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Rapid Profiling of Enteric Coated Drug Delivery Spheres via Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS)

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There is an increased trend towards the use of drug and enteric coated sugar spheres for controlled oral delivery of active pharmaceutical ingredients (API). This trend is driven by increased efficacy and ease of formulation of different dosage levels. However, difficulties exist in determining the thickness of drug and enteric coatings in a time efficient manner during manufacture, quality assurance and stability testing. The thickness of the coating determines the dosage of the API and the thickness of the enteric coating determines the release rate of the drug in the gastro-intestinal tract.

Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) offers a rapid new approach to characterising the enteric coating thickness and the raw materials used in their manufacture. BARDS applications are based on reproducible changes in the compressibility of a solvent during dissolution which is monitored acoustically due to associated changes in the speed of sound in solution. It is demonstrated how core delivery sugar spheres have unique acoustic spectra attributable to the mean size distribution of the spheres. A steady state acoustic lag time is associated with the disintegration of the enteric coating, in basic solution. This lag time can be manipulated by varying the concentration of the base which affects the rate at which the coating dissolves. It is anticipated that the thickness / loading of the spheres can be estimated from the lag time.

1 Introduction

Enteric coatings are used to control the release of acid labile APIs by protecting the drug dosage against the acidic conditions in the stomach, allowing both sustained release and targeted delivery to the small intestine.[1] Many enteric coated formulations employ the use of core sugar spheres which are layered with API and enteric coating as shown in Figure 1.

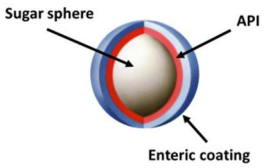

Figure 1: Schematic diagram showing layers of a coated drug delivery sphere.[2]

The enteric coated spheres are contained in a capsule which dissolves at low pH in the stomach allowing the spheres to be released. The spheres continue to travel intact to the duodenum where the enteric coating disintegrates at the higher pH releasing the drug.

There is an increased trend towards the use of drug and enteric coated sugar spheres for controlled oral delivery. This trend is driven by increased efficacy and ease of formulation of different dosage levels. However, difficulties exist in determining the thickness of drug and enteric coatings in a time efficient manner during manufacture, quality assurance and stability testing. The thickness of the coating determines the dosage of the API and the thickness of the enteric coating determines the release rate of the drug in the gastro-intestinal tract. Determining coating thickness and therefore API content for these pharmaceutical dosage forms and can take up to 24 hours to complete.[3] The dissolution testing of these formulations can also be problematic when the potency / toxicity of the API is high.[4] There are three commonly used types of enteric coatings, namely, polymethacrylates, cellulose esters and polyvinyl derivatives. In this study, a prescribed drug

product Lanzol is investigated which contains enteric coated drug delivery spheres. The API lansoprozole is prescribed as a proton pump inhibitor which is used to supress the production of gastric acids in peptic ulcers and acid reflux diseases. The drug coated spheres are coated with a methacrylic acid - ethyl acrylate copolymer (Eudragit®) before encapsulation.

BARDS analysis is a new approach used to monitor the unique acoustic signature profiles of the core spheres and the coated product, as it dissolves. The BARDS signal results from reproducible changes in the compressibility of a solvent during the dissolution of a compound. This alters the speed of sound resulting in frequency changes within the solution.

The principles underlying the BARDS response are as follows. The sound velocity (v) in a medium whether air or liquid phase is determined by Equation 1.

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

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 liquid. The following relationship between the fractional bubble volume and the sound velocity in water was derived by Frank S. Crawford as given in equation 2.[5]

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

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:

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

Where ρ_w = the density of water, γ = the ratio of specific heats for dry air and p = the atmospheric air pressure. Equation 2 is based on the approximation presented originally by A.B. Wood.[6]

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;

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

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 or reabsorption of the gas. A detailed and comprehensive outline of the principles and underlying processes involved in BARDS analysis is given by Fitzpatrick *et al*.[7]

Figure 2 shows a BARDS spectrum of the dissolution of core sugar spheres (710-850 um). 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 liberation of gas from the surface of the solvent. 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 spheres. Thereafter, the resonant frequency at 14.5 kHz decrease to 12 kHz and gradually returns to steady state after ~200 s. The constant frequency at 11 kHz is just one of many resonant frequencies of the vessel that is not depending on the liquid compressibility and therefore remains unchanged.

