Lasers Med Sci (2018) 33:263–270
https://doi.org/10.1007/s10103-017-2358-8

ORIGINAL ARTICLE

Rapid analysis of pharmaceutical drugs using LIBS coupled with multivariate analysis

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Received: 31 January 2017 / Accepted: 10 October 2017 / Published online: 27 October 2017

Abstract Type 2 diabetes drug tablets containing voglibose having dose strengths of 0.2 and 0.3 mg of various brands have been examined, using laser-induced breakdown spectroscopy (LIBS) technique. The statistical methods such as the principal component analysis (PCA) and the partial least square regression analysis (PLSR) have been employed on LIBS spectral data for classifying and developing the calibration models of drug samples. We have developed the ratio-based calibration model applying PLSR in which relative spectral intensity ratios H/C, H/N and O/N are used. Further, the developed model has been employed to predict the relative concentration of element in unknown drug samples. The experiment has been performed in air and argon atmosphere, respectively, and the obtained results have been compared. The present model provides rapid spectroscopic method for drug analysis with high statistical significance for online control and measurement process in a wide variety of pharmaceutical industrial applications.

Keywords LIBS · PLSR · Pharmaceutical drugs · Voglibose

Introduction

It is difficult to achieve online in-situ analysis of dosage strength and composition of pharmaceutical drugs. The elemental analysis of pharmaceutical drugs is becoming more important, both from product quality and patient safety perspectives. In general, the most basic form of the drug matrix is made up of organic compounds containing carbon, hydrogen, nitrogen and oxygen [1, 2]. Typically, all pharmaceutical drugs are manufactured by compacting mixture of organic active pharmaceutical ingredient (API) and excipients [1–3]. In the matrix of drug, excipients may be additional inorganic elements or impurities due to manufacturing sources of error [1–3]. Furthermore, in the manufacturing of pharmaceutical drugs, the active ingredients can be typically as low as 1–2% and as high as 50–60% of the tablet weight [2]. In pharmaceutical industries, analytical techniques that provide rapid characterizations of pharmaceutical drug samples have great significance. The near-infrared (NIR) spectroscopy and high-performance liquid chromatography (HPLC) are worldwide accepted techniques for the analysis of pharmaceutical drug samples [2–5]. In case of quantitative analysis of pharmaceutical drug samples, NIR technique requires to form statistical manipulation of the spectra [4, 5]. Additionally, the NIR measurement of samples outside the range of calibration is invalid and the sensitivity goes down to concentration 2–5% by weight of drug [4, 5]. In the manufacturing of pharmaceutical drugs, the analytical technique HPLC has been effectively used, but, as a matter of cost, HPLC is not so efficient for rapid and online monitoring [2, 3, 5]. The major drawbacks of HPLC technique are as follows: (i) requirement of extraction sample with the need of organic solvent as for standard, (ii) destructive and labour intensive and (iii) time consuming [2, 3, 5]. Laser-induced breakdown spectroscopy (LIBS) is achieving significant popularity for rapid chemical analysis in solid matrix as compared to other direct analysis techniques such as INAA, LA-ICPMS, GDMS and XRF [2, 5–7]. Although these techniques are highly accurate, in some cases, these techniques are not preferred because of their

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sophistication of instrument and requirement of sample preparation before the measurements [3, 5–7]. LIBS offers several remarkable features like in-situ and real-time monitoring of chemical species, dosage strength identification and classifications of pharmaceutical samples [2, 5]. LIBS is a non/minimal distractive technique which can detect all integral parts (organic and inorganic) of pharmaceutical sample in a single step. In essence, LIBS is an elemental analysis technique for rapid and spot analysis of wide range of samples. It offers the capability to analyse different phases, i.e. solid, liquid, gas, aerosol, powders, biological material, polymers, etc., of samples under any atmospheric condition [5–9]. This technique does not require additional chemicals, which makes it safe and environment friendly. LIBS can play a major role in elemental analysis of surface and internal distribution of drug samples.

