

Determining the suitability of mass spectrometry for understanding the dissolution processes involved with pharmaceutical tablets.

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ABSTRACT

RATIONALE: A current challenge for analytical chemists is the development of measurement systems and approaches required to understand dynamic processes such as tablet dissolution. The design and development of oral tablets could be improved by the availability of detailed information about the rates of release of the individual tablet components. Small footprint mass spectrometry (MS) systems are gaining use for on-line reaction monitoring because of their ability to rapidly determine multiple reactant, intermediate, and product species. We have therefore assessed the utility of such MS systems to the study of dissolution processes.

METHODS: Aqueous dissolution media containing phosphate and other non volatile buffer salts were pumped from a standard USP II dissolution vessel through an active splitter and back. The splitter sampled the dissolution stream and diluted it into a make-up flow which was pumped to a small single quadrupole mass spectrometer. Single ion monitoring was used to quantify the ions of interest. Three different bio-relevant dissolution media were studied to gauge the impact of the sample matrix.

RESULTS: Individual dissolution profiles were obtained from a tablet containing three drugs and lactose as the soluble filler. This was successfully demonstrated with three different bio-relevant media designed to reflect the pH of the different sections of the human gastrointestinal tract. Component concentrations as low as 0.06 µg/mL (representing 1% dissolution) were detected. The MS dissolution profiles correlated with the visual observation of tablet dissolution. MS gave linear responses with concentration for the individual components, although analysis of the tablet solution indicated that ion suppression is an area for further investigation

CONCLUSIONS: An on-line MS system was used to determine the individual dissolution profiles of three drugs and lactose as they are released from the same tablet. The level of each of these components in solution was determined every 10 seconds, and each had a similar release profile. The dissolution profiles were determined using inorganic buffer solutions at three different bio-relevant pHs.

INTRODUCTION

Pharmaceuticals are typically administered as solid oral tablets but for the drug to be available for absorption in the Gastro Intestinal Tract (GIT) it must be in solution. Therefore, the process whereby the tablet disintegrates and the components dissolve and disperse (tablet dissolution) is of great importance. Because of this, standardized dissolution testing equipment was introduced in the 1970s and 1980s as a Quality Control (QC) measure.^[1, 2] In recent years the dissolution test has also been used as a tool to improve understanding of dissolution mechanisms, and so aid in the design and development of new formulations. The expectation of regulatory authorities is also that the conditions used in the registered dissolution test will be related to those which exist in the GIT. This has led to increasing emphasis on the use of dissolution media with pHs and other characteristics which are relevant to those of the GIT. For example, HCl/NaCl buffers at pH 1.2 simulate the fasted state of the stomach, acetate buffers at pH 4.5 the fed state of the stomach, and phosphate buffers at neutral pHs the conditions in the small intestine.^[3] Recent reviews have also emphasised the need for better *in vitro* tools that are predictive of *in vivo* behavior.^[4] There is therefore a need for improved analytical methods to improve our understanding of tablet dissolution processes.

Conventional analytical approaches to dissolution rely on using sampling and single wavelength UV measurement to determine the extent of drug release at a small number of time-points. This approach is adequate for QC purposes but is not very helpful in establishing the underlying mechanisms which control drug release. More helpful are high performance liquid chromatography (HPLC) methods and on-line fibre-optic UV spectroscopy.^[5-7] These approaches mean that the release of multiple UV absorbing components can be followed, and there are sufficient time-points to think of dissolution in terms of a process with associated kinetics and rates.

Pharmaceutical formulations contain many components but typically only the drug has a UV chromophore. This means if we are to understand the role of these components in tablet dissolution, we need to look beyond UV measurement.

Coombes *et al*, investigated the potential of nuclear magnetic resonance (NMR) spectroscopy to monitor the dissolution process.^[8] NMR allowed for greater analyte selectivity and had the ability to detect non-UV-absorbing species such as sugars. This method, however, relies on large NMR instruments, which are fixed to one site and cannot easily be moved around to be near the dissolution instrumentation.

To the best of our knowledge the application of mass spectrometry (MS) to monitor dissolution has not been previously reported, and it is this that we report here. On-line MS is potentially a sensitive and selective method to monitor dissolution: allowing constituents to be monitored at low concentrations, based solely on mass-to-charge ratio. Like the NMR method, it overcomes problems surrounding the need for UV chromophores, allowing numerous individual constituents (including excipients) to be monitored simultaneously, without the limitation of spectral overlap, as experienced by UV.^[7]

On-line monitoring of chemical reactions by MS has previously been described; MS can provide considerable detail about starting materials, intermediates and products, as well as identifying route-specific impurities along the way.^[9-14] Such an approach has clear application in the monitoring of a dynamic process such as dissolution, as a number of tablet components are monitored in real time in a selective and accurate manner.

Recent developments in small footprint atmospheric pressure ionisation transportable mass spectrometers allow instruments to be easily positioned alongside the reaction system. The low cost of these systems relative to NMR makes on-line MS a much more cost-effective, but still selective, option for dissolution monitoring. The instrument can easily be taken to the sample and effectively interfaced with numerous dissolution set-ups.^[15-17]

For MS detection to be a suitable technique for monitoring of dissolution, certain criteria must be met:

- 1) The response must be linear within the required dynamic range and in the presence of non-volatile dissolution buffers;
- 2) There must be suitable selectivity between analytes and ions formed from the dissolution media or other components of the tablet;
- 3) The sensitivity for each component must be such that 10 % dissolution can be detected, to aid in understanding the underlying mechanisms of drug release;
- 4) Insoluble material present in the dissolution bath must not interfere with the analysis; and
- 5) The frequency of measurement must be sufficient to define the profile of the species present.

To achieve these criteria, the sample taken must be representative of the dissolution sample while also being compatible with the mass spectrometer. However, dissolution experiments are commonly performed in non-volatile bio-relevant media such as fasted state simulated intestinal fluid (FaSSIF) which is a phosphate-containing buffer. These media are not commonly interfaced with MS due to the detrimental effects of non-volatile buffers on ionisation. Relevant steps therefore should be imposed to allow successful monitoring in this medium to ensure compatibility with the MS detection method.^[18-19]

Other commonly used dissolution media include simulated gastric fluid (SGF) and Fed state simulated intestinal fluid (FESSIF, an acetate buffer). These three buffers mimic different states and parts of the gastro-intestinal tract, by simulating different pH environments commonly experienced by solid dosage forms.^[3]

In this paper we describe real-time monitoring of the dissolution of a solid dosage form using a small footprint mass spectrometer. Dissolution of the tablet using a variety of common buffers was successfully carried out and the potential for using MS to monitor dissolution is demonstrated.