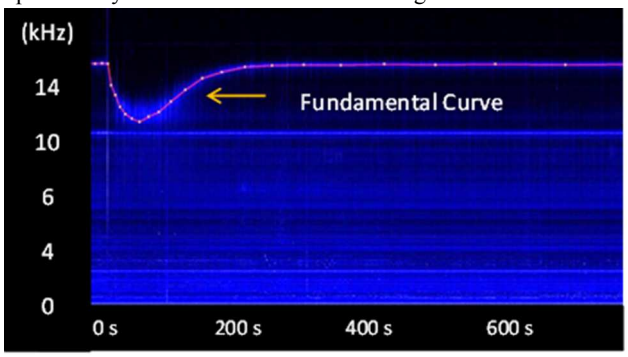

Figure 2: BARDS Spectrum of the dissolution of 0.3 g of sugar spheres (710-850 um) dissolved in 25 mL 0.01 M NaOH.

2 Experimental

2.1 Materials

Sodium Hydroxide of analar grade and was purchased from Sigma Aldrich and Riedel-de Haen.

Sugar spheres (suglets) of varying size distributions were obtained from Colorcon. The size distributions obtained were 500-600 µm, 600-710 µm, 710-850 µm and 1180-1400 µm. Lanzol product was obtained from a local pharmacy and is manufactured by Rowa Pharmaceuticals, Bantry, County Cork, Ireland. Doubly distilled water was used for the preparation of all solutions used in experiments.

2.2 Instrumentation

A custom prototype spectrometer was built and used to investigate the BARDS responses.[8,9] It consists of a chamber with a glass tumbler, microphone (Sony ECM-CS10, range 100 Hz – 16 kHz), a magnetic stirrer and follower. There is access at the front for the dissolution vessel and at the top in order to place a sample in a weighing boat on a tipper motor for introduction of the solute. The microphone is positioned above the top of the

glass within the housing. The glass, containing 25 mL of water is placed on the stirrer plate. The stirrer motor underneath is positioned so as to allow the magnetic follower to gently tap the inner glass wall. In this way, 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 audio is sampled at a rate of 44.1 kHz. A fast fourier transform is applied to the signal. The resulting spectra are then buffered to form a non-overlapping spectrogram of the BARDS response. The resonances of the liquid vessel are recorded in a frequency band of 0-20 kHz.

2.3 Experimental Procedure

In a typical 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 change significantly, when the solute is added, before gradually returning to steady state over several minutes. The amounts added are expressed by mass in all figures. Gas oversaturation of solutions was removed through agitation by shaking vigorously for 60 seconds and then resting for 10 minutes.

The frequency time course of the fundamental resonance is presented, as manually extracted data from the total acoustic response. There is also an auto-extraction facility within the software. Spectra were recorded for 300-800 seconds. All experiments were performed in triplicate and an average reading with error bars representing the standard deviation are presented. The time courses of the observed acoustic profiles are shown to be highly reproducible under standardised conditions (constant volume, mass, temperature and stirring rate).

The steady state frequency before addition of the solute is designated as the 'volume line', so called as it varies depending on the liquid volume in the vessel.

3 Results and Discussion

In general, when a compound is dissolved in aqueous solvent, there is an introduction of entrained gases between and within particles. Also, a reduction in the solubility of gases in solution will take place, resulting in gas oversaturation. This gas oversaturation may partly be removed by generation of gas bubbles in the solution. 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.