In the present study, we have examined five uncoated drug samples named by A, B, C, D and E which contain only voglibose as API, of dose strength 0.3, 0.2, 0.3, 0.2 and 0.3 mg, respectively, using LIBS. The above five samples belong to three different brands; A and B belong to one brand, C and D belong to the second brand and E belongs to third brand. Six spectra of each tablet have been recorded and each spectrum has an accumulation of 50 laser shots. Five tablets of each sample have been investigated for the study. Voglibose ($C_{10}H_{21}NO_7$) was discovered in Japan in 1981 and it is a class of competitive alpha-glucosidase inhibitors (α-GIs) which is used for the treatment of type 2 diabetes [10]. Due to high complexity of LIBS data, multivariate analysis (MVA) has been used for the study of different drug samples. MVA is a well-established chemometric method that can be employed on variables of LIBS spectral intensities corresponding to different wavelengths [11]. Notably, MVA along with LIBS is a powerful technique for pharmaceutical drug samples [11, 12]. The multivariate statistical methods, PCA has been used to analyse the LIBS spectral data set for the discrimination of different drugs, whereas partial least square regression analysis (PLSR) has been used to build up the calibration models to predict the relative concentrations of different elements in unknown samples [11, 12]. With the development of calibration modal and the optimization of various parameters, LIBS is more promising for qualitative as well as quantitative analysis of various elements in a wide range of samples [5–9, 11, 12]. Therefore, we have incorporated multivariate statistical methods to utilise the full extent of available LIBS spectral data of pharmaceutical drug samples. In the present study, LIBS spectra of drug samples A, B, C, D and E have been recorded in air and argon atmosphere, respectively. The results obtained in air and argon atmosphere of relative concentrations of organic elements in drug samples have been calculated and compared. Thus, our developed PLSR model can be used to predict the relative concentrations of various elements as well as different dosage strengths of unknown drug samples.

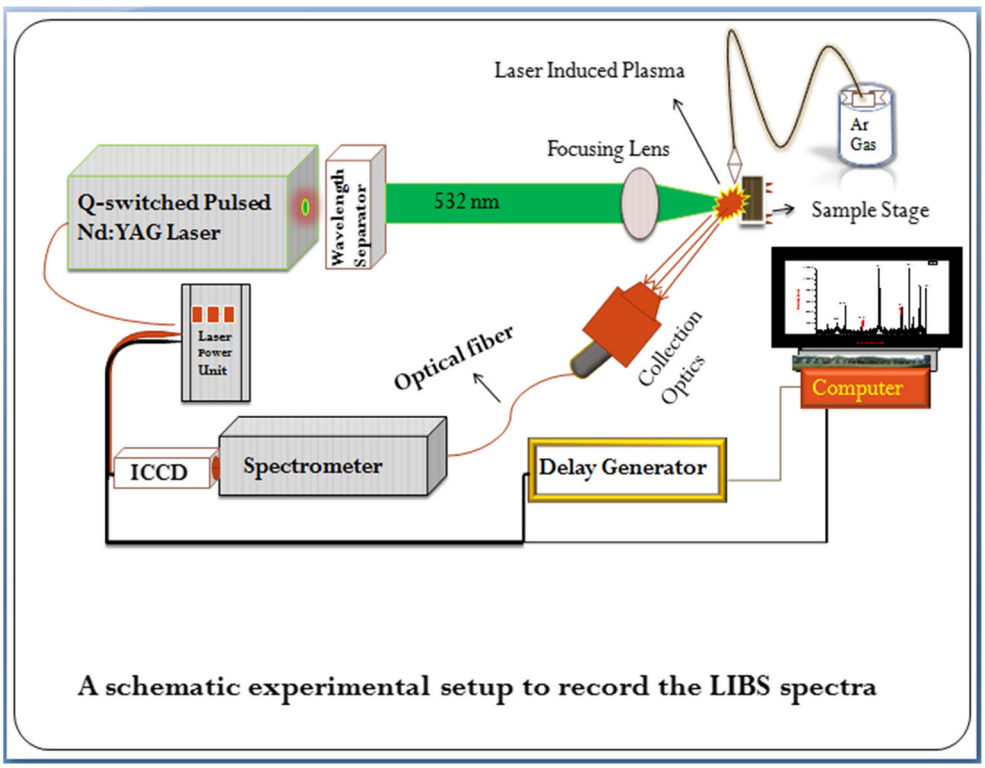

Fig. 1 A schematic experimental setup to record the LIBS spectra

