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

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11 Abstract

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

27 1. Introduction

28

29 Standard dissolution testing is a familiar, routine and regulatory test for product release for a
30 wide range of formulations. Typical apparatus consists of ~6 stirred dissolution vessels which are
31 sampled periodically either manually or automatically in order for drug concentration to be
32 determined. The apparatus has been standardised and in use by the pharmaceutical industry for
33 decades with little adaptation. The methodology of tablet disintegration and hardness testing are
34 also rudimentary in design and operation. Traditional approaches to characterising tablets include
35 visual observations of disintegration, tablet hardness testing and dissolution testing where the
36 concentration of drug in solution is used to determine an endpoint *via* Ultra Violet-Visible
37 Spectroscopy (UV-Vis) and/or High-Performance Liquid Chromatography (HPLC)
38 measurements. There have been few if any disruptive technologies in this pharmaceutical
39 *physical testing* space for many years, most likely due to regulatory protocols¹ and this is likely
40 to remain the status quo in the long term. However, given the time and expense of standard
41 dissolution testing and associated delays with batch release, there is an onus on the industry to
42 explore faster, greener and more data-rich complimentary dissolution methods to statistically and
43 scientifically support current testing methods.

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

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

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

$$58 \quad v_{(sound)} = \sqrt{\frac{1}{K\rho}} \quad \text{Equation 1}$$

59 where ρ = mass density in kg/m^3 and K = compressibility, the inverse of the bulk modulus, of
60 the medium. Generation of micro gas bubbles in a liquid decreases the density in a negligible
61 way in comparison to the significant increase in compressibility. The net effect is a substantial
62 reduction of the sound velocity in the liquid. The relationship between the fractional bubble
63 volume and sound velocity in water is given in eqn (2).¹⁵

$$64 \quad \frac{v_w}{v} = \sqrt{(1 + 1.49 \times 10^4 f_a)} \quad \text{Equation 2}$$

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

$$68 \quad (v_a)^2 p_a \frac{1}{\gamma\rho} = 1.49 \times 10^4 \quad \text{Equation 3}$$

69 where ρ_w = the density of water, γ = the ratio of specific heats for dry air and p = the atmospheric
70 air pressure. Eqn (2) is based on the approximation, which was initially presented by A. B.
71 Wood¹². BARDS analysis of an induced acoustic excitation of the containing vessel is focused
72 on the lowest variable frequency-time course, i.e., the fundamental resonance mode of the liquid.
73 The fundamental resonant frequency is determined by the sound velocity in the liquid and the
74 approximate but fixed height of the liquid level, which corresponds to one-quarter of its
75 wavelength. The frequency response is described as;

$$76 \quad freq = \frac{freq_w}{\sqrt{1+1.49 \times 10^4 \cdot f_a}} \quad \text{Equation 4}$$

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

82 The acoustic profile of interest is called the fundamental curve. The frequency minimum (f_{\min})
83 represents an equilibrium between the rate of formation of gas in solution and the rate of gas
84 liberation at the surface. In BARDS analysis, the fundamental curve is used to make comparisons
85 between individual experiments. As an example, Figure 1 shows a typical BARDS spectrum of
86 the dissolution of sodium carbonate in 25 mL of deionised water. Note the overtones and
87 harmonics also changing above the fundamental curve.

88 *Figure 1*

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

96 BARDS is also applied initially in this study to give an indication of tablet coating thickness and
97 consistency. The use of BARDS as an in-process technique to track coating thickness in real-
98 time has been previously reported¹³⁻¹⁶. Current methods of monitoring coating thickness include
99 scanning electron microscopy (SEM)¹⁷ energy dispersive X-ray imaging (EDX),¹⁸ fluorescence
100 microscopy¹⁹, confocal laser scanning microscopy (CLSM)²⁰, atomic force microscopy (AFM),
101 confocal Raman micro-imaging^{21,22} air-coupled acoustics²³, direct/contact ultrasonic methods²⁴
102 and Optical Coherence Tomography (OCT). The ability of terahertz pulsed imaging to analyse
103 coatings have also been reported with the capability to interrogate single drug-containing pellets,
104 yielding quantitative measurements²⁵.

105 Pantoprazole is among the top twenty selling drugs in the world under various trade names²⁶. It
106 is an over the counter and prescription medication used in the treatment of symptomatic gastro-
107 oesophageal reflux disease, prophylaxis and treatment of gastroduodenal ulcers. It is
108 administered as a racemic mixture of *R*- (+)- pantoprazole and *S*- (-)- pantoprazole²⁷ with
109 weakly basic and acidic properties. Pantoprazole is one of several approved irreversible proton
110 pump inhibitors (PPIs) which have been used worldwide over the past 25+ years. PPIs suppress

111 gastric acid secretion through the irreversible inhibition of H^+ /K^+ - ATPase on the cell
112 membranes of gastric parietal cells²⁸.

