Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Pharmaceutical and Biomedical Analysis 36 (2004) 277–284
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Rapid analysis of liquid formulations containing sodium chloride using laser-induced breakdown spectroscopy

Louis St-Onge [a,*], Elizabeth Kwong [b], Mohamad Sabsabi [a], Elizabeth B. Vadas [c]

[a] *National Research Council Canada, Industrial Materials Institute, 75 de Mortagne Blvd., Boucherville, Que., Canada J4B 6Y4*
[b] *Merck Frosst Canada & Co., P.O. Box 1005, Pointe-Claire-Dorval, Que., Canada H9R 4P8*
[c] *InSciTech Inc., 1215 Morris Avenue, Dorval, Que., Canada H9S 1Z8*

Received 28 March 2004; received in revised form 17 May 2004; accepted 20 May 2004
Available online 29 July 2004

Abstract

The purpose of this work was to demonstrate the possibilities offered by laser-induced breakdown spectroscopy (LIBS) for the direct and rapid analysis of pharmaceutical liquid formulations. Sodium chloride in solution was chosen as a model compound. A pulsed Nd:YAG laser (1064 nm) was used to produce a gaseous plasma from the liquid sample. The ensuing plasma emission was spectrally analysed, and the intensity of an atomic line from sodium was used to quantitate the sodium chloride. Using surface analysis of a flowing solution, the precision (%R.S.D.) of a measurement lasting 50 s (average of 50 laser shots at 1 shot/s) was approximately 0.5% for isotonic solutions. On a non-flowing solution, a 50 s measurement had an R.S.D. of 1.8%. Direct analysis in closed (transparent) bottles was possible but more complex, requiring the superimposition of two sequential laser sparks. Using a surface procedure, common commercial isotonic products (including injectable, bacteriostatic injectable, and nasal solutions) were analysed. Their sodium content (corresponding to 0.9% sodium chloride) was accurately determined in all cases, demonstrating the capabilities of LIBS for the rapid analysis of liquid pharmaceutical products.

Keywords: Laser-induced breakdown spectroscopy (LIBS); Sodium chloride; Isotonic solution; Liquid formulation; Process analytical technologies (PAT)

1. Introduction

Laser-induced breakdown spectroscopy (LIBS) is a rapidly evolving analytical technique utilizing the optical emission spectroscopy of a laser-produced plasma. A small volume (10^{-8} to 10^{-5} cm^3) of the solid, liquid or gaseous sample is intensely heated by a focused laser beam, and thus brought to a gaseous plasma state where the sample components are substantially broken down to atoms. Light given off by this plasma is spectrally analysed and, through a calibration, the intensity of spectral lines from the elements detected in the plasma provide a measure of their concentration in the sample.

LIBS finds more and more application in process monitoring due to its rapidity, its non-contact optical nature, and its freedom from a sample preparation step, characteristics which together enable real-time in situ measurements in a laboratory or industrial setting. The capabilities of LIBS for quantitative elemental analysis have been demonstrated in metallurgy, mining, environmental analysis and numerous other fields [1–4]. In the pharmaceutical sector, the interest in LIBS has appeared only recently [5–9].

To date, LIBS in the pharmaceutical field has been applied exclusively to the analysis of solid dosage forms, namely to quantitate the active pharmaceutical ingredient (API) [7,9]. The analysis is then based on an element specific to the API (e.g., chlorine, sulfur, fluorine or bromine). The same analytical scheme applies in principle to liquid formulations. However, the analysis of pharmaceutical products in solution by LIBS has not been reported yet. Compared to available methods for the analysis of pharmaceutical liquids (colorimetric or potentiometric titration, chromatography, or spectrometric methods), LIBS is a direct and rapid method that does not involve sample preparation. It can also offer advantages such as specificity (analyte versus other excipients) and the possibility of avoiding sample transfer, making it a suitable tool in the rapidly evolving field of process analytics [10].

* Corresponding author. Tel.: +1-450-641-5123; fax: +1-450-641-5106.
E-mail address: louis.st-onge@cnrc-nrc.gc.ca (L. St-Onge).

0731-7085/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2004.06.004

When LIBS is used to analyse liquids, one encounters a set of specific technical issues. In particular, the shock wave accompanying the plasma formation can cause splashing, waves, bubbles, and aerosols, that can all affect the analytical performance, especially the precision. Various approaches have been described in the literature that overcome these problems to different extents. These include analysing (i) the surface of a static liquid body [11–15], (ii) the surface of a vertical flow of liquid [16] or of infalling droplets [17], (iii) the bulk of a (static or moving) liquid [18,19], or (iv) a dried sample of the liquid deposited on a solid substrate [20].

In order to demonstrate the applicability of LIBS to the analysis of liquid pharmaceutical formulations, sodium chloride solution has been chosen as the model liquid system. Apart from providing a convenient proof-of-principle, the study of saline solutions (in particular, isotonic solutions) is relevant in itself as these solutions are present in a great variety of products in use in the medical sector. Therefore, in addition to studying solutions of different NaCl concentration, commercial isotonic products including nasal and injectable solutions were included in this study.

