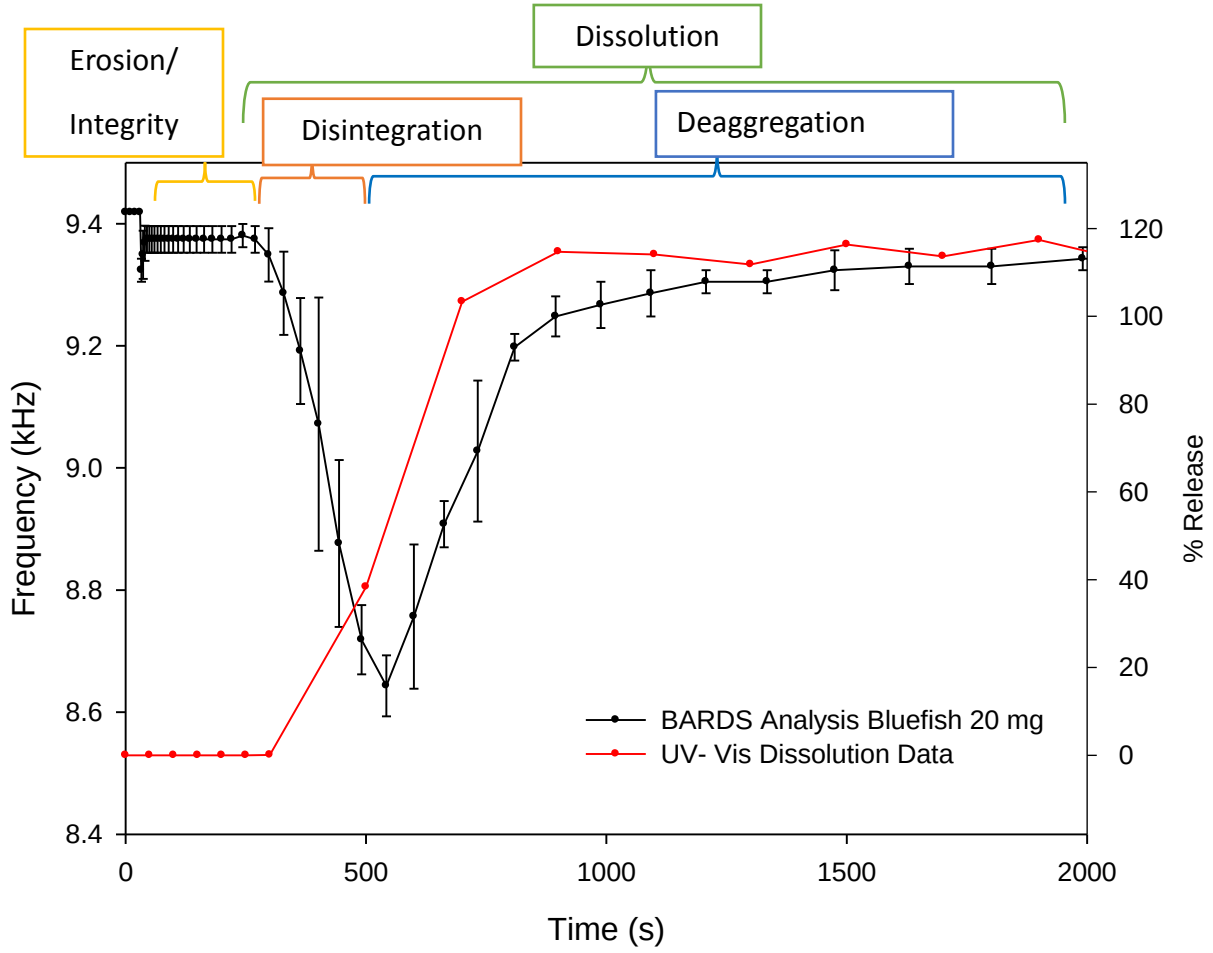
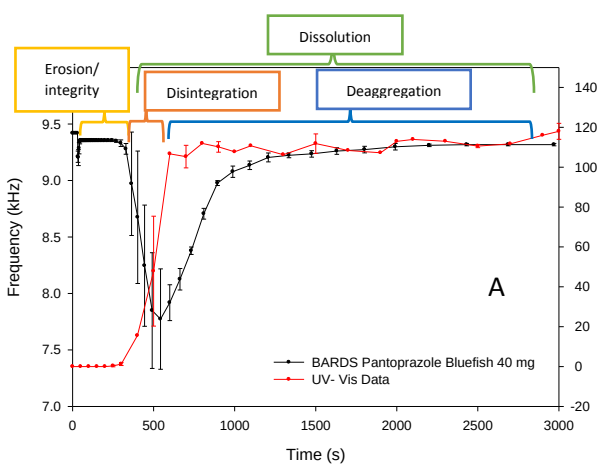
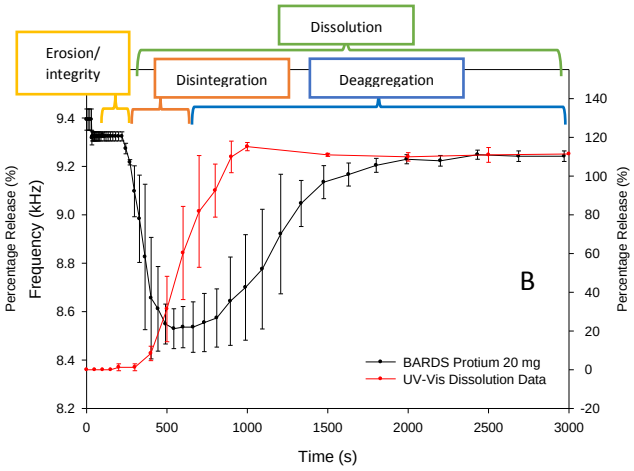