113 Pantoprazole is commercially available as an oral suspension and as enteric-coated tablets²⁹. The
114 stability of the drug in aqueous solution is pH-dependent, where the rate of degradation increases
115 with decreasing pH. Pantoprazole is preferably absorbed in the small intestine³⁰. Therefore, an
116 enteric coating is utilised in formulations of the drug to prevent drug degradation in the stomach
117 before its systemic absorption.

118 Functional enteric coatings control the location of drug release within the digestive system from
119 solid oral dosage forms³¹. The most commonly used enteric coating polymer classes are the
120 poly(meth)acrylates known in general as Eudragit®, manufactured by Evonik®. These polymers
121 are chemically designed to target drug release within the gut depending on the pH environment.
122 Tablets coated with enteric coating polymeric excipients are typically designed to dissolve to
123 allow subsequent drug release in the small intestine which has an enteral alkaline pH of about 7-
124 9. The majority of currently used enteric coating polymers are weak acids (pKa typically ~5)
125 which remain un-dissociated in the low pH environment of the stomach, depending on their pKa,
126 but readily ionise in pH environments above their pKa.³² The polymer may be applied at very
127 thin coating thicknesses to tablet or pellet surfaces.

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

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

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

151

152 2. Experimental

153 2.1 Materials

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

157 Table 1:

158 2.2 Instrumentation

159

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

172

173 2.3 Experimental Procedure

174

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

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

185 *Figure 2*

186

187 3. Results and Discussion

188 Pantoprazole tablets are commercially available in two typical dosage forms, containing either,
189 20 mg or 40 mg of active pharmaceutical ingredient (API) (equivalent to 22.6 mg and 45.2 mg
190 pantoprazole sodium sesquihydrate respectively). EDDDI analysis of a variety of formulations
191 from multiple manufacturers (Table 1) was performed and described below.

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

200 *Figure 3*

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

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

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

219 Somac Control® and Pantoloc Control® are both manufactured by Takeda but marketed by
220 Takeda and GlaxoSmithKline (GSK), respectively. The solvent used for the EDDDI BARDS
221 analysis of these tablet formulations was 0.01 M aq. The time it takes for the enteric coating to
222 erode is directly related to the hydroxide ion concentration in solution¹⁵. This relationship can be
223 potentially used as a proxy to predict the erosion time, depending on the pH of the media.

224 *Figure 4*

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

231 The lag time of the black profile for the single tablet analysis of Pantoloc Control® can be seen
232 in Figure 4 (B) and is approximately the same as that of the two tablet analysis (blue profile).
233 This result mirrors a previous study which shows the lag time is independent of the number of
234 microspheres dissolved in basic solution which have the same coating¹⁴ The f_{\min} is lower in the
235 two tablet analysis due to the higher mass of API and excipients present in the dissolution media.
236 However, the disintegration rate of both experiments appears the same as indicated by the

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

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

246

247 *Figure 5*

248

249 Pantoprazole Bluefish 20 mg and 40 mg tablet formulations were also comparatively analysed to
250 determine their respective EDDDI profiles by BARDS, as shown in Figure 5(A). Tablets were
251 added after 30 s of initiating the acquisition of acoustic data. The lag time is similar for both the
252 20 mg and 40 mg tablets indicating the same enteric coating thickness has been applied to both
253 formulations. Figure 5 (B) compares the simultaneous addition of one (black profile), two (red
254 profile) or three (blue profile) 20 mg tablets to the dissolution vessel. The lag time of 270 s
255 indicates that tablet erosion time remains the same irrespective of the tablet number. This
256 observation is also true of enteric-coated microspheres and is only expected as long as the basic
257 solution is not the limiting reagent of the enteric polymer carboxylic acid deprotonation.²² There
258 is no buffer capacity available to maintain this trend with an increasing number of tablets.

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

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

270

271

Figure 6

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

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

289

Figure 7

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

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

298 In comparison, the acoustic profiles of 40 mg pantoprazole-containing tablets from three
299 different manufacturers are concurrently shown in Figure 7 (B). Their lag times, frequency
300 minima and return to steady-state times are significantly different for all three formulations.
301 Pantoprazole Mylan 40 mg tablets (black profile) have the thickest enteric coating as indicated
302 by the longest lag time of 336 seconds. Protium® 40 mg (red profile) has the thinnest enteric
303 coating corresponding with the shortest coating erosion time. Meanwhile, Pantoprazole Bluefish
304 40 mg tablets (blue profile) exhibited the fastest rate of disintegration and also the lowest f_{min} of
305 the 40 mg formulations studied.

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

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

317 *Figure 8*

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

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

331 *Figure 7*

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

340

341 5. Conclusion

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

354 C). A different BARDS response is evident when a different formulation is used for
355 pantoprazole, as shown in Figure 6 (B) even though the same manufacturer makes the tablets.
356 Figure 7 shows that BARDS can qualitatively discriminate between pantoprazole formulations.
357 The data represents a potential new regulatory method for the quality assurance of tablet
358 formulations and product performance. It is therefore highly relevant to the topical discussion
359 surrounding the quality of medicines and specifically what constitutes so-called ‘critical quality
360 attributes’.