Initial characterisation of the core delivery spheres (Suglets) was carried out by obtaining acoustic profiles for each size distribution with varying sample mass. Figure 3(A), 3(B) and 3(C) show acoustic profiles for spheres in the size range 500-600 µm, 600-710 µm and 710-850 µm, respectively. All three graphs show a decrease to f_{min} in the acoustic response with increasing mass of sample. All three also show subtle, yet significant, changes in the acoustic profiles with increasing size distribution. Figure 4(A) shows the acoustics profiles of the additional size distribution of 1080-1400 µm. These profiles display double f_{min} in contrast to the smaller size distributions. All spheres are made from the same raw material, therefore, differences in the acoustic profiles is mainly attributable to the different size distributions. There is an increase in the time taken (Δt) for the profiles to reach f_{min} from t=30s , as the average particle size of the sphere increases. The f_{min} correspond to an equilibrium between the liberation of gas in solution and the exiting of gas from the solution. It also represents the maximum compressibility of the solution. There is an expected decrease in dissolution rate of the spheres with increasing mean size due to a decrease in overall surface area per unit weight. This corresponds with the positive shift along the time axis of f_{min}. The profiles in Figure 4(A) would appear to contradict this trend as a double minima is observed. However, the initial f_{min} of the profiles are related to entrained gases trapped between the particles, which escape rapidly before the dissolution of the large particles proceeds in earnest. This initial deflection is also known as the entrained response point (ERP)[8]. This effect is masked in the data of the other size distributions due to more rapid outgassing. Therefore, the trend is maintained as demonstrated by the second f_{min}. Another possibility, which has yet to be investigated, is that the formulation of the larger spheres may be somewhat different from the smaller spheres.

A comparison of size distributions at a sample mass of 0.5 g is presented in Figure 4(B). This data clearly shows the significant differences between the acoustic profiles of the different types of

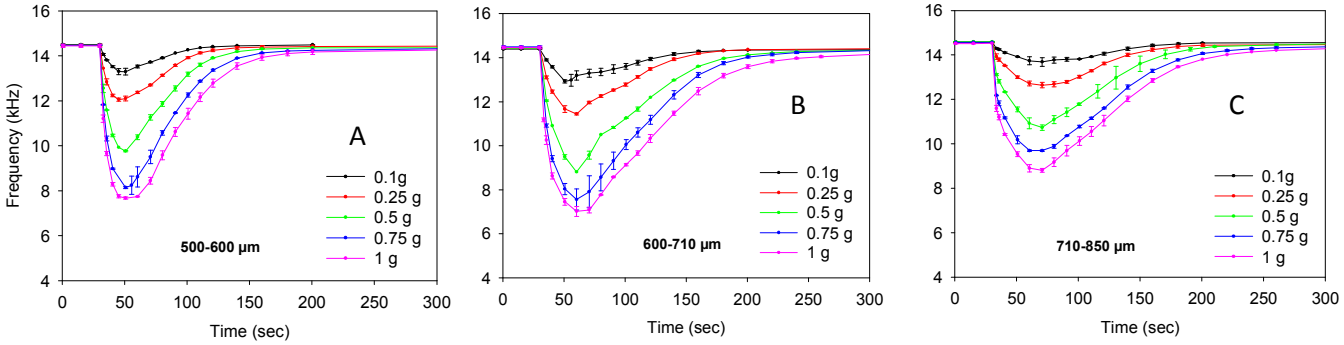

Figure 3: (A) BARDS spectra of 500-600 µm sugar spheres dissolved in 25 mL H_2O. (B) BARDS spectra of 600-710 µm sugar spheres dissolved in 25 mL H_2O (C) BARDS spectra of 710-850 µm sugar spheres dissolved in 25 mL H_2O.