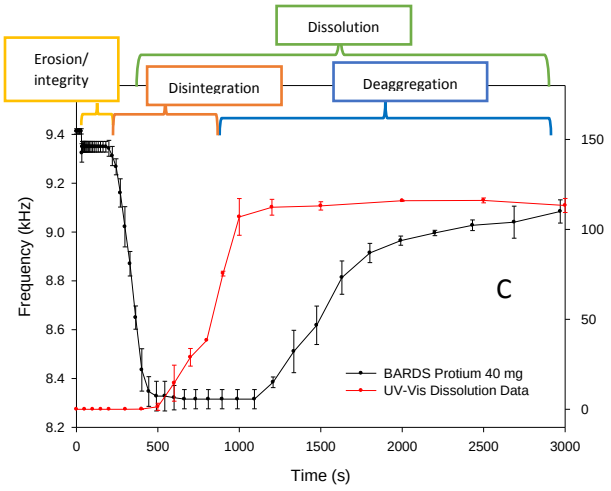
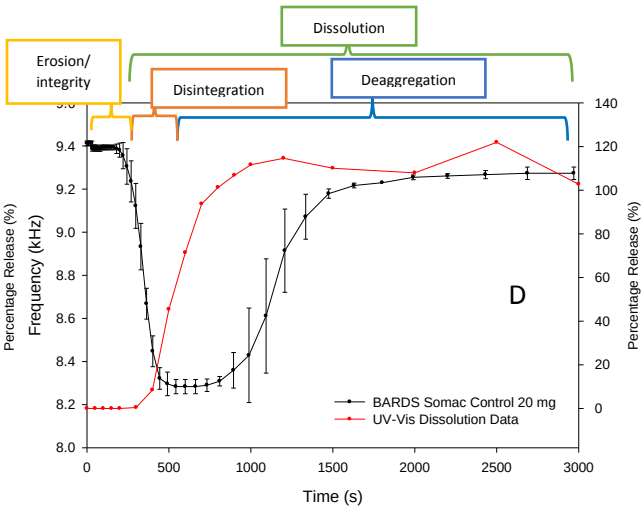