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363 [Disclosure](#)

364 Both Seán McSweeney and Dara Fitzpatrick are directors of the spin-out company BARDS
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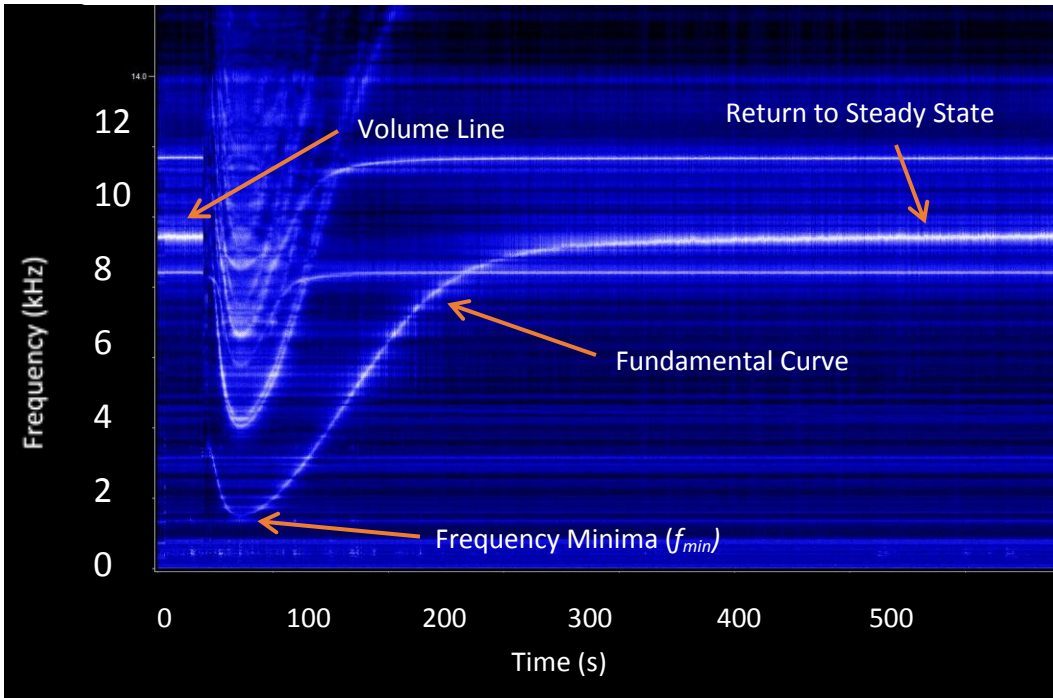


Figure 1: BARDS spectrum of the dissolution of Sodium Carbonate in 25 mL of Deionised water. Note the sample addition at the 30 s time point.

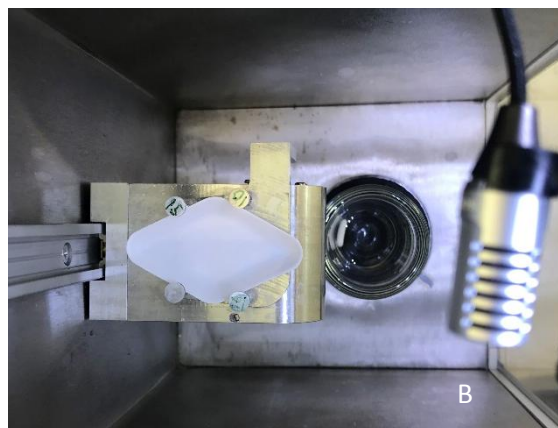
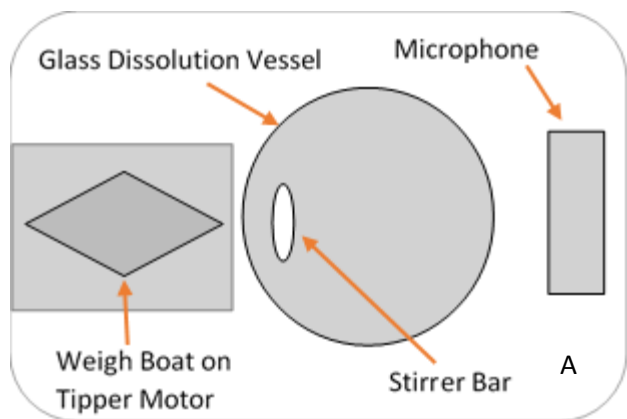


Figure 2 (A) Top view schematic diagram representing the contents of the dissolution chamber. (B) Top view photograph of the BARDS dissolution chamber. (C) External view of the instrument. (D) Tipper motor with a tablet sample of pantoprazole in a weighing boat ready for addition to the stirred solution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