EXPERIMENTAL SECTION

MATERIALS:

A widely available over-the-counter cold and flu tablet was investigated, containing the three Active Pharmaceutical Ingredients (APIs) (i) acetaminophen (250 mg), (ii) guaifenesin (100 mg), and (iii) phenylephrine hydrochloride (5 mg) as well as (iv) α -lactose monohydrate (190 mg), as an excipient. The immediate release formulation aims to reduce fever (acetaminophen) and act as an expectorant (guaifenesin) and a decongestant (phenylephrine hydrochloride) to relieve patients' symptoms.

Acetaminophen, guaifenesin, phenylephrine hydrochloride and lactose α -monohydrate were obtained from Sigma-Aldrich Company Ltd (Gillingham, UK) and used without further purification.

The sample make-up flows used are as described in Table 1. Formic acid and ammonium acetate used were obtained from Fisher Scientific (Loughborough, UK), analytical grade acetonitrile was obtained from Sigma-Aldrich and de-ionised water from a MilliQ unit (Millipore, Watford, UK).

The compositions of the dissolution media are shown in Table 2. The dissolution standards were dissolved in either 900 mL of water or the relevant dissolution media to that experimental series.

Table 1 Composition of make-up flows for dissolution media used

Dissolution medium	Make-up flow
FaSSIF	0.1 % formic acid in (50:50 MeCN/H ₂ O)
SGF	0.1 % formic acid in (50:50 MeCN/H ₂ O)
Acetate buffer	0.1 % ammonium acetate in (50:50 MeCN/H ₂ O)

Table 2 Dissolution media (all reagents obtained from Sigma-Aldrich)

Medium	pH	Reagents
Blank FaSSIF	6.8	Sodium dihydrogen phosphate 0.2 M Sodium hydroxide 0.2 M Pure water
SGF	1.2	Sodium chloride 0.2 M HCL 0.2 M Pure water
Acetate buffer	4.5	Sodium acetate trihydrate 2.99 g Glacial acetic acid 1.6 mL Pure water 1 L

METHODS:**COMPONENTS & TABLET DISSOLVED IN WATER / FaSSIF:**

Initial investigations were performed with a sample introduced using a syringe pump (11 plus, Harvard apparatus, Cambridge, UK), operating at a flow rate of 5 μ L/min. The sample entered the mass rate attenuator (MRA; Rheodyne, Rohnert Park, CA, USA), an active splitter, where the flow was sampled and diluted (1000:1 split ratio) into a make-up flow from the HPLC pump (515, Waters, Manchester, UK) operating at a flow rate of 1 mL/min, and was passed into the mass spectrometer.

Individual components were dissolved in water (concentration representative of analyte content in tablet / dissolution volume of 900 mL), and then diluted to create a series representing 0-100 % dissolution. The same set of dilutions were also performed in FaSSIF. Samples were analysed by positive ion electrospray ionisation (ESI⁺)-MS using a α -QDa single quadrupole mass spectrometer (Waters), capable of detecting ions up to m/z 1250. The α -QDa is a small footprint mass spectrometer (dimensions: 35.3 x 20 x 75cm) that is transportable because of its low weight (approx 30kg). The MS conditions were kept constant with a source temperature of 100 °C, a probe temperature of 300 °C, a capillary voltage of 1.5 kV and cone voltage 25 V.

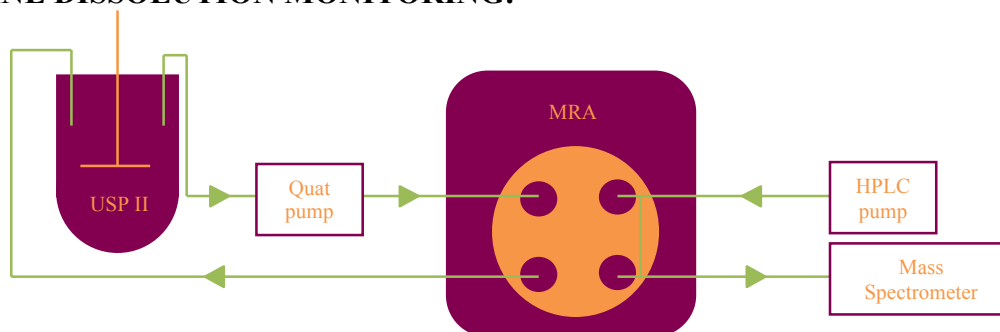
ON-LINE DISSOLUTION MONITORING:**Figure 1** Apparatus used to measure dissolution using online mass spectrometry

Figure 1 shows the configuration used when connecting the mass spectrometer to the dissolution bath. An Agilent 1100 Quaternary pump (Agilent Technologies, Stockport, UK) was used to pump the medium from the dissolution bath (through a standard Inlet filter in the dissolution bath). A KrudKatcher 0.5 μ m on-line filter (Phenomenex, Macclesfield, UK) was placed in-line just prior to the MRA to prevent any solid material blocking the MRA. The MRA sampled and diluted the flow from the bath into the make-up flow which then passed to the mass spectrometer as described above. The remaining effluent is pumped back into the dissolution bath. A bridge of PEEK tubing was used for the make-up flow entering the MRA to reduce pressure fluctuations which produced a more even signal response.

Dissolution experiments were performed using a homemade USP II like system,^[8] 900 mL of dissolution medium, a paddle speed of 53 rpm, a water bath temperature of 37°C, a flow rate of 1 mL/min from the dissolution bath and an MRA split ratio of 100:1 (decrease in ratio from initial investigations so that a greater volume of dissolution effluent was sampled, thus providing an improved MS response). Filters were used at sample inlet as well as in-line, both prior to the MRA and prior to the MS capillary.