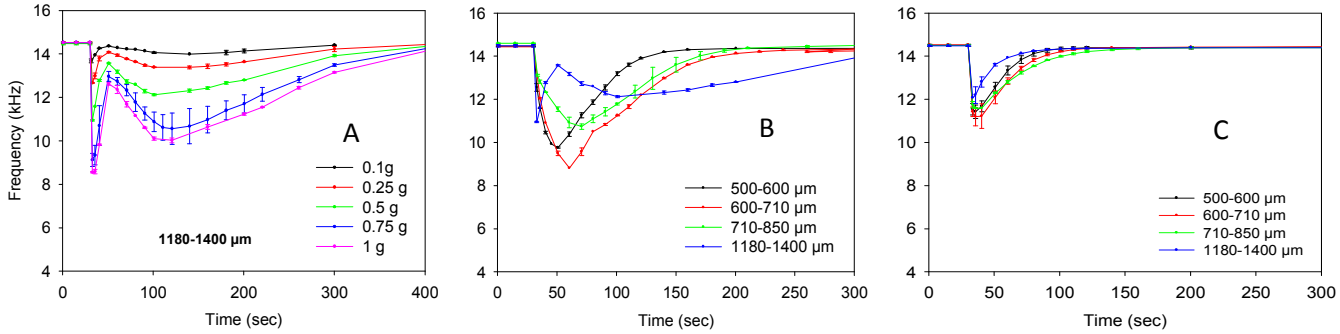

Figure 4: (A) BARDS spectra of 1180-1400 µm sugar spheres dissolved in 25 mL H_2O (B) Comparison of acoustic spectra of various sugar sphere distributions at 0.5 g (C) Comparison of acoustic spectra of 0.5 g of various sugar sphere distributions after grinding to a uniform consistency.

sphere. In order to verify that the differing median particle size is the major contributing factor to the difference in the acoustic profiles, spheres of different size distributions were ground to a fine consistency. The results of this control experiment show comparable behaviour in Figure 4(C).

There is a notable shift in the time taken (ΔT) for the acoustic profiles to return to steady state from f_{min}, both with increasing mass and mean particle size of the spheres. However, there is no trend evident in the magnitude of the frequency response to f_{min} with an increase in mean particle size. The reproducibility of the spectra is evidenced by the small standard deviation in the data. This indicates that the nature of the dissolution process is a highly ordered event under standardised experimental conditions. The same batches of spheres were again analysed eight weeks later and there was no statistical difference in the acoustic profiles from the initial experiments. The data demonstrates that the unique acoustic signature profiles of the various size distributions can be used to qualitatively discriminate between the spheres.

There is a non-linear relationship between frequency change and gas bubble volume in the solution. In general, gas bubble volume production and change is related to solute dissolution rate and the rate of gas bubble disappearance from the solution. The BARDS frequency data can be transformed into gas volume data using Equation 4. Analysis of the gas volume data in Figure 5(A) shows an approximately linear relationship between concentration and maximum gas volume. The r-squared values are in the range 0.97-0.99. It may also be questioned whether the rate of gas production is linear to the amount of suglets added. A method to test this hypothesis is to normalize the gas volume data to a concentration of 1 gram as shown in Figure 5(B). The slopes of the smaller concentrations (0.1 and 0.25 g /25 mL) are shown to be lower than the three higher concentrations. Also, the volume maxima are lower for these two concentrations. This indicates a relatively lower and slower rate of gas production. The normalized plots for the three higher concentrations are in agreement, which indicates the rate of gas production is proportional to the amount added. The gas is assumed to exit from the solution after reaching a maximum, in all experiments, according to a first order rate process in Equation 5.

$$V(t) = V(p).e^{-k.(t-p)} \qquad (5)$$

where k is the (process) rate constant, and V(p) is the gas volume at a time point p, after passing the volume maximum. Log plots of equation 5 yield a straight line from which the value k can be derived. It can be concluded that within a suglet size distribution that the return rate to equilibrium is independent of the concentration.

The next phase of investigations focussed on the acoustic responses of a finished pharmaceutical product which contains drug and enteric coated delivery spheres.