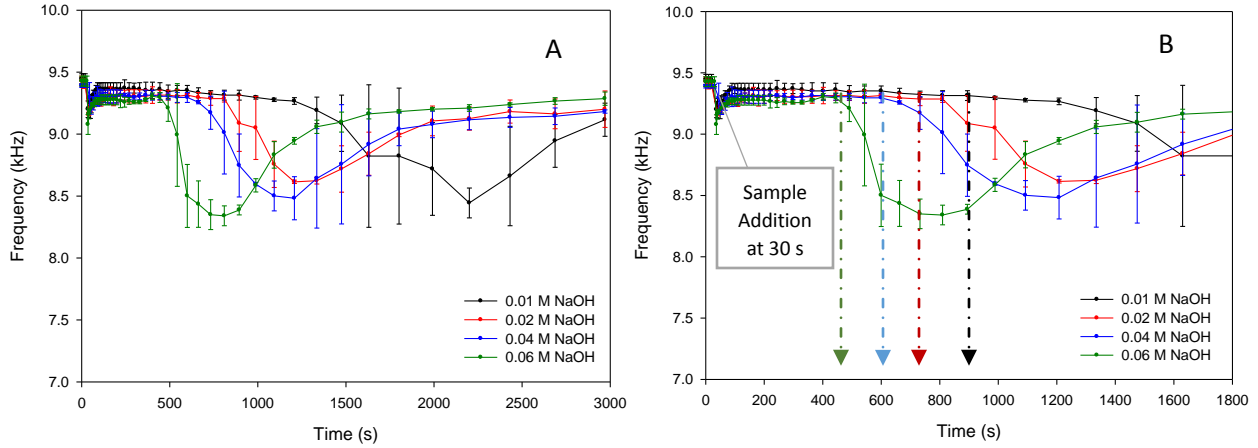


Figure 3 (A) BARDS analysis of a Pantoprazole Mylan 40 mg tablet in various concentrations of aq. NaOH (B) Labelled and the adjusted x-axis of BARDS spectra Pantoprazole Mylan 40 mg tablet in various concentrations of aq. NaOH. The vertical lines indicate the end of the lag time for each concentration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

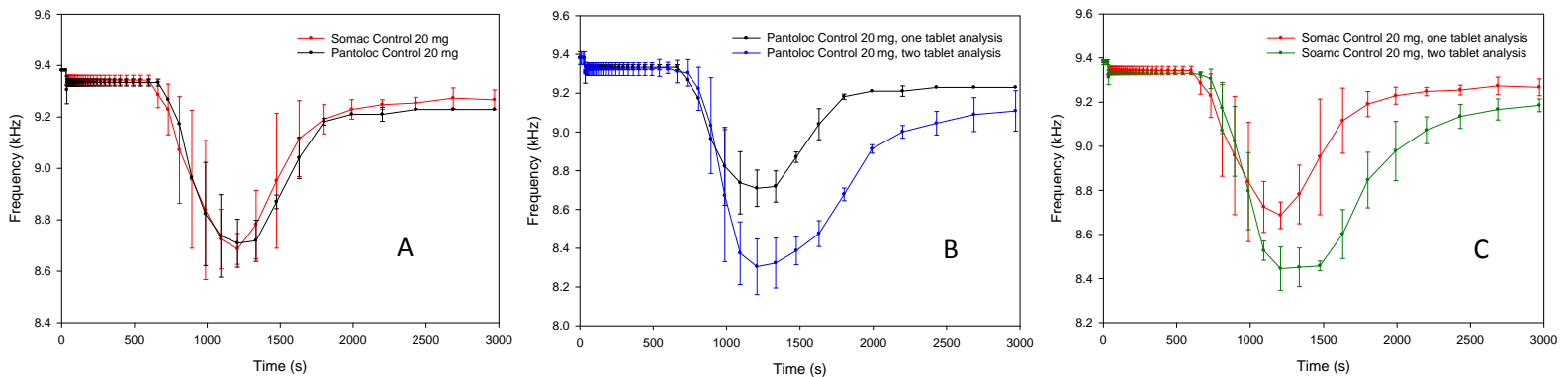


Figure 4 (A) BARDS analysis of Somac Control® (red) and Pantoloc Control® (black) 20 mg tablets in 0.01 M aq. NaOH, (B) BARDS multi-tablet analysis of Pantoloc Control® 20 mg tablets in 0.01 M aq. NaOH (one tablet – black; two tablets – blue) (C) BARDS multi-tablet analysis of Somac Control® 20 mg tablets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