For each dissolution medium used, primary ESI+ investigations were performed with the α -QDa mass spectrometer in scan mode to determine the most abundant ion present for each component and to optimise the composition of the make-up flow. This ensured that the maximum ionisation of components was achieved (data not shown) through appropriate choice of buffer. The four individual components were dissolved in each of the respective media at a concentration representative of 100 % dissolution. These solutions were then infused into the dissolution setup and the most abundant ion selected in scan mode was then employed in single ion recording (SIR) mode to monitor each component. During dissolution experiments a dwell time of 0.245 s was used for each ion, with all four ions being monitored within one experiment. The SIR data for the 100% dissolution standards could then be used for comparison with the tablet dissolution data.

Prior to a dissolution experiment, the system was flushed first with water and then with the respective dissolution medium. The dissolution vessel was sampled to equilibrate the system and ensure background measurement. Testing was initiated upon addition of the tablet to the vessel and starting of MS on-line monitoring. Following a dissolution experiment, the system was flushed with the relevant medium until only background levels of the ions of interest were observed. Water and/or methanol flushes were performed where required to return signals to normal.

Three commonly used dissolution media were investigated: FaSSIF (7 tablets), SGF (6 tablets) and acetate buffer (2 tablets). Dissolution profiles were monitored for at least 15 minutes with measurements of the intensity of the individual ions taken every 10 s.

RESULTS & DISCUSSION

COMPONENTS & TABLET DISSOLVED IN WATER / FaSSIF:

Initial investigations were performed using a syringe pump to introduce the tablet components dissolved in water. This provided insight into the sensitivity of response and the ionisation of each component. As well as showing how reproducible the results were, this approach also demonstrated the stability of the MS response over time, as samples were injected over 5-min periods. The four ions of interest for the tablet components were selectively monitored (Table 3).

Table 3 Mass-to-charge ratio (m/z) of the most abundant ions for each component of interest in water

Component	Ion	m/z
Acetaminophen	$[M+H]^+$	152
Guaifenesin	$[M+Na]^+$	221
Phenylephrine hydrochloride	$[M+H-H_2O]^+$	150
Lactose	$[M+Na]^+$	365

The same procedure was then performed by dissolving the APIs and the lactose standards in blank FaSSiF buffer, a commonly used dissolution medium, representative of fluid from the intestine in its fasted state. This allowed the effect of FaSSiF on ionisation to be understood and also allowed a more direct comparison with conditions to be used in the dissolution test itself. Figure 2 shows linearity of response of guaifenesin when dissolved in water, with an R^2 of 0.9982. Ion abundance in excess of 9×10^6 was observed at a concentration equivalent to 100 % dissolution. This linearity was retained ($R^2 = 0.9938$) when guaifenesin was analysed in FaSSiF, with a reduction in ion abundance at each concentration. The reduction in response is probably a matrix effect causing a change in the ionisation efficiency of guaifenesin, compared to the idealised water system.

Each data point plotted in Figure 2 is also the result of at least three analyses, demonstrating the results are reproducible in both systems, with the linear trend remaining throughout. This suggests a robust method, stable MS response and reproducible ionisation, although sample suppression is observed.

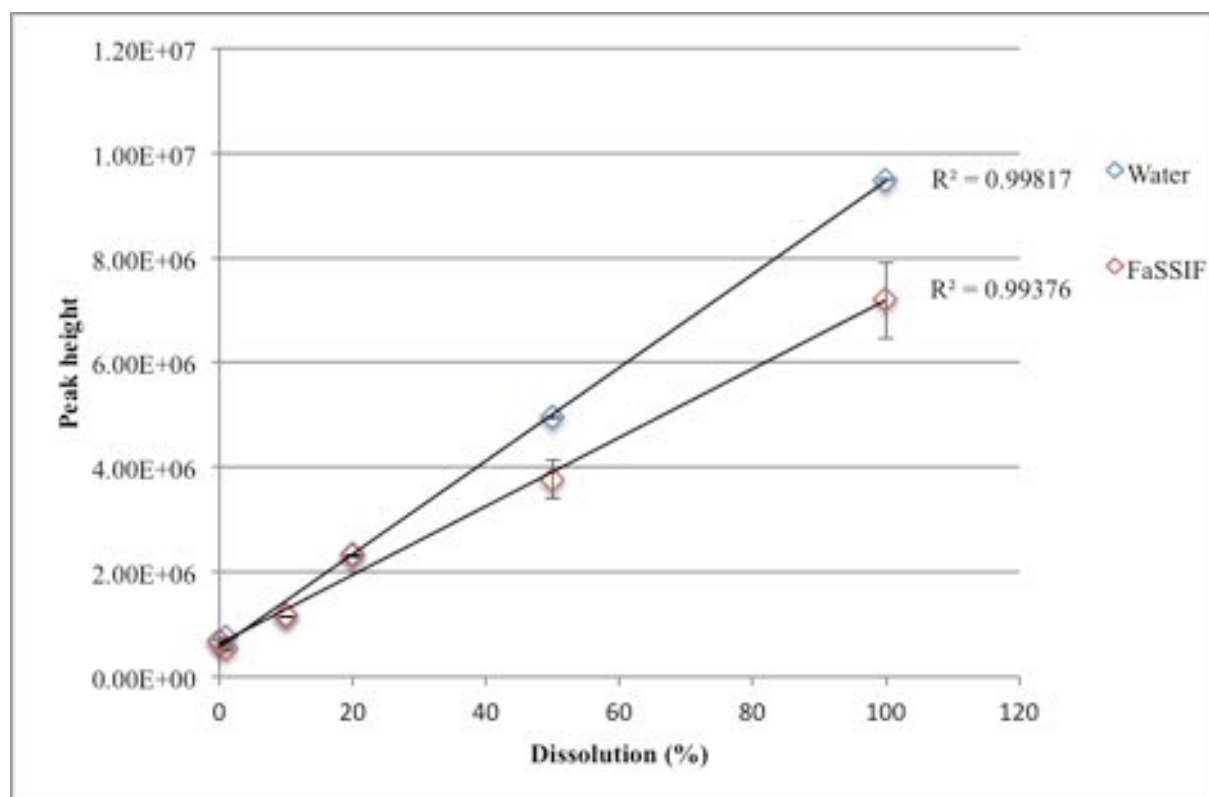


Figure 2 Guaifenesin dissolved in water and in FaSSiF, diluted to represent 0 – 100% dissolution (data of $n \geq 3$ shown).