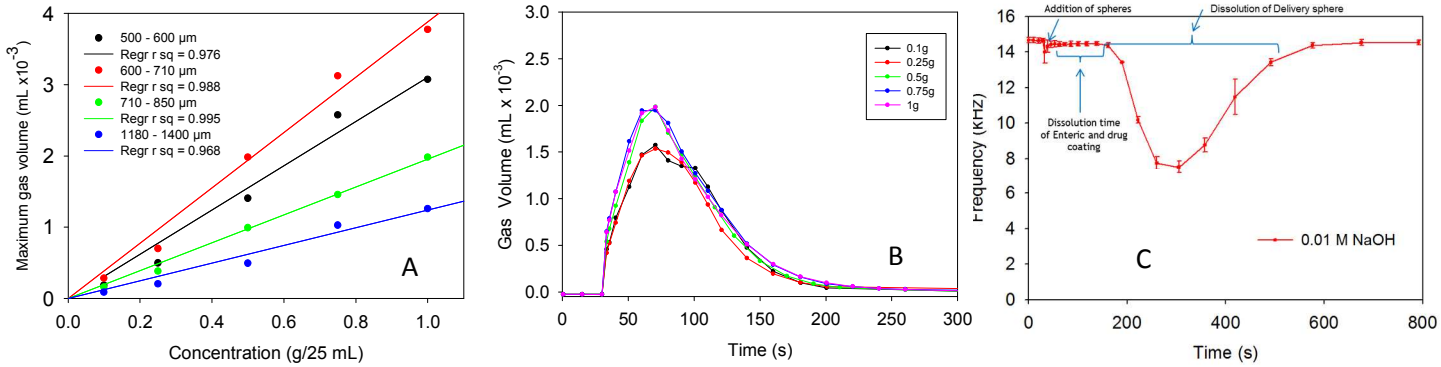

Figure 5: (A) The maximum gas volume versus concentration of suglets added is compared for the 4 suglet types. (B) Normalised gas volume plots of increasing concentrations of 710-850 µm suglets. (C) BARDS spectra of the dissolution of 0.3 g of Lanzol in 0.01 M NaOH.

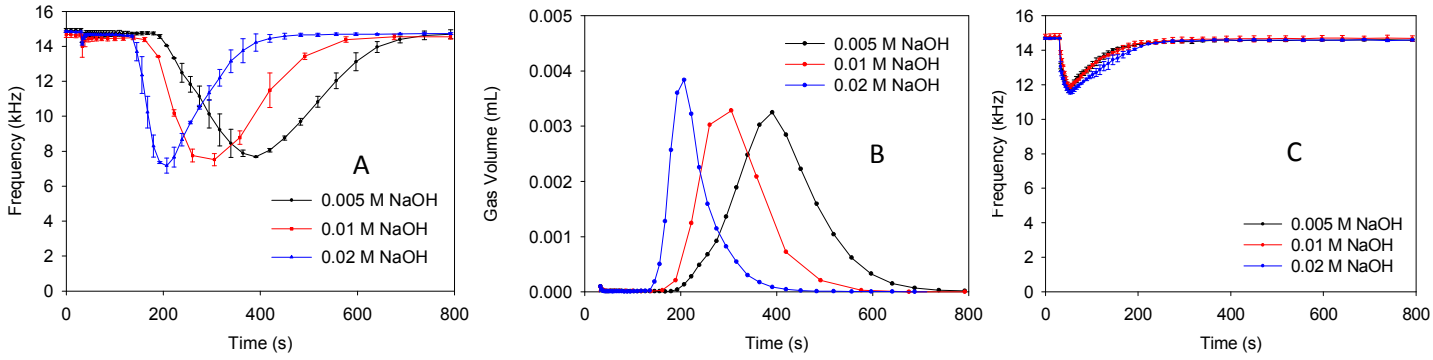

Figure 6: (A) Comparison of the dissolution of 0.3 g Lanzol in varying concentrations of NaOH (B) Gas volume profiles calculated from the data presented in Fig 6(A). (C) Acoustic profiles of Lanzol, ground to a uniform consistency, in increasing concentrations of NaOH.