Sodium chloride was quantitated using emission from atomic sodium. In principle, chlorine emission could also be used, but it is much more difficult to detect because of its high activation energy. The isotonic solutions quantitated contained 0.9% NaCl, which is equivalent to about 0.35% Na. At this sodium concentration, sensitivity was not a major concern and measurement precision was the main analytical parameter to be optimized.

Finally, instead of presenting the liquid sample to the analytical instrument in a very specific and inflexible manner, the versatility inherent in the LIBS technique enables the opposite approach: to adapt the analytical instrument to the sample and its environment. Accordingly, three very different schemes were investigated and compared: bulk liquid analysis (in a closed bottle), analysis of a flowing horizontal surface, and analysis of a non-flowing surface inside a container.

2. Experimental

The first scheme used here for the analysis of liquid has been devised by Cremers et al. [18] for analysing bulk transparent liquids, with the laser beam tightly focused inside a liquid cell through a quartz window. The plasma produced with this laser pulse decays rapidly, being quenched by the surrounding liquid. However, an expanding gaseous cavity is left behind. Another laser pulse is then fired (after tens of microseconds) to produce a second plasma inside this bubble. In this way, plasma is surrounded by gas and is thus longer-lived, making it more useful analytically. The same scheme will be applied here, but directly in closed glass bottles containing the solution.

Although analysis of vertical liquid flows using LIBS is well known [16], the analysis of horizontally flowing liquid has been reported only recently [21]. Sabsabi et al. described a prototype developed for industrial applications necessitating the analysis of continuous horizontal flows. The second scheme investigated here uses the same setup, which can function also as a closed-loop system, as long as a minimum of 1.5 l of liquid is present. Here, double pulses are not required since the plasma is formed on the liquid surface and evolves in air, and thus has a longer lifetime than that observed for bulk analysis.

The third scheme studied in the present work is the simplest. It consists in replacing the flow cell of Scheme 2 with an open bottle containing the sample, and the non-flowing liquid surface is subjected to analysis.

The three schemes investigated had several features in common. Laser radiation at 1064 nm was provided in pulses of approximately 10 ns duration by a solid-state Nd:YAG laser. The laser beam was focused on the sample in order to provide a sufficient energy density for the formation of a plasma. The plasma light emission was collected and transported to the entrance slit of a grating Czerny-Turner-type spectrograph using either fiber or lens optics. Time-resolved detection of the dispersed light was carried out using either an intensified photodiode array (IPDA) or intensified charge-coupled device (ICCD). The detection gate (delayed relative to the laser pulse) was provided by a high-voltage pulse on the intensifier, triggered by a photodiode that collected scattered laser light. In LIBS, such temporal resolution is required in order to gate off the early period of the plasma, characterized by an intense featureless background emission and wide spectral lines.

In the following, details of the experimental arrangement are given for each of the three schemes investigated.

2.1. Scheme 1: analysis of bulk

Similarly to Cremers et al. [18], a double-pulse approach was implemented, using a single Nd:YAG laser (Surelite I-10, Continuum, Santa Clara, CA, USA) configured so that the Q-switch could be triggered twice in the same flashlamp pulse. The two laser pulses were controlled externally by an electronic circuit, with an interpulse interval Δt adjustable in the range 0–65 μs. The energy of each pulse was chosen based on previous literature [18,22] and kept constant at 40 and 135 mJ for the first and second pulses, respectively. In order to obtain a well-localized breakdown in the liquid, the laser-focusing system consisted of two plano-convex lenses, 12.7 mm in diameter and each with a focal length of 38 mm, spaced by 1 mm. The resulting focal length of the lens pair was approximately 19 mm. This lens arrangement was similar to that of Knopp et al. [19]. The laser beam was incident horizontally on the bottle, which was held vertically in a three-finger clamp. The distance between the lens and bottle was adjustable. A circular fiber-optic bundle was brought as close as possible to the bottle at 90° from the laser beam in order to capture light from the whole volume of plasma. The fiber-optic bundle was converted to a linear array at

the other end of the cable, and was aligned with the entrance slit of a 0.66 m monochromator (McPherson, Acton, MA, USA) equipped with a 600 grooves/mm grating. The dispersed light was detected by an IPDA (Princeton Instruments, Trenton, NJ, USA). The samples consisted of a commercial bacteriostatic sodium chloride injection with 0.9% (w/v) NaCl (isotonic), used as is or diluted to concentrations of 0.7, 0.5, 0.3, 0.1, 0.05% with deionized water, as well as a 0% sample (deionized water). It was verified that the latter sample did not give rise to sodium signal significantly above noise. Separate (closed) transparent bottles were prepared for each concentration, with a volume of 18 ml in all cases. The undiluted solution could also be analysed in its original packaging (hermetically closed transparent bottle).