ON-LINE DISSOLUTION MONITORING IN FASSIF:

The four ions of interest were selectively monitored (Table 4), one for each of the three APIs and one for lactose, for a time scale of 30 min, enough to visualise tablet disintegration and a full dissolution profile.

Table 4 Mass-to-charge ratios (m/z) of the most abundant ions for each component of interest in all three dissolution media

Component	Ion	m/z
Acetaminophen	$[M+H]^+$	152
Guaifenesin	$[M+Na]^+$	221
Phenylephrine hydrochloride	$[M+H-H_2O]^+$	150
Lactose (in FaSSIF)	$[M+H]^+$	343
Lactose (in SGF & acetate buffer)	$[M+Na]^+$	365

Note that we monitored the lactose $[M+H]^+$ ion in FaSSIF and the $[M+Na]^+$ ion in SGF, acetate buffer and water.

Figure 3 shows the dissolution profile of a tablet in FaSSIF. It is clear that each of the four components of interest is released from the tablet at a similar rate. Acetaminophen, phenylephrine hydrochloride and lactose were released fully from the tablet within a 15-20-min period, while guaifenesin took longer. This is consistent with the time taken for the tablet to fully dissolve, approx. 12 min (in each of the repeats), as shown in Figure 4.

Whilst the signal for guaifenesin did not appear to plateau in the 30-min time period (shown in Figure 3), this did hold true when dissolution was monitored over a 60-min period. This phenomenon, however, was also observed during direct infusion of the compound alone (dissolved in FaSSIF) as no plateau was obtained after a 1-h infusion. This upward drift of the signal was, however, only observed using FaSSIF. As the tablet had reached full disintegration (Figure 4) after ~12-min and full dissolution after ~30-min, it is likely that guaifenesin dissolution had reached near completion after the 30-min period seen in Figure 3 (or at least shortly afterwards). This increasing guaifenesin signal has not as yet been explained.

Figure 2 shows the suppression effect of FaSSIF on the guaifenesin signal; however, monitoring the dissolution of phenylephrine and guaifenesin produced a response greater than would be expected for 100 % dissolution compared with infusion of the compounds alone, whereas lactose achieved a response equivalent to only 50 % dissolution. It can be inferred that with the FaSSIF medium the guaifenesin and phenylephrine ions are experiencing an enhancement effect from another tablet component and, conversely, the lactose ion is experiencing a suppression effect.^[20]

The dissolution profiles are similar to those obtained by Coombes *et al.* who investigated the same dosage form by H^1 -NMR analysis.^[8] They also observed that the dissolution process began quickly and reached 100 % dissolution after about 15 min for all four components with similar release rates for all components. This comparison also suggests that the guaifenesin phenomenon is an artifact of our system, as well as suggesting we are experiencing possible suppression of the lactose $[M+H]^+$ ion at m/z 343 in FaSSIF. The suppression and enhancement effects observed require further significant fundamental investigation of the observations to fully validate the methodology.

From Figure 4, it is apparent that the most significant changes in tablet disintegration happen within the first 10 min (Figure 4(A)). Less noticeable changes then occur over the next 5 min (the tablet becomes fully dissolved after approximately 12 min), and the dissolution vessel becomes slightly cloudier over the remaining 15 min (Figure 4(B)) as particles in suspension dissolve further.