The next phase of investigations focussed on the acoustic responses of a finished pharmaceutical product which contains drug and enteric coated delivery spheres. The prescription product Lanzol was chosen randomly from a range of suitable formulations to investigate. The enteric coated spheres were tested in aqueous solution initially which resulted in no apparent or usable spectra, i.e., there was no measurable outgassing or change in the compressibility of the solution. Therefore, solutions of sodium hydroxide of increasing concentration were used to accelerate the disintegration of the coatings. Figure 5(C) shows the results of dissolving 0.3 g of Lanzol in 0.01 M NaOH. There is a slight response upon addition of the spheres followed by a flat response for 100 s. This was an unexpected result at first until a large response appeared in the spectrum thereafter. This significant response is associated with the dissolution of the core sugar sphere once the drug and enteric coating have dissolved. Therefore the flat response / lag time is indicative of the dissolution rate of the coatings on the core sphere. The typical thickness of the drug layer is 40-50 micron and the thickness of the enteric coating is of the same order.[10] In order to validate this hypothesis, several concentrations of hydroxide solutions were used for further experiments. The results of which are shown in Figure 6(A).

The disintegration time of the coatings is reduced as illustrated by the shorter lag times with increasing concentration of sodium hydroxide. There is an increase in the solubility of the enteric coating due to the de-protonation of carboxylic acid groups in the presence of sodium hydroxide.[10] Lanzol experiments suggest a linear relationship between the lag time and NaOH concentration in Figure 6(A). A plot of [NaOH] versus lag time yields a straight line. This may be expected due to the rates at which the surface areas of the spheres are altered during the reaction between the enteric coating and the base. A key feature of the lag time is the expectation that the thickness / loading of the enteric coating can be estimated at a fixed concentration of basic solution. This capability, if proven, would be a considerable advance on current approaches to characterising enteric coated spheres.

The slope of the down curve of the profiles is related to the rate of outgassing, which appears to accelerate with increasing base concentration. This indicates that the dissolution rate of the sugar sphere also increases with increasing base concentration due to occluded gases in the spheres being released more rapidly. The return to steady state (ΔT) occurs at faster timescales with increasing hydroxide concentration i.e. the dissolution and outgassing is complete.

Figure 6(B) shows a plot of the gas volumes calculated from the frequency data shown in Figure 6(A) using equation 4. The gas volume production rate (R) is estimated from the upwards slope in the gas volume plot and calculated as $R = \Delta Vol / \Delta t$. It is not corrected for escape of gas bubbles from the solution. The gas production rates are shown in Table 1.

Table 1: Gas volume production rates during the dissolution of the core sugar sphere of Lanzol.

Base Concentration (M)	Gas Volume Production Rate (R) (mL s^{-1} x 10^{-5})	Time Range (s)
0.02	8.4	156-193
0.01	4.0	190-260
0.005	First slope = 1.0 Seconds slope = 2.4	193-275 275-364

The calculated values in Table 1, show that the gas volume production rate is approximately proportional to the NaOH concentrations, suggesting that the disintegration of the core spheres is a first order process with respect to NaOH. Note that the hydroxide concentration and other reactant concentrations will not remain constant during the dissolution process but decrease, due to consumption as the outer layers disintegrate. This will complicate the analysis, since decreasing concentrations during the reaction will also gradually decrease the reaction rate. Also, the additional slope for the lowest base concentration may relate to the drug layer disintegrating.