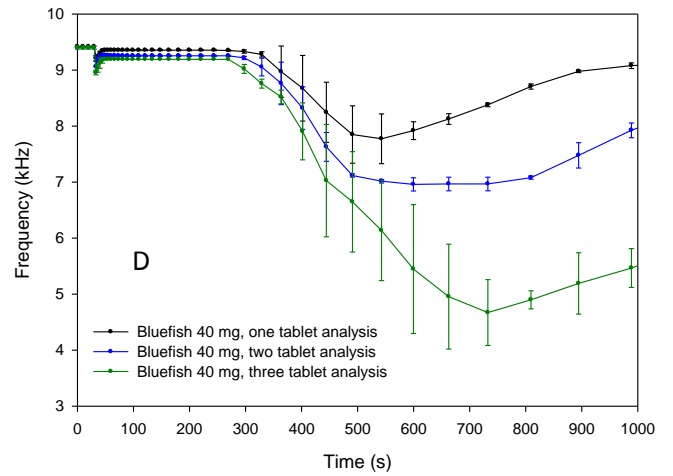
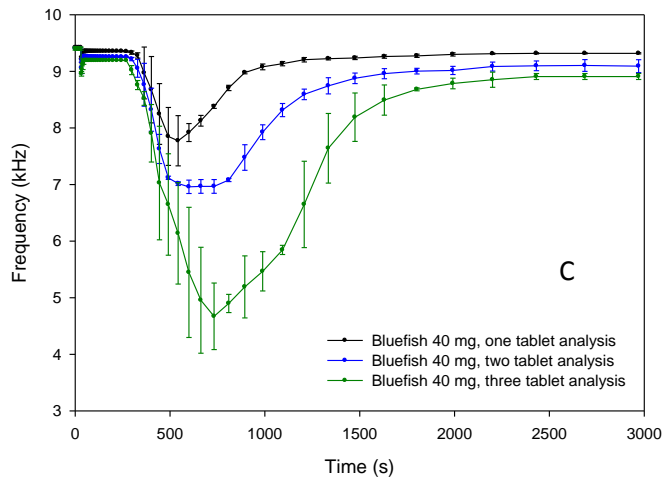
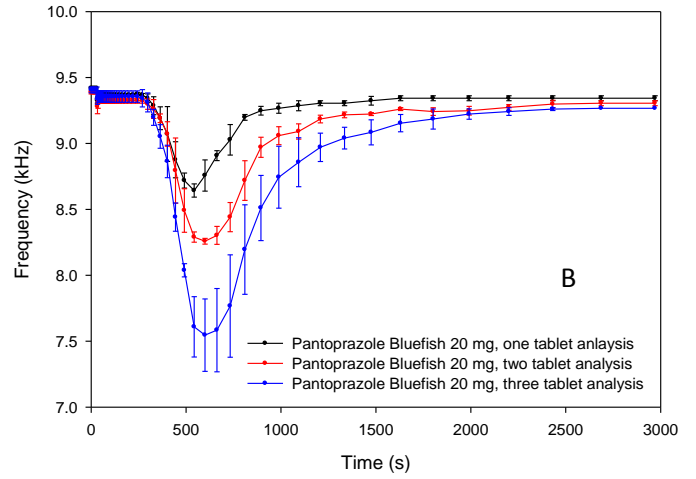
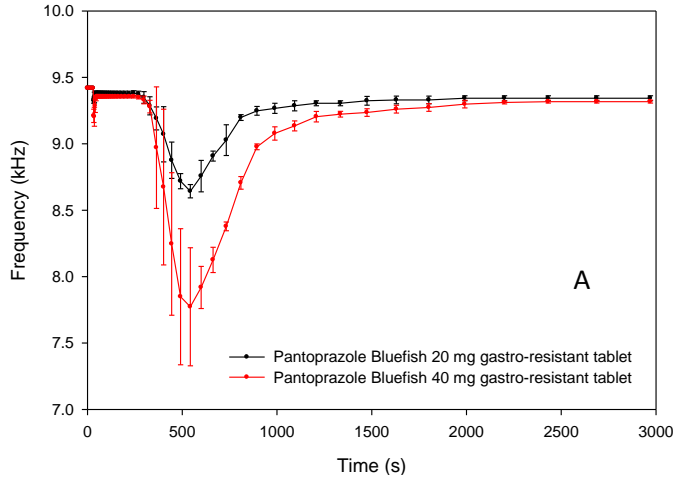


Figure 5 (A) BARDs EDDDI analysis of Pantoprazole Bluefish 20 mg (black) and 40 mg (red) tablet formulations in 0.06 M aq. NaOH (B) BARDs multi-tablet analysis of Pantoprazole Bluefish 20 mg tablets in 0.06 M aq. NaOH (C) BARDs multi-tablet analysis of Pantoprazole Bluefish 40 mg tablets in 0.06 M aq. 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.