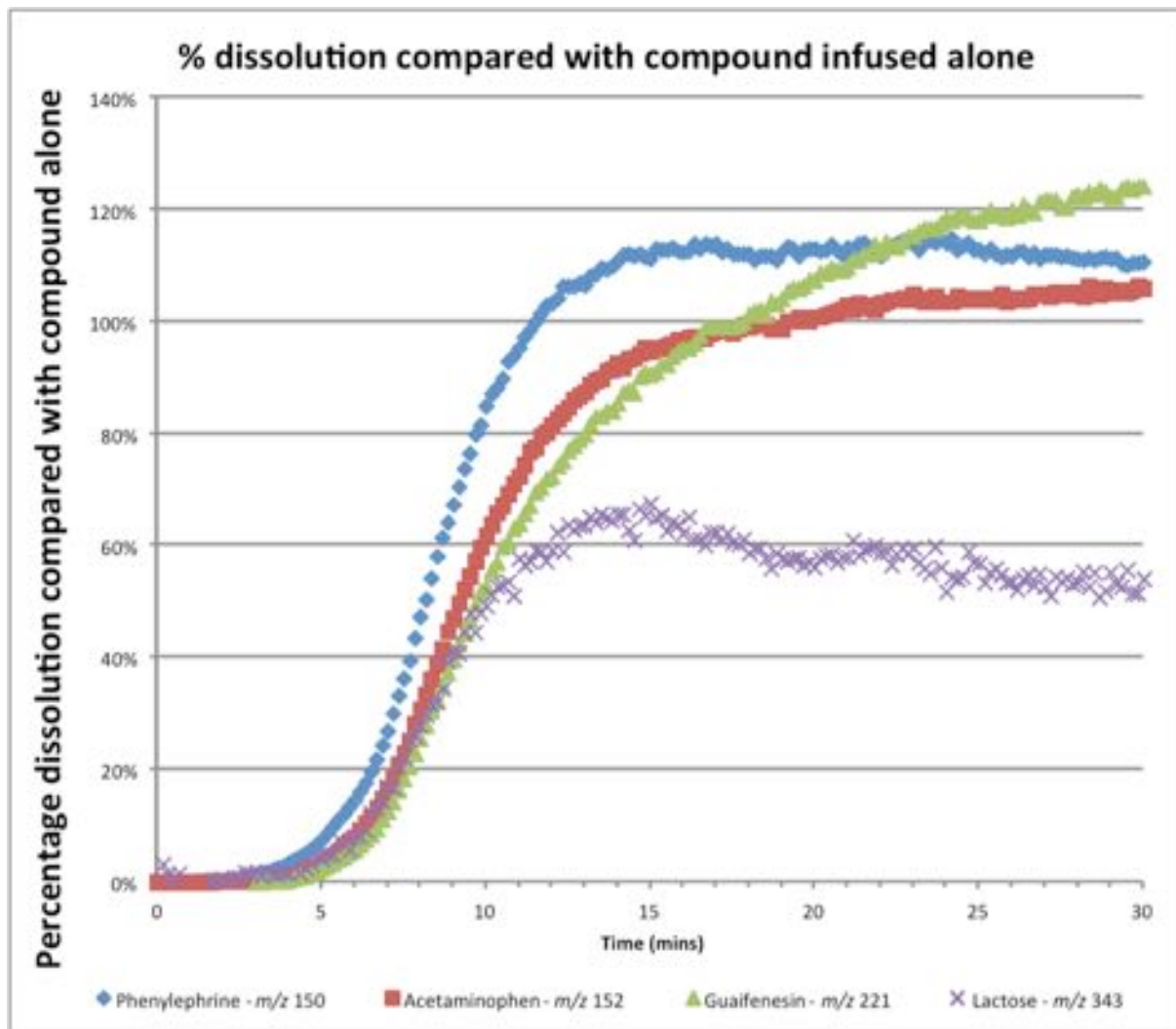


Figure 3 Dissolution profiles of each component in FaSSIF buffer (typical data of n=7 shown, background signal subtracted).

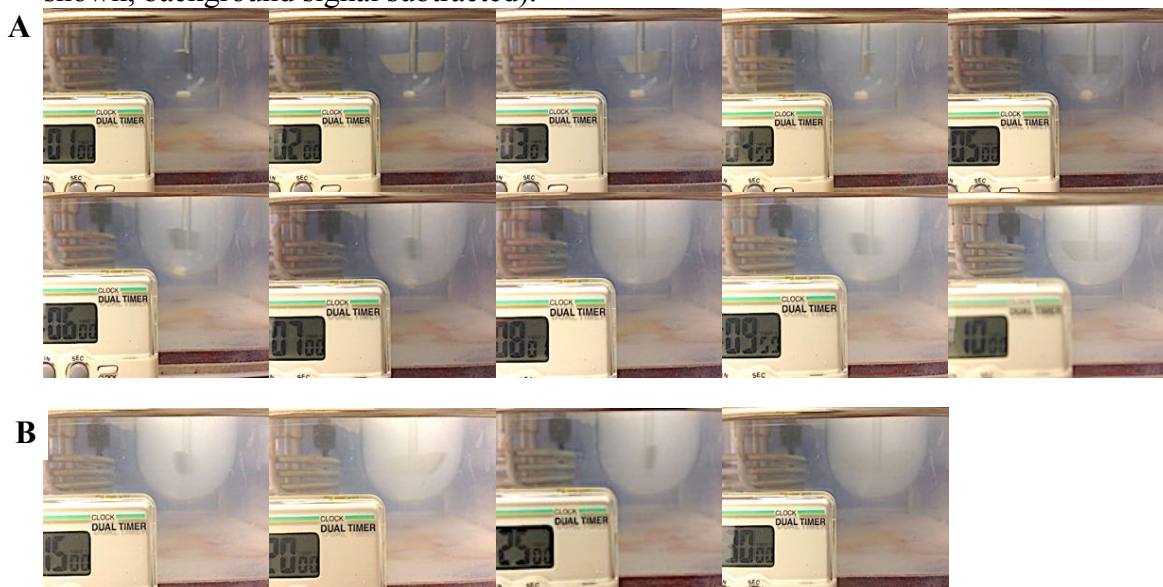


Figure 4 Photographs of tablet disintegration in FaSSIF: (A) early stages showing most significant changes in tablet morphology and (B) later stages of dissolution process.

DISSOLUTION MONITORING IN SGF:

Figure 5 shows the dissolution profile for a tablet in SGF. It can be seen that the tablet dissolved much more quickly in the SGF than in both other dissolution media investigated, with the tablet fully dissolved in approx. 8 min (true for four repeats). This was in agreement with the visual data. This is again consistent with the plateauing of the dissolution profiles shown in Figure 5 after approx. 12 - 13 min in the case of acetaminophen, guaifenesin and lactose, with phenylephrine hydrochloride following shortly afterwards.