2.2. Scheme 2: analysis of flowing surface

The experimental setup is shown in Fig. 1. The closed-loop system operated with 3 l of liquid with a flow rate of 1 l/min, corresponding to a flow speed of approximately 2 cm/s. The flow of liquid ensured the analysis of a renewed surface at each laser pulse since the moving liquid continuously removed bubbles created by previous laser pulses. The design of the cell is such that waves created by the laser-induced shock wave were rapidly eliminated and a stable surface was analysed. It also ensured vertical mixing of the liquid so that the analysis was representative of the whole volume. The droplets and aerosols produced by the laser–liquid interaction were deflected from the optical path using an air jet and exhaust, reducing significantly the problems associated with secondary breakdown in the air space above the sample. The Nd:YAG laser (Big Sky Laser Technol., Bozeman, MT, USA) fired 220 mJ pulses (at 1 pulse/s) in a beam focused from above on the liquid surface, with a focusing length of approximately 400 mm. The plasma light was collected and brought to a 0.55 m spectrograph (Triax Series, Jobin Yvon, Edison, NJ, USA) using a lens-fiber system. A 1200 grooves/mm grating was used. Detection was ensured by an ICCD camera (Andor Technol., South Windsor, CT, USA). In order to obtain a response curve for the sodium signal, a batch of approximately 1% NaCl solution was prepared using table salt (which also contains a small amount of sodium in other compounds). It was successively diluted several times by a factor of two with deionized water.

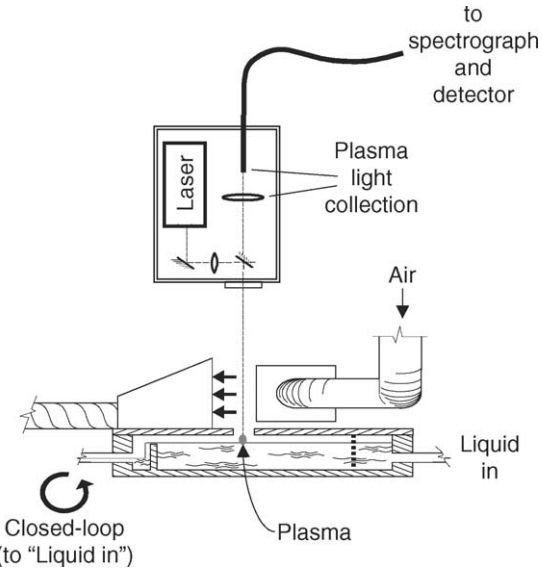

Fig. 1. Schematic drawing of the experimental setup for the surface analysis of a flowing liquid (Scheme 2).

2.3. Scheme 3: analysis of non-flowing surface

The same instrumentation was used as for Scheme 2 (Fig. 1). The flow cell was removed and an open bottle containing the sample was put in its place on a platform positioned vertically so that the liquid surface was approximately at the laser focus position. Displacing the focus position inside the liquid led to more bubbles and splashing. Better results were obtained with the focus at, or slightly above the surface. The same laser energy was used as in Scheme 2. In these experiments, a 600 grooves/mm grating was used. The samples consisted of a calibration set and a commercial sample set. The calibration set was prepared using Reagent A.C.S. sodium chloride (Fisher) with >99% purity, diluted in deionized water to concentrations around the isotonic conditions (0, 0.5, 0.7, 0.9, 1.1, 1.3%). The commercial sample set consisted of: a 0.9% NaCl injectable (sample A), a 0.9% NaCl bacteriostatic injectable (sample B), an isotonic nasal mist (sample C) with 0.7% NaCl and other sodium (edetate disodium and sodium phosphate) in non-disclosed concentration, and a 0.9% NaCl nasal solution (sample D). In all cases, a 15 ml volume was put in a small straight-sided plastic (LDPE) container without any constriction at the opening.

3. Results

3.1. Analysis of bulk

Cremers et al. [18] noted that an elongated and less reproducible plasma resulted when focusing the laser in the liquid far from the window of their cell. In the present experiments with glass bottles, the laser focus was always positioned as close as possible to the bottle inner wall but far enough to avoid laser-induced breakdown (and therefore irreversible damage) in the wall. Plasma formation was seen to occur approximately 1–2 mm from the wall.

In terms of vertical positioning, it was found that focusing the laser just a few millimetres below the surface resulted in instability of the surface due to perturbation by the laser-induced shock wave. Measurements were therefore performed at approximately 1 cm from the bottom of the ~5 cm high bottles.