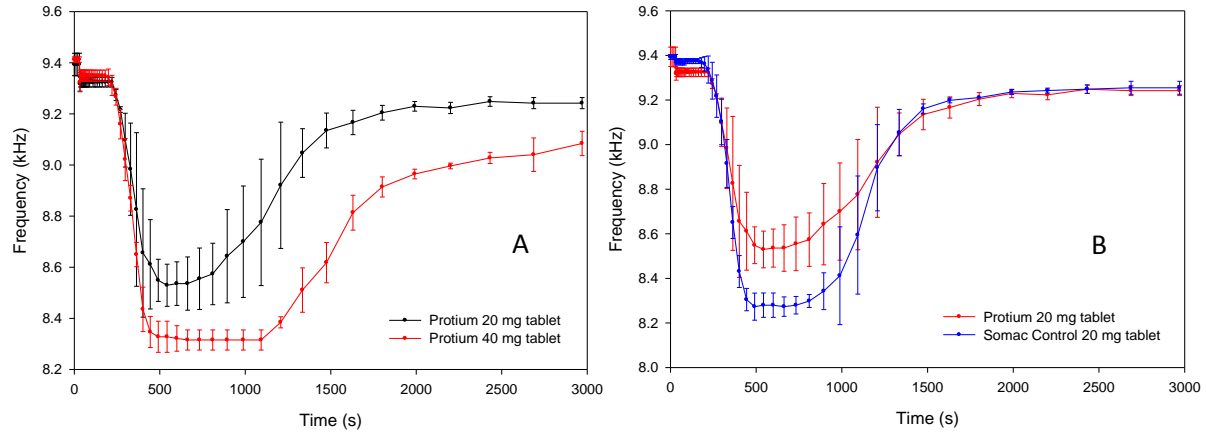


Figure 6 (A) BARDs EDDDI acoustic spectra of Protium® 20 mg (black) and 40 mg (red) gastro-resistant tablets in 25 mL of 0.06 aq M NaOH (B) BARDs acoustic spectra of Takeda-manufactured products, Protium® 20 mg (red) and Somac Control® 20 mg (blue) tablet analysis in 0.06 M aq. NaOH.

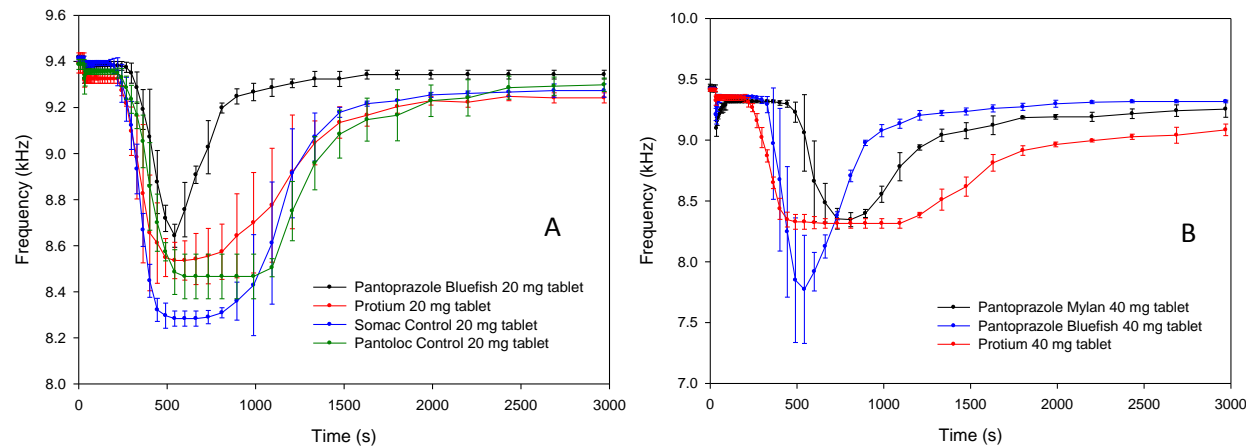


Figure 7 BARDs spectra of a selection of (A) 20 mg and (B) 40 mg pantoprazole-containing enteric-coated tablet formulations in 25 mL of 0.06 M aq. NaOH. Note that the NaOH concentration is different from Figure 5(A).