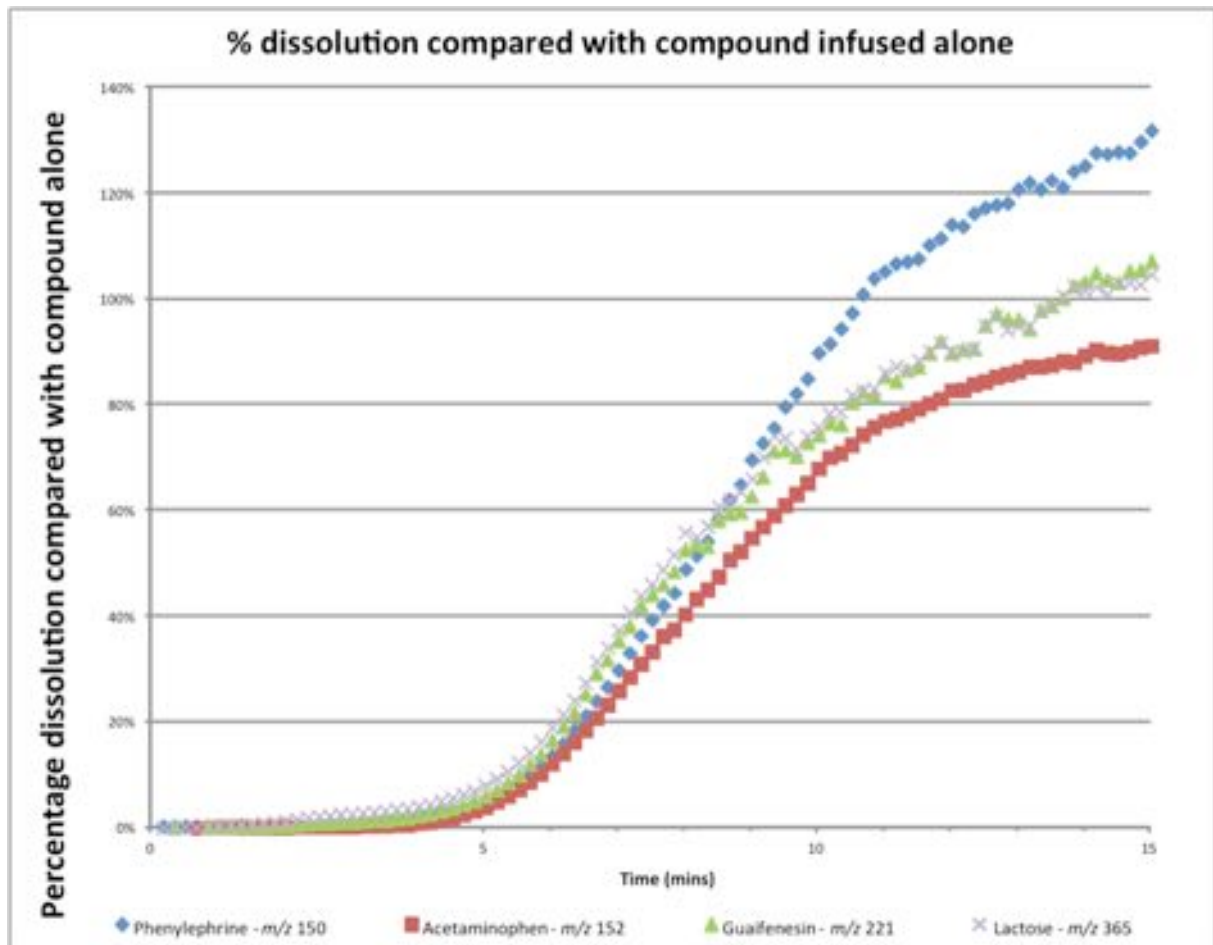


Figure 5 Dissolution profiles of all tablet components in SGF buffer (typical data of n=5 shown, background signal subtracted).

Interestingly, one tablet took much longer to disintegrate than expected, approximately 15 min. This is represented in the MS data (Figure 6) and visualised in the photographs taken (not shown). As can be seen in Figure 6, none of the four components reached even 10 % dissolution (compared with the standard in SGF) after a 15-min time period. After this time, photographs suggested that the dosage form was fully disintegrated, however. On previous occasions the dosage form released all four components with dissolution in excess of 90 % (Figure 5) after this time. Subsequent tablet analysis produced profiles like those observed in Figure 5, indicating the system was functioning correctly but issues with sampling cannot be ruled out. Further work is required to understand these differences.

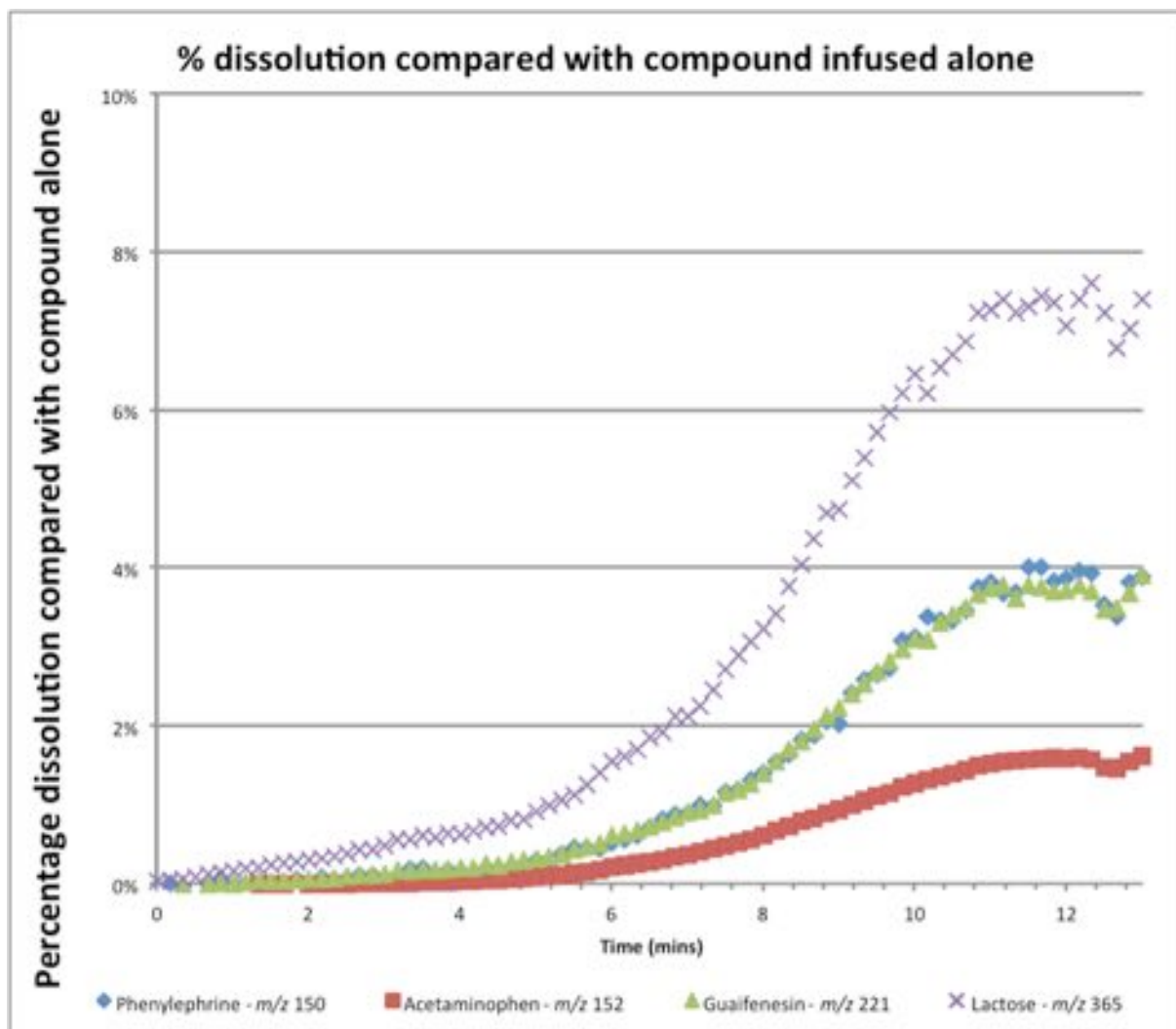


Figure 6 Dissolution profiles of the four components when tablet disintegrated unusually slowly in SGF (background signal subtracted).