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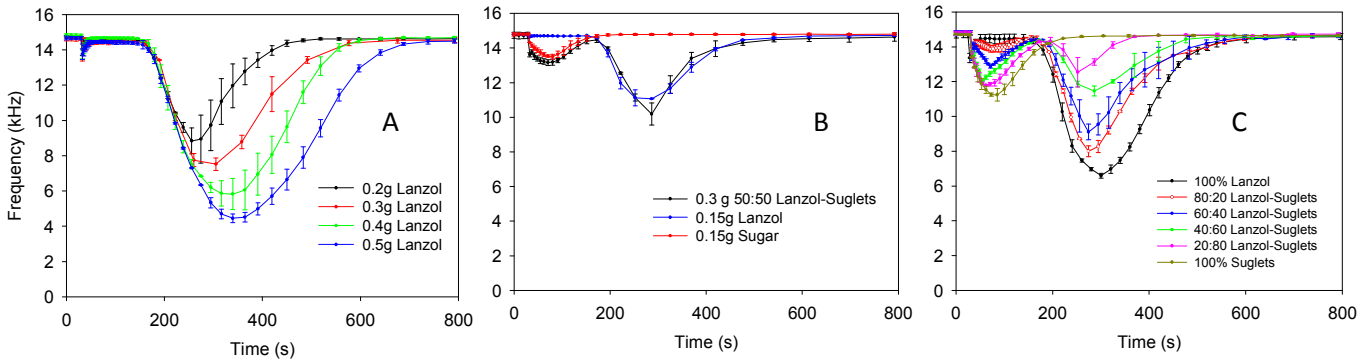

Figure 7: (A) BARDS spectra of increasing sample mass of Lanzol dissolved in 0.01 M NaOH. (B) Comparison of a 50:50 mixture of Lanzol–sugar spheres with the individual components of the mixture. (C) Acoustic spectra of mixture ratios of Lanzol and sugar spheres (710 – 850 µm). Samples mass = 0.3 g.

Analysis of the return slopes to steady state in Figure 6(B), using equation 5, yield rate constants of k = 0.0158 /s for 0.005 M NaOH, k = 0.0193 /s for 0.01 M NaOH and k = 0.0215 /s for 0.02 M NaOH, respectively. This indicates a first order process which is independent of the base concentration.

In a further effort to evaluate the data in Figure 6(A), samples of Lanzol were ground to a uniform consistency and dissolved in solutions of NaOH of three different concentrations. Figure 6(C) shows that the behaviour is the same for the ground material regardless of the concentration of the base. This experiment confirms that the disintegration of coatings on the sphere is responsible for the observed lag time.

Figure 7(A) shows the results of experiments whereby the sample mass of Lanzol is increased steadily, while the concentration of the base solution is maintained the same. It is notable that the disintegration time of the coatings remains the same regardless of sample mass. This may be expected with a uniform particle size distribution and fixed base concentration. Particles of similar size will reduce in surface area at the same rate as they dissolve. The downward curve of all profiles all have the same slope which indicates the core spheres are also dissolving at the same rate as opposed to the data in Figure 6(A) and Table 1. The continued outgassing, at higher masses, delays the onset of f_{min} by over 150 s when comparing the smaller mass with the greater mass of sample. There is also a decrease to f_{min} with increasing mass of sample. The rate of return to steady state is approximately the same for all experiments. This graph in particular demonstrates the useful data that can be obtained from BARDS spectra when the sample type is well described and the experimental conditions are standardised. For further discussion of the limits of detection and other statistical parameters of BARDS refer to Fitzpatrick *et al*.[8]

It is not uncommon for lower dosage forms to require a small number of drug delivery spheres for encapsulation, particularly if the API is potent. In these cases, uncoated spheres are used as a bulking agent. Figures 7(B) shows the acoustic profile of a mixture of equal mass (0.5 g) of sugar spheres (710 – 850 µm) and Lanzol. The black profile shows a dual response (two frequency minima), the initial response for the sugar spheres and a delayed response for Lanzol. The contribution of the two components of the mixture to the overall response is confirmed by their individual responses shown by the red and blue profiles, which together equal the data of the black profile. This example can be applied to determining / validating the mixture ratio of active spheres v placebo spheres in a capsule as demonstrated in Figure 7(C). The intermediate ratios of 90:10, 70:30, 50:50, 30:70 and 10:90 were also investigated and fit the trend precisely but have been omitted from the figure for clarity. The presence of an 'isosbestic type' point at 200 s is a product of the method development. The dual responses would most likely overlap at higher concentrations of base.