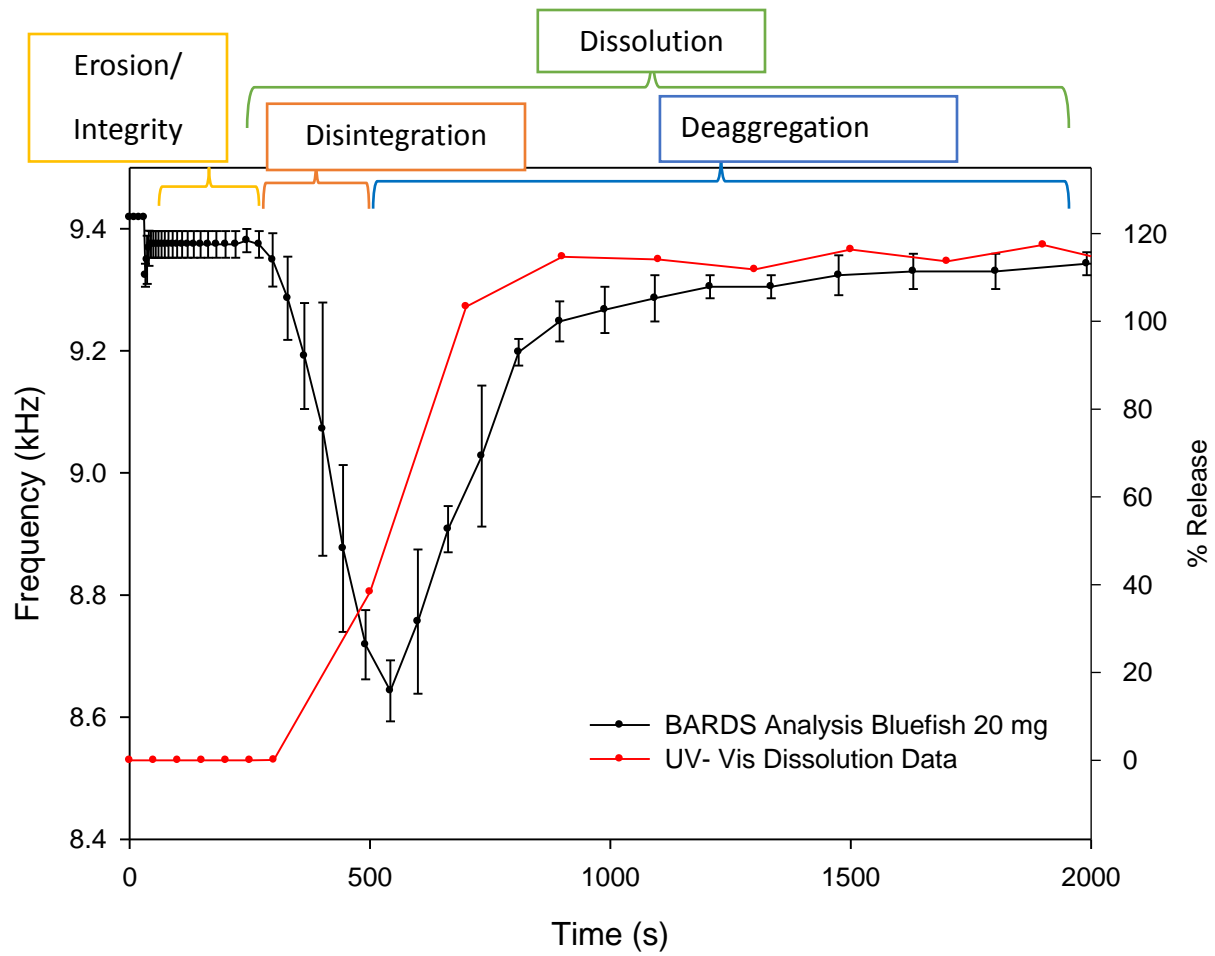


Figure 8 EDDDI plot (black profile) of the dissolution of a Bluefish pantoprazole 20 mg tablet in 25 mL of 0.06M aq. NaOH. Note: the red profile represents the UV-Vis analysis of the tablet, showing the percentage release of API during the BARDS analysis.