DISSOLUTION MONITORING IN ACETATE BUFFER:

Figure 7 shows the dissolution profile for a tablet in acetate buffer. It can be seen that each of the four tablet components takes around 20-25 min to become completely released from the tablet. This was consistent with the tablet dissolving slowest in this medium, taking around 15 min to become fully dissolved in the two repeats. Interestingly, the components are released at slightly different rates here, with the acetaminophen and lactose being released at similar rates, and likewise the guaifenesin and phenylephrine.

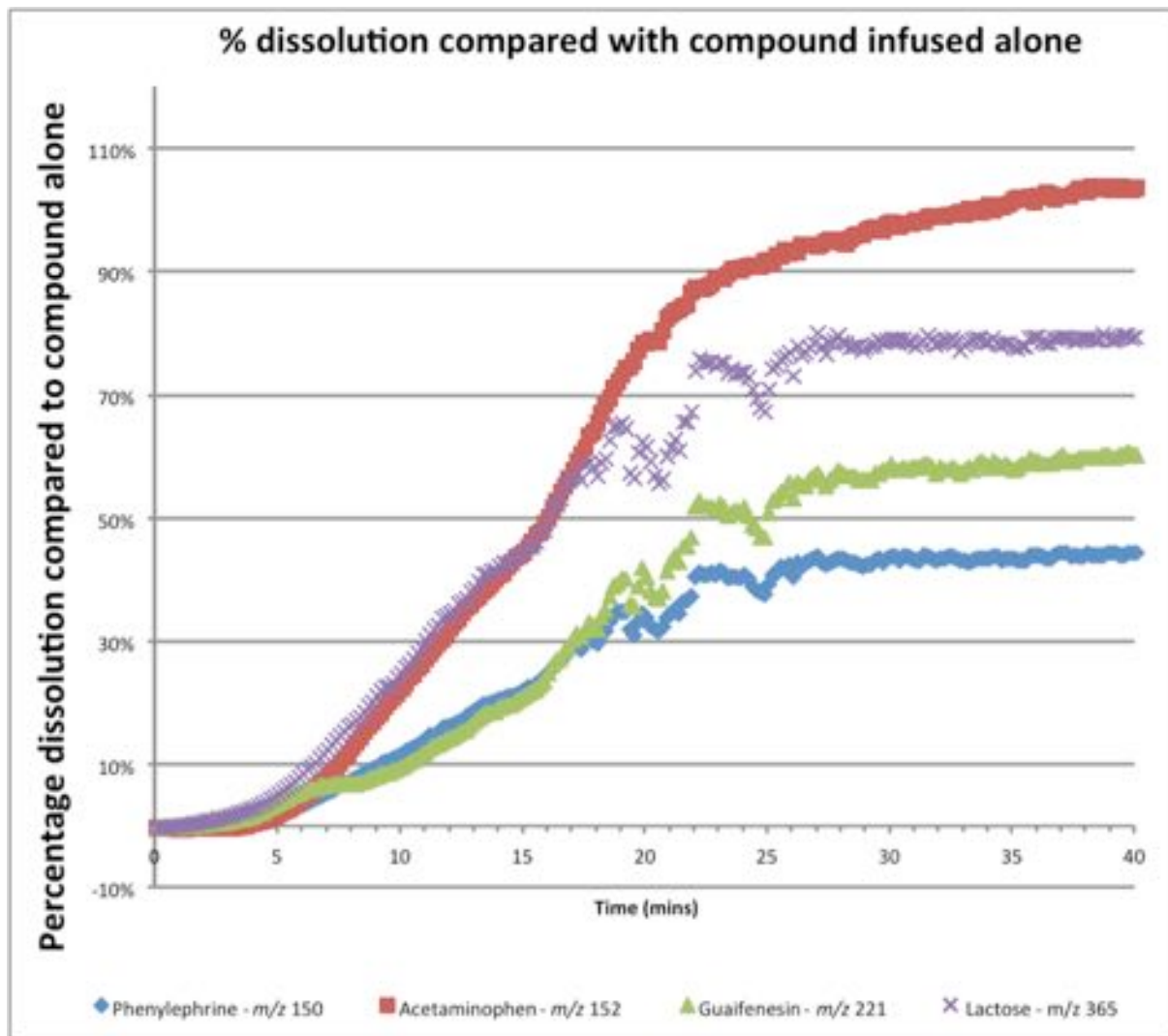


Figure 7 Dissolution profile of each respective component (typical data of n=2 shown, background signal subtracted).

When comparing the three dissolution media, the four tablet components are released from the dosage form at similar rates (with only slight differences in rate observed in the acetate buffer). This is consistent with what was found by Coombes *et al.* using H^1 -NMR^[8] to investigate the same dosage form, and would suggest that the same underlying mechanism(s) control the rate of release of all four tablet components. This information enables a more complete understanding of the fundamental tablet dissolution process. Coombes *et al.* suggested that the tablet may disintegrate to produce small particles and that the soluble components are then released rapidly from those particles. Taking this suggestion into account, perhaps we can begin to explain the changes in dissolution profile seen across the different media. Given that all three APIs monitored as well as lactose are highly water-soluble and are neutral, changes in pH would be unlikely to alter the dissolution of these components. However, if the mechanism Coombes *et al.* postulate is correct, perhaps it is the disintegration of the tablet that is being influenced by the change in buffer. In certain instances disintegration can be a critical parameter of drug release, and the change in pH here may, for example, be altering this step, changing the rate of particle formation and consequently the

rate of component release.^[20] Hence we see differences both in the time taken for the tablet to dissolve visually and in the MS data. Thus, the criteria initially stated for successful interfacing of mass spectrometry to dissolution have been achieved:

- 1) The linearity of response has been demonstrated in the presence of dissolution buffer (Figure 2) although some suppression in signal is observed. Furthermore, analysis in the presence of non-volatile buffers using this method did not significantly reduce the performance of the instrument; however to maintain this performance, the source was regularly cleaned to prevent any build up of non-volatile buffers.
- 2) No interference has been observed between components.
- 3) Detection of 10 % dissolution was achieved for all four analytes.
- 4) The use of in-line filters meant that no effect was observed from insoluble material from the tablet and no issues with blocking were observed from insoluble tablet components or non-volatile buffers.
- 5) The frequency of sampling has been shown to be sufficient to follow the profile of the species as they are released and is generally greater than would be traditionally be obtained by off-line LC/UV.