The acoustic response of the sugar spheres in NaOH does not change significantly compared to the response when they are dissolved in water (Figure 3(C)).

The contribution of the drug coating to the acoustic response must not be overlooked. There is no clear delineation during the lag time to indicate the complete disintegration of the enteric coating before the dissolution of the API coating. However, it is possible to obtain drug coated spheres during manufacturing which have yet to be coated with the final enteric coating for

analysis. It would also be useful to obtain enteric coat spheres with no drug coating. Comparison of BARDS spectra of these types of sphere would indicate the relative contribution of both the drug and the enteric coatings to the lag time. Sampling of the solvent, during the lag time, and analysis using LC, could also be used to validate the beginning of the dissolution of the API coating.

Conclusions

It has been shown how core delivery sugar spheres have unique acoustic spectra attributable to the mean size distribution of the spheres. Therefore, BARDS can be used for qualitative and stability testing of sugar spheres. Equally, the drug and enteric coated spheres have also been found to have reproducible and interpretable spectra. The steady state lag time, post addition of the coated spheres to the solution, is associated with a stoichiometric reaction due to the disintegration of the enteric coating in basic solution. This lag time can be manipulated by varying the concentration of the base which affects the rate at which the coating dissolves. It is anticipated that the thickness / loading /stability of the spheres can be estimated from the lag time. The lag time has also been found to be independent of the mass of sample / spheres added to the solvent. BARDS can also be used to determine a mixture ratio of enteric coated spheres and non-coated spheres which are used as a bulking agent. This can be used as a confirmatory test for the correct loading of the encapsulated formulation. All of these tests can also be used to identify counterfeit products. BARDS spectra indicate its potential as a quality control tool, for stability testing and for inter/intra batch comparison.

Future work will relate to the possibility of designing enteric coated spheres with thin intermediate layers which trigger small changes in the compressibility of a solvent as the spheres dissolve. Formulations are available where a micro layer of Mg carbonate between the enteric and drug layer exists, which may have the desired effect.[10] These layers would act as a marker indicating the dissolution rate of the layers in between.

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Notes

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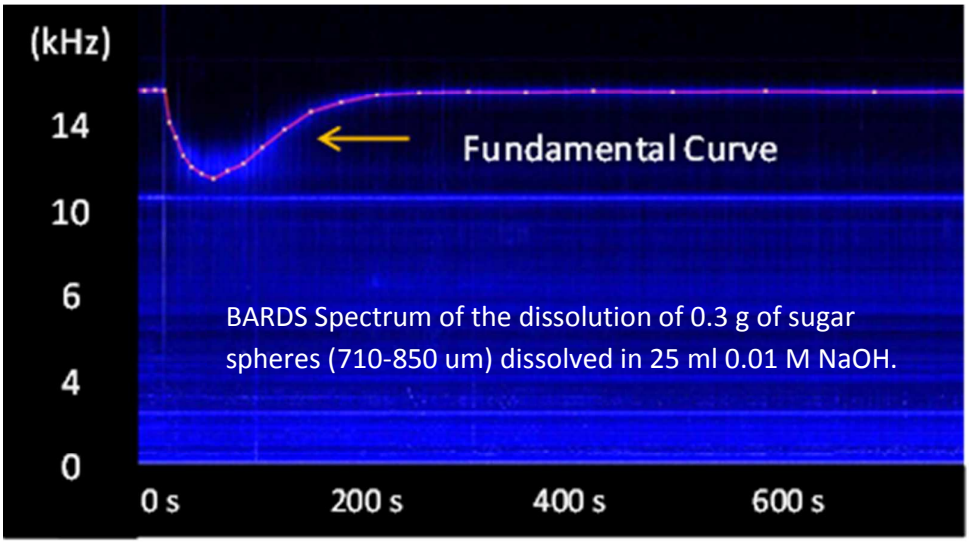

BARDS Spectrum of the dissolution of 0.3 g of sugar spheres (710-850 um) dissolved in 25 ml 0.01 M NaOH.