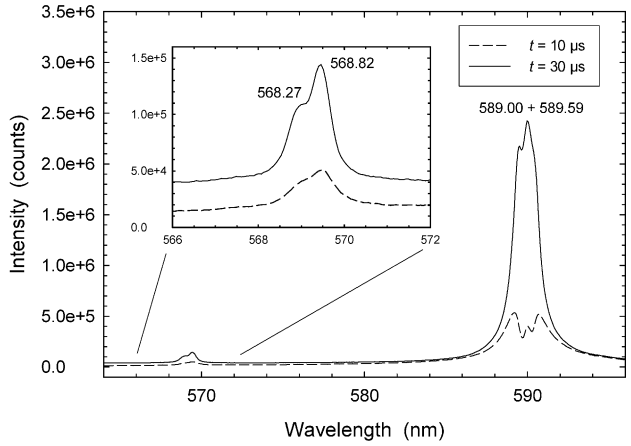

Fig. 2. LIBS spectra in the vicinity of the two sodium doublets, obtained using Scheme 1 at two values of the interpulse interval Δt. The inset shows a zoom on the 569 nm doublet.

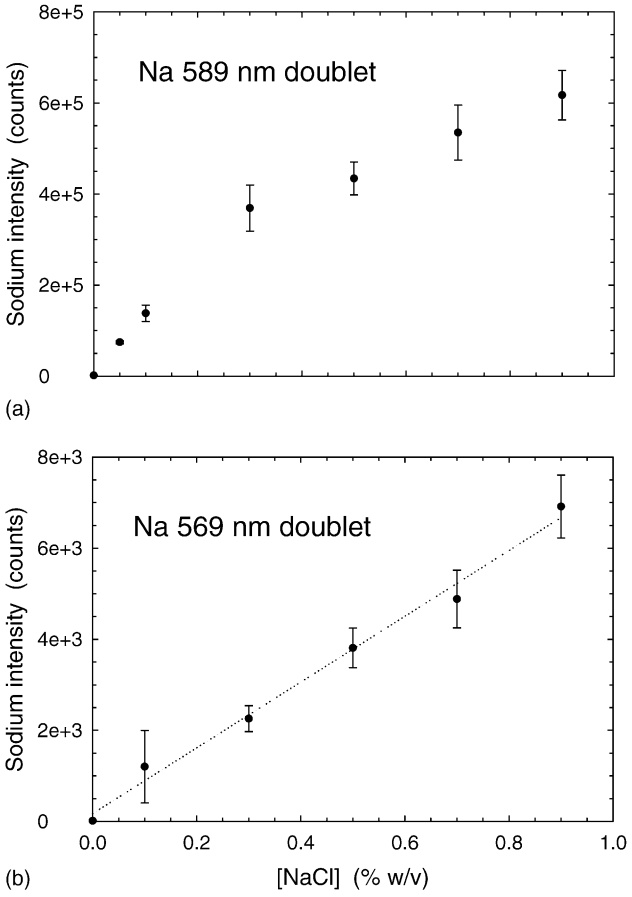

Fig. 3. Response curves for the atomic sodium signal as a function of NaCl concentration (Scheme 1), based on the area of (a) the 589 nm doublet and (b) the 569 nm doublet.

The main parameter to be optimized in this experiment was the time interval Δt between the two pulses of a burst. Spectra were obtained for different values of Δt, from 0 μs (single pulse) to 60 μs. Fig. 2 shows two spectra for $\Delta t = 10$ and 30 μs. The sodium emission in this spectral region consists of two doublets (i.e. groups of two lines). The one around 589 nm is a resonance transition (it connects a low-lying excited level to the ground state of the atom). Since the ground state population is larger than the excited state population, resonance lines are subject to self-absorption, a phenomenon wherein light emitted at one position in the plasma is reabsorbed elsewhere. The doublet at 569 nm is non-resonant (the lower level of this transition is not the ground state), therefore it is much less subject to self-absorption.

In Fig. 2, self-absorption of the 589 nm doublet is observed for $\Delta t = 10$ μs as line reversal. After 30 μs, this phenomenon was much less important, indicating that the gas became less dense as the bubble was allowed to expand. No reversal of the 569 nm doublet was observed, but there was a better separation of the two lines for larger Δt. Nevertheless, both 569 and 589 doublets were not completely resolved. This is mainly due to line emission coming from a dense and hot medium which causes line broadening, and not to a limited resolving capability (the instrumental linewidth is estimated at 0.1 nm). A Δt of 30 μs was used as it also ensured optimal sensitivity and precision. Detection of the plasma emission was delayed by 1 μs relative to the second laser pulse, and the signal integration time was 2 μs. These parameters ensured that the background signal was sufficiently low, and that most of the Na signal was detected. The laser repetition rate was fixed at 1.25 s^{-1}. A higher rate led to the accumulation of tiny bubbles in the volume of liquid. This led to a large signal variability and a weaker average signal, probably through misfocusing of the laser beams.

Fig. 3a and b shows response curves for the sodium 589 and 569 nm doublets, respectively, as a function of sodium chloride concentration. The characteristics of these two response curves are typical of those observed for resonance and non-resonance lines in general. By using the 589 nm doublet, a greater sensitivity is achieved but self-absorption is more important, as shown by a decreasing slope at high concentrations. The use of the 569 nm doublet, on the other hand, leads to a linear response over a wider concentration range, but with a lower sensitivity (by approximately two orders of magnitude as seen in Fig. 3). Thus, the former line is well-suited for the detection of traces, while the latter has a greater dynamic range.