CONCLUSIONS

We have successfully demonstrated, for the first time to the best of our knowledge, that on-line mass spectrometry can be used to monitor the dissolution of pharmaceutical tablets containing non-chromophore-containing components. This technique enables multiple APIs and excipients to be monitored simultaneously. We have observed inconsistencies in the results and the causes of these need to be more fully understood, although we believe them to be caused by suppression and enhancement effects. Further work is required to allow accurate quantitation of drug substance dissolution.

Non-volatile buffers such as FaSSIF have not proved to be a problem provided that a suitable make-up flow and sample dilution are used. We have also shown that dissolution media such as SGF and acetate buffer can be interfaced with this detection method, offering a versatile dissolution monitoring facility.

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REFERENCES

- 1) A. Dokoumetzidis, P. Macheras, A century of dissolution research: From Noyes and Whitney to the Biopharmaceutics Classification System. *Int. J. Pharm.* **2006**, *321*, 1
- 2) S. Azarmi, W. Roa, R. Lobenberg, Current perspectives in dissolution testing of conventional and novel dosage forms. *Int. J. Pharm.* **2007**, *328*, 12
- 3) E. S. Kostewicz, B. Abrahamsson, M. Brewster, J. Brouwers, J. Butler, S. Carlert, P. A. Dickinson, J. Dressman, R. Holm, S. Klein, J. Mann, M. McAllister, M. Minekus, U. Muenster, A. Müllertz, M. Verwei, M. Vertzoni, W. Weitschies, P. Augustijns *In vitro* models for the prediction of *in vivo* performance. *Eur. J. Pharm. Sci.* **2014**, *57*, 342
- 4) C. A. S. Bergström, R. Holm, S. A. Jørgensen, S. B. E. Andersson, P. Artursson, S. Beato, A. Borde, K. Box, M. Brewster, J. Dressman, K.-I. Feng, G. Halbert, E. Kostewicz, M. McAllister, U. Muenster, J. Thinnis, R. Taylor, A. Mullertz, Early pharmaceutical profiling to predict oral drug absorption: Current status and unmet needs. *Eur. J. Pharm. Sci.* **2014**, *57*, 173
- 5) K. H. Wiberg, U.-K. Hultin, Multivariate chemometric approach to fiber-optic dissolution testing. *Anal. Chem.* **2006**, *78*, 5076
- 6) R. M. Maggio, M.A. Rivero, T.S. Kaufman Simultaneous acquisition of the dissolution curves of two active ingredients in a binary pharmaceutical association, employing an on-line circulation system and chemometrics-assistance. *J. Pharmaceut. Biomed.* **2013**, *72*, 51
- 7) C. Schatz, M. Ulmschneider, R. Altermatt, S. Marrer, H. Altorfer, Thoughts on Fiber Optics in Dissolution Testing. *Dissolut. Technol.* **2001**, *8*, 1
- 8) S. R. Coombes, L. P. Hughes, A. R. Phillips, S. A. C. Wren, Proton NMR: A New Tool for Understanding Dissolution. *Anal. Chem.* **2014**, *86* 2474
- 9) B. J. McCullough, A. W. Bristow, G. O'Connor, C. Hopley., On-line reaction monitoring by extractive electrospray ionisation. *Rapid Commun. Mass Spectrom.* **2011**, *25* 1445
- 10) E. L. Harry, A. W. Bristow, I. D. Wilson, C.S. Creaser, Real-time reaction monitoring using ion mobility-mass spectrometry. *Analyst* **2011**, *136*, 1728
- 11) K. M. Roscioli, X. Zhang, S. X. Li, G. H. Goetz, G. Cheng, Z. Zhang, W. F. Siems, H. H. Hill Jr. Real time pharmaceutical reaction monitoring by electrospray ion mobility-mass spectrometry. *Int. J. Mass Spectrom.* **2013**, *336*, 27
- 12) D. Fabris, Mass spectrometric approaches for the investigation of dynamic processes in condensed phase. *Mass Spectrom. Rev.* **2005**, *24*, 30
- 13) P. Dell'Orco, J. Brum, R. Matsuoka, M. Badlani, K. Muske Monitoring process-scale reactions using API mass spectrometry. *Anal. Chem.* **1999**, *71*, 5165
- 14) L. Zhu, G. Gamez, H. W. Chen, H. X. Huang, K. Chingin, R. Zenobi, Real-time, on-line monitoring of organic chemical reactions using extractive electrospray ionization tandem mass spectrometry. *Rapid Commun. Mass Spectrom.* **2008**, *22*, 2993–2998
- 15) A. Malcolm, S. Wright, R. R. A. Syms, R. W. Moseley, S. O'Prey, N. Dash, A. Pegus, E. Crichton, G. Hong, A. S. Holmes, A. Finlay, P. Edwards, S. E. Hamilton, C. J. Welch A miniature mass spectrometer for liquid chromatography applications. *Rapid Commun. Mass Spectrom.* **2011**, *25*, 3281
- 16) D. L. Browne, S. Wright, B. J. Deadman, S. Dunnage, I. R. Baxendale, R. M. Turner, S.V. Ley, Continuous flow reaction monitoring using an on-line miniature mass spectrometer. *Rapid Commun. Mass Spectrom.* **2012**, *26*, 1999
- 17) A. W. T. Bristow, A. D. Ray, A. O'Kearney-McMullen, L. Lim, B. McCullough, A. Zammataro On-line monitoring of continuous flow chemical synthesis using a

portable, small footprint mass spectrometer *J. Am. Soc. Mass Spectrom.* **2014.** *25,*
1794

- 18) A. Cappiello, G. Famiglioni, L. Rossi, M. Magnani Use of nonvolatile buffers in liquid chromatography mass spectrometry: Advantages of capillary scale particle beam interfacing. *Anal. Chem.* **1997,** *69,* 5136
- 19) T. M. Annesley Ion suppression in mass spectrometry. *Clin. Chem.* **2003.** *49,* 1041
- 20) N. Donauer, R. Loebenberg, A mini review of scientific and pharmacopeial requirements for the disintegration test. *Int. J. Pharm.* **2007,** *345,* 2