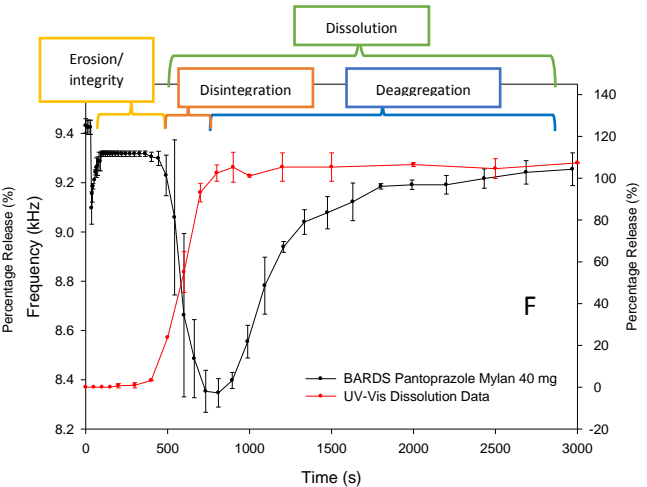
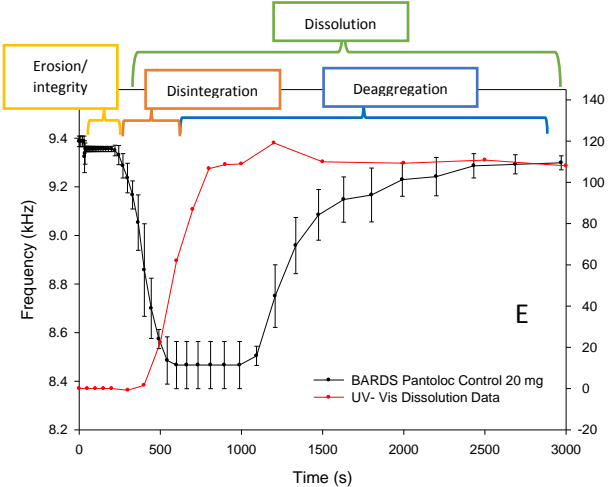
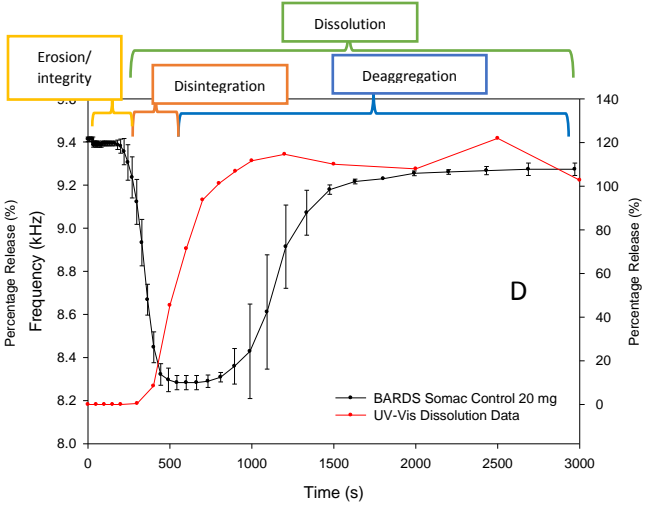
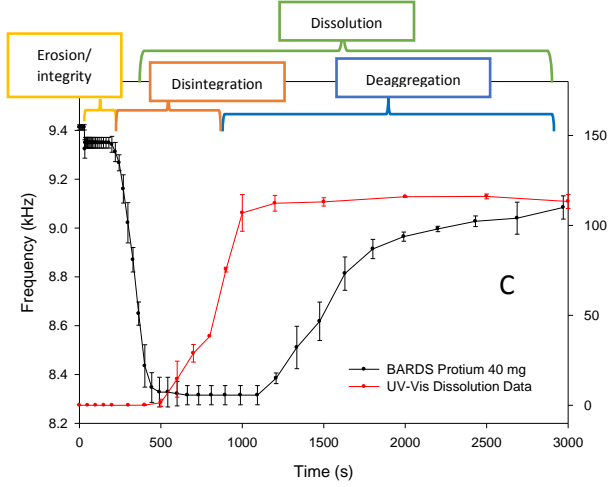
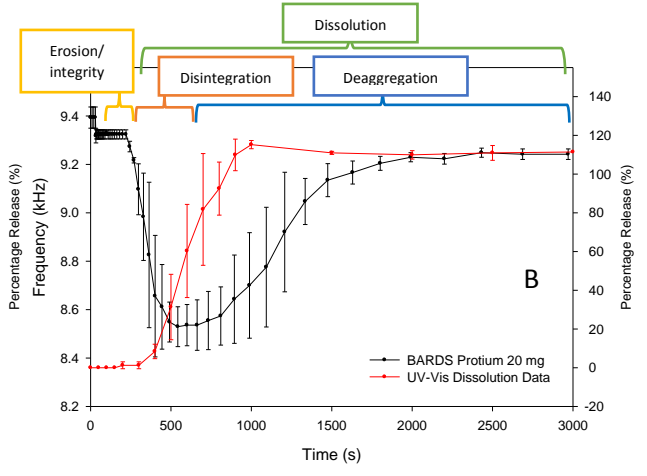
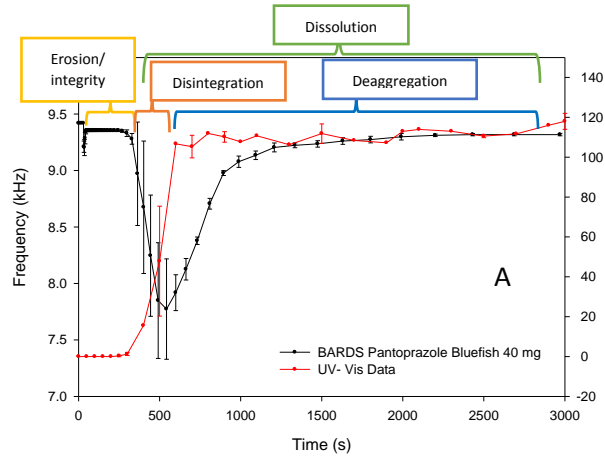


Figure 9 EDDDI plots of Bluefish 20 mg (A), Protium® 20 mg (B), Protium® 40 mg (C), Somac Control® 20 mg (D), Pantoloc® 20 mg (E) and Mylan 20 mg (F) pantoprazole tablets . All samples were dissolved in 25 mL of 0.06M aq. NaOH. All BARDS measurements are in triplicate. The red profiles represent the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

Table 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

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.

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.