Due to the difficulty of precisely superimposing the focus positions of the two laser pulses in a small volume, and of occasional misfocusing of the beams due to the presence of bubbles remaining after previous laser bursts, the variability of the signal was quite high on a shot-to-shot basis. Group averaging was used to increase precision. The error bars in Fig. 3 correspond to ±1 standard deviation for measurements defined as averages of 50 shots, i.e. for measurements lasting 40 s (at 1.25 pulses/s). The relative standard deviation (R.S.D.) was around 10%. It would be possible to improve the precision with even longer measurements, or through better laser

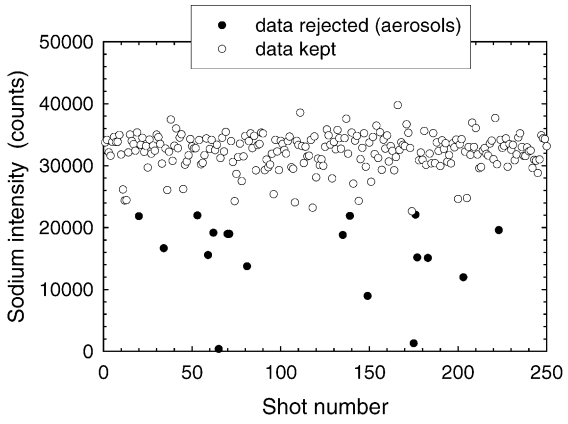

Fig. 4. Intensity (peak height) of the 589 nm doublet for 250 consecutive laser shots using Scheme 2, for a 1% (w/v) NaCl solution. Shown in solid circles are those shots ascribed to aerosols events, as defined in the text.

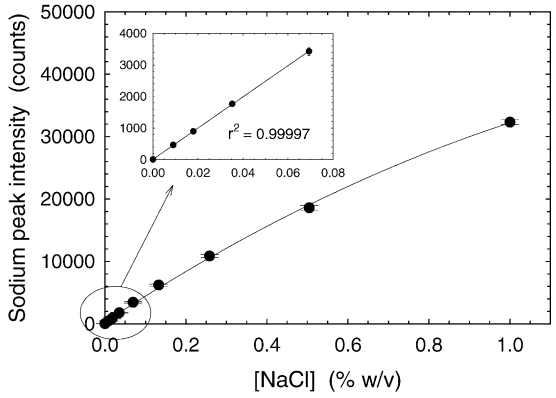

Fig. 5. Response curve for the atomic sodium 589 nm peak height as a function of NaCl concentration (Scheme 2). The inset shows the highly linear part of the curve at low concentrations.

beam alignment and filtering out of data that correspond to laser bursts where the desired laser–gas interaction does not occur.

3.2. Analysis of flowing surface

The main experimental parameter that needed to be optimized in this case was the observation delay, i.e. the time after the (single) laser pulse when signal integration starts. In this scheme, as well as for the analysis of non-flowing solutions (Section 3.3), it was observed that the background signal decreased rapidly with increasing delay (from 0.5 to 10 μs). In a situation where a small atomic signal would need to be distinguished from the background, a large delay would therefore be better. However, it was also found that the shot-to-shot %R.S.D. of the sodium signal increased with the delay. For the analysis of isotonic solutions (0.9% NaCl), the sodium signal was large and therefore a relatively large background could be tolerated. It was decided to select a delay that provided instead a good precision of measurement. A small delay of 1 μs was chosen, with an integration time of 2 μs.

In the experimental setup developed for this scheme, several provisions were included to improve the measurement precision (see Section 2.2). Nevertheless, because of the high laser pulse energy (220 mJ), some laser pulses led to breakdown above the liquid surface due to the occasional presence of aerosols in the laser beam. The sodium signal corresponding to these events was systematically lower than average because energy was absorbed in the undesired breakdown, leaving less energy for analysis of the liquid surface. This resulted in outliers, as illustrated by the sodium intensity plot shown in Fig. 4 for a 1% NaCl solution. These outliers were all below the main distribution of intensities.

A simple empirical criterion can be used to reject the outliers. If I_{max} is the maximum intensity in the group of data points (here, consisting of 250 shots) and I_{ave} is the average intensity of the same group, a data point with intensity I is rejected if

$$I < I_{ave} - (I_{max} - I_{ave}). \quad (1)$$

Since undesired aerosol events never lead to larger intensities than for the desired surface analysis, the difference $I_{max} - I_{ave}$ is considered the largest "normal" scatter above the average value. Allowing for the same normal scatter *below* the average value, the above criterion then consists in rejecting intensities not included in this normal scatter range. In Fig. 4, the data points that satisfied this criterion, and that were therefore rejected, are shown as solid circles.

Compared to bulk analysis, the response curve obtained with surface analysis for the resonance doublet at 589 nm showed a smaller deviation from linearity, as shown in Fig. 5. Self-absorption was less important in the latter case because the laser-produced plasma could expand in the open atmosphere, resulting in a lower atomic sodium density. The inset of Fig. 5 shows that the portion of the response curve at low concentrations has very good linearity. For this figure, a measurement was defined as the average of 25 shots (lasting 25 s at 1 pulse/s). Table 1 reports in detail the precision (%R.S.D.) as a function of NaCl concentration and measurement time. The measurement precision was better than for bulk analysis. Predictably, it increased with measurement

Table 1
Precision of measurement as a function of NaCl concentration and measurement time, using the analysis of flowing solution

[NaCl] (%, w/v)	Precision (%R.S.D.) for given measurement time			
	1 s	10 s	25 s	50 s
1.0	8.60	2.86	1.21	0.520
0.504	11.0	3.46	2.06	0.529
0.258	12.7	4.04	2.21	0.917
0.133	11.1	3.60	2.72	1.85
0.0693	13.4	5.46	3.71	3.42
0.0352	16.8	5.85	3.52	2.95
0.0179	28.3	11.0	9.24	2.38
0.0091	41.7	13.8	7.03	5.61

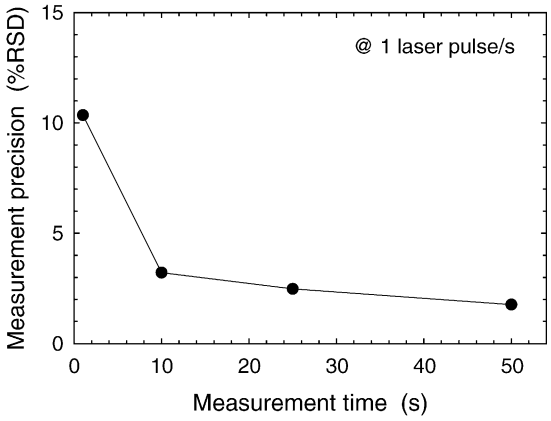

Fig. 6. Measurement precision (%R.S.D.) as a function of measurement time using Scheme 3, for commercial sample A (0.9% (w/v) NaCl).

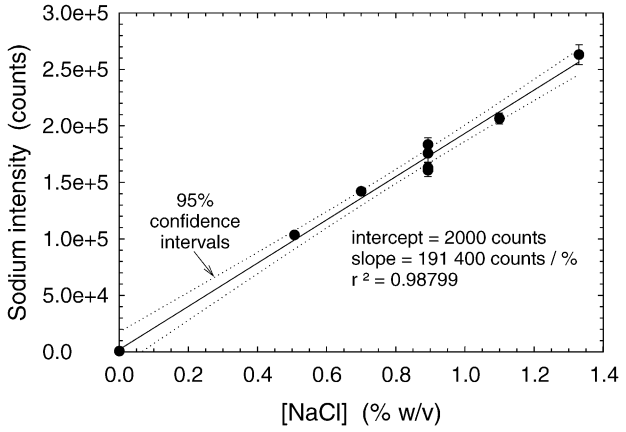

Fig. 7. Calibration curve for the atomic sodium 589 nm doublet area as a function of NaCl concentration (Scheme 3). The curves of 95% confidence are shown.

time and sodium concentration. An R.S.D. of 0.5% was achieved for concentrations higher than 0.5% (w/v) of NaCl in a measurement time of 50 s, i.e. in less than 1 min. These results apply to the commercially relevant range of isotonic solutions (0.9% NaCl).

At a low laser repetition rate (1 pulse/s), the R.S.D. values were similar to those reported in Table 1 even when aerosol events were not rejected. Additional experiments showed however that for higher rates (2 or 5 pulses/s), aerosol events were more numerous, and precision improved significantly when these events were not included.

3.3. Analysis of non-flowing surface

For the analysis of a non-flowing surface, the timing parameters consisted of an observation delay of 1 μs and an integration time of 1 μs. Acquisitions consisted of series of 300 laser shots, at 1 pulse/s.

Fig. 6 shows the measurement precision (%R.S.D.) as a function of measurement time using the sodium 589 nm doublet, for commercial sample A (a 0.9% NaCl injectable solution). The best precision (%R.S.D.), obtained as before with a long measurement time (50 s), was approximately 1.8%. Although quite good, it was 3.5 times larger than when analysing a flowing solution (Section 3.2). This is explained by the occurrence of surface perturbations and bubbles remaining from previous shots, which can affect somewhat the reproducibility of the laser–sample interaction.

Fig. 7 shows the calibration curve built using the set of calibration samples described in Section 2.3. The linear regression curve, along with 95% confidence intervals, are shown. The regression coefficient is very good, considering that the resonance doublet at 589 nm was used, and that concentrations up to 1.3% were analysed. The data include four separate analyses of the 0.9% solution performed at different times. The four measurements showed slight variability, as seen in Fig. 7. The cause for such variability may be related to changes in the height of the liquid surface relative to the focusing position of the laser beam. Since the laser-induced shock wave led to some splashing, therefore causing loss of liquid, repeated firing of the laser eventually led to a lowering of the liquid level, which necessitated refilling the container to a certain predetermined position corresponding to 15 ml. The full length of the error bars shown in Fig. 7 corresponds to twice the standard deviation for 25 s measurements.

3.4. Quantitation of commercial products

Using Scheme 3 (analysis of non-flowing surface) and the linear regression coefficients calculated from the data shown in Fig. 7, the predicted sodium signal for an isotonic solution (0.9% NaCl) is given in Table 2, together with the signal obtained from the four commercial isotonic solution samples included in this study. The standard deviation (S.D.) for the predicted value is obtained from the 95% confidence interval for the regression shown in Fig. 7. The standard deviation for the commercial samples is based on two or more replicate analyses of each sample (each analysis corresponding to the average of 300 laser shots). The results in Table 2 for the commercial products showed estimates very close to the label claim. It should be stressed again that LIBS uses the signal from atomic sodium to infer, through calibration, the concentration of the sodium source, NaCl in this case. If

Table 2
Measured intensity (area) of the 589 nm doublet for the four different commercial isotonic samples, and predicted Na intensity for a 0.9% (exact) NaCl solution

Sample ID	Na intensity ($\times 10^3$ counts)	S.D. ($\times 10^3$ counts)	[NaCl][a] (%, w/v)
A	172.9	2.0	0.893
B	176.7	1.5	0.913
C	174.3	5.0	0.900
D	167.5	1.6	0.865
0.9% NaCl	174.3[a]	7.0[a]	

Also given is the "equivalent" NaCl concentration inferred from the calibration.

[a] Calculated from the calibration curve of Fig. 7.

sodium comes from other sources, the total sodium content is observed, without distinction of the source. This is the case of sample C, which contains two other sources of sodium in addition to NaCl (see Section 2.3). Table 2 shows that, in fact, sample C has about the same total atomic sodium content as the samples with 0.9% NaCl (i.e. ∼0.35% Na). LIBS provides in such a case a measurement of total sodium in "NaCl equivalent", as shown in the last column of Table 2.

4. Discussion

In the previous section, results were shown that illustrated the use of three different schemes for the rapid analysis of liquid preparations. The quantitation of sodium chloride (through the sodium signal) was found to be feasible in all three cases, albeit with different analytical performances. The advantages and disadvantages of each scheme will be discussed in order to assist in the choice of a particular scheme for a given application in a given industrial or laboratory setting.

Scheme 1 is obviously the method of choice if measurements in closed (transparent) bottles are required. This does not guarantee however a fully non-destructive monitoring of a finished bottled product in that the content of the bottle does not necessarily remain unaffected by the measurement. For more complex compounds than sodium chloride, the laser vaporization process might lead to the formation of degradation products. However, if only a small number of laser shots are fired in the liquid for a given measurement (e.g., 50 shots), degradation may turn out to be very limited. This would be product-specific and should be evaluated carefully for any given product. Finally, it must be noted that among the three schemes, the lowest precision was obtained with Scheme 1. This particular approach would require improvements in the instrumental setup to obtain a more appropriate precision.

Scheme 2 was found to provide the highest precision. This is due primarily to analysing a renewed, stable and flat surface at each laser shot in this configuration. In contrast to the previous scheme, a double-pulse approach is not necessary because the plasma quenching by the liquid is much less significant and the plasma is therefore longer lived. Moreover, the liquid is not required to be substantially transparent. In fact, an absorbing liquid might bring a more reproducible laser–sample interaction in the case of surface analysis. Spurious measurements can result from the release of aerosols above the sample in the path of the laser beam but, as shown in this work, there are ways to control aerosol production or minimize their impact on the analytical performance. Scheme 2 does however bring the possibility of contamination, through sample manipulation and the apparatus required for producing flow. Further work aimed at designing an apparatus fully adapted to pharmaceutical liquids would be able to address this issue. Such an apparatus could also be miniaturized in order to accommodate much smaller volumes of liquids, as commonly encountered during the development and manufacture of small volume parenterals.

Scheme 3 offers acceptable precision and is the easiest to implement; it requires a relatively simple optical setup and no flow cell. Although it is not as precise as Scheme 2, primarily because of occasional surface instability or bubbles, this approach still offers %R.S.D.s lower than 2% for measurements lasting less than a minute. Scheme 3 requires optical access to the liquid surface, but the sample handling can be reduced to a minimum: all results presented here were obtained by transferring the contents of commercial solutions from their original containers to cylindrical plastic containers having no constriction at their opening. Some tests were performed in the original glass container of one of the commercial products (sample A), with the closure removed. This bottle had a narrow opening and the liquid surface was situated below the constriction. As a result, evacuation of aerosols was not very efficient and the precision was reduced by a factor of three compared to the results presented in Section 3.3. It should be noted that, even if transferring the solution to a container without a constricted opening to increase precision, the liquid level should not be too far below the top of the container in order to ensure efficient evacuation of aerosols by the blower/exhaust system (see Fig. 1). In addition to aerosol evacuation, it is likely that the dimensions and shape of the container, as well as the liquid level influence the dynamics of bubbles produced inside the liquid, which also affect the analytical precision. Further studies to address this issue are warranted.

5. Conclusions

The present study evaluated three different configurations for the analysis of liquid formulations using LIBS: analysis in closed (transparent) bottles, on the surface of a flowing liquid stream, or in open containers (on the non-flowing liquid surface). Using sodium chloride in solution as the model compound, it is concluded that the analysis of a non-flowing surface (Scheme 3) provides the best compromise in terms of ease of implementation and precision. This approach is also the one most adapted to the configuration of an existing commercial LIBS instrument (Pharma Laser, Boucherville, Que., Canada). The choice of a given configuration may however depend on other practical issues. In an industrial setting, the first scheme could be used for quality control of the final bottled product, while the other two schemes could be used for process monitoring or quality control prior to packaging. In the present case, it was demonstrated that LIBS analysis can provide an accurate and precise (down to 0.5% R.S.D.) determination of NaCl content in different commercial isotonic products. Unlike conventional methods such as one described in the USP [23] for testing commercial sodium chloride solution, LIBS measurements do not require sample preparation and can provide an analytical result in less than 1 min. Furthermore, with the current prototype,

LIBS could be utilized for the quantitation of more than one compound, using the emission of more than one specific element. Indeed, based on the results of this proof-of-concept study of saline solution, it is anticipated that LIBS would be equally suited for the rapid analysis, possibly on-line, of other compounds (e.g., drugs) in liquid pharmaceutical products, making it a valuable process analytical technology [10].

Acknowledgements

The authors wish to acknowledge the skilled technical support of Mr. R. Héon, as well as useful discussions with Dr. S. Béchard.

References

[1] L.J. Radziemski, Microchem. J. 50 (1994) 218–234.
[2] D.A. Rusak, B.C. Castle, B.W. Smith, J.D. Winefordner, Crit. Rev. Anal. Chem. 27 (1997) 257–290.
[3] J. Sneddon, Y.-I. Lee, Anal. Lett. 32 (1999) 2143–2162.
[4] E. Tognoni, V. Palleschi, M. Corsi, G. Cristoforetti, Spectrochim. Acta, Part B 57 (2002) 1115–1130.
[5] M. Sabsabi, J. Bussière, US Patent 5,781,289 (14 July 1998).
[6] L. St-Onge, R. Sing, S. Béchard, M. Sabsabi, Appl. Phys. A 69 (1999) S913–S916.
[7] S. Béchard, Pharm. Formulation Qual. 3 (2001) 37–40.
[8] M.D. Mowery, R. Sing, J. Kirsch, A. Razaghi, S. Béchard, R.A. Reed, J. Pharm. Biomed. Anal. 28 (2002) 935–943.
[9] L. St-Onge, E. Kwong, M. Sabsabi, E.B. Vadas, Spectrochim. Acta, Part B 57 (2002) 1131–1140.
[10] S.M. Arrivo, Am. Pharm. Rev. 6 (2003) 46–53.
[11] J.R. Wachter, D.A. Cremers, Appl. Spectrosc. 41 (1987) 1042–1048.
[12] G. Arca, A. Ciucci, V. Palleschi, S. Rastelli, E. Tognoni, Appl. Spectrosc. 51 (1997) 1102–1105.
[13] L.M. Berman, P.J. Wolf, Appl. Spectrosc. 52 (1998) 438–443.
[14] P. Fichet, A. Toussaint, J.-F. Wagner, Appl. Phys. A 69 (1999) S591–S592.
[15] B. Charfi, M.A. Harith, Spectrochim. Acta, Part B 57 (2002) 1141–1153.
[16] N.H. Cheung, E.S. Yeung, Appl. Spectrosc. 47 (1993) 882–886.
[17] H.A. Archontaki, S.R. Crouch, Appl. Spectrosc. 42 (1988) 741–746.
[18] D.A. Cremers, L.J. Radziemski, T.R. Loree, Appl. Spectrosc. 38 (1984) 721–729.
[19] R. Knopp, F.J. Scherbaum, J.I. Kim, Fresenius J. Anal. Chem. 355 (1996) 16–20.
[20] R.L. Vander Wal, T.M. Ticich, J.R. West Jr., P.A. Householder, Appl. Spectrosc. 53 (1999) 1226–1236.
[21] M. Sabsabi, R. Héon, J. Lucas, L. St-Onge, V. Detalle, A. Hamel, in: Laser Induced Plasma Spectroscopy and Applications, OSA Technical Digest Series 81, Optical Society of America, Washington, DC, 2002, pp. 45−47.
[22] A.E. Pichahchy, D.A. Cremers, M.J. Ferris, Spectrochim. Acta, Part B 52 (1997) 25–39.
[23] USP25/NF20, United States Pharmacopeial Convention, Inc., MD, USA, 2002.