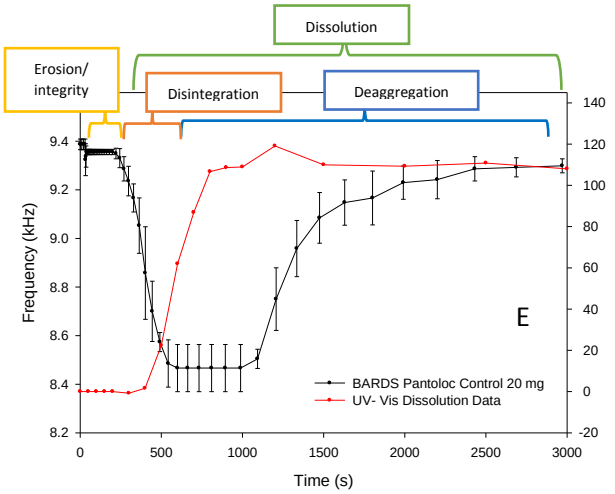
Figure 8 EDDDI plot (black profile) of the dissolution of a Bluefish pantoprazole 20 mg tablet in 25 mL of 0.06M aq. NaOH. Note: the red profile represents the UV-Vis analysis of the tablet, showing the percentage release of API during the BARDS analysis.


Dissolution
Erosion/ integrity
Disintegration
Deaggregation
A
BARDS Pantoprazole Bluefish 40 mg
UV- Vis Data
Frequency (kHz)
Percentage Release (%)
Time (s)


Dissolution
Erosion/ integrity
Disintegration
Deaggregation
B
BARDS Protium 20 mg
UV-Vis Dissolution Data
Frequency (kHz)
Percentage Release (%)
Time (s)


Dissolution
Erosion/ integrity
Disintegration
Deaggregation
C
BARDS Protium 40 mg
UV-Vis Dissolution Data
Frequency (kHz)
Percentage Release (%)
Time (s)


Dissolution
Erosion/ integrity
Disintegration
Deaggregation
D
BARDS Somac Control 20 mg
UV-Vis Dissolution Data
Frequency (kHz)
Percentage Release (%)
Time (s)


Dissolution
Erosion/ integrity
Disintegration
Deaggregation
E
BARDS Pantoloc Control 20 mg
UV- Vis Dissolution Data
Frequency (kHz)
Percentage Release (%)
Time (s)

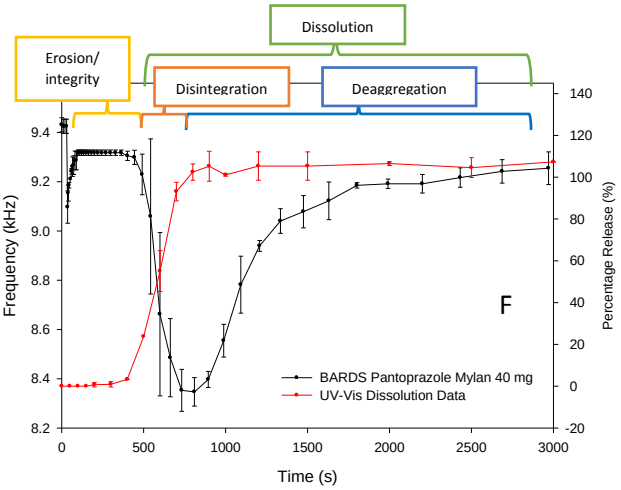

Dissolution
Erosion/ integrity
Disintegration
Deaggregation
F
BARDS Pantoprazole Mylan 40 mg
UV-Vis Dissolution Data
Frequency (kHz)
Percentage Release (%)
Time (s)

Figure 9 EDDDI plots of Bluefish 20 mg (A), Protium® 20 mg (B), Protium® 40 mg (C), Somac Control® 20 mg (D), Pantaloc® 20 mg (E) and Mylan 20 mg (F) pantoprazole tablets . All samples were dissolved in 25 mL of 0.06M aq. NaOH. All BARDS measurements are in triplicate. The red profiles represent the UV-Vis data measured in duplicate.

Table(s)

Table 1: Pantoprazole-containing tablets under investigation.

Name	**Dosage**	**Manufacturer**	**Licensed by**	**Batch Number**	**Expiration Date**
Somac® Control	20 mg	Takeda	Takeda	402042	10/2020
Pantoloc® Control	20 mg	Takeda	GlaxoSmithKline	11518723	04/2021
Pantoprazole Mylan	40 mg	Gerard Laboratories	Gerard Laboratories	8075526	03/2021
Protium®	20 mg	Takeda	Takeda	08291	01/2021
Protium®	40 mg	Takeda	Takeda	08518	01/2021
Pantoprazole Bluefish	20 mg	Bluefish Pharmaceuticals	Bluefish	418678	05/2021
Pantoprazole Bluefish	40 mg	Bluefish Pharmaceuticals	Bluefish	428400	08/2021

***Conflict of Interest**

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Drs. Seán McSweeney and Dara Fitzpatrick are directors of BARDS Acoustic Science Labs.

***Credit Author Statement**

Niamh O'Mahoney is a graduate student working under the supervision of Dara Fitzpatrick and carried out the majority of experiments using BARDS. Niamh also helped in drafting the manuscript and generation of Figures and Tables.

John J Keating is a lecturer in Pharmacy and was involved in the conceptual discussions and experimental design of the research. He was involved in reviewing the manuscript and making significant improvements.

Seán McSweeney is responsible for the development of the hardware and software of BARDS and it's optimization.

Sam Hill is a student at the David Jack Centre for R&D as a visiting undergraduate from Aston University, UK as part of the GSK Summer Work Experience. Sam worked on BARDS and EDDDI plots during his placement and applied the rationale to rapid disintegration tablets.

Simon Lawrence worked on formulation studies at GSK which fed into this BARDS study. Simon supervised Sam on associated BARDS projects in GSK, Ware, UK.

Dara Fitzpatrick is the originator of BARDS and supervises Niamh and was centrally involved in the development of the study and co-authoring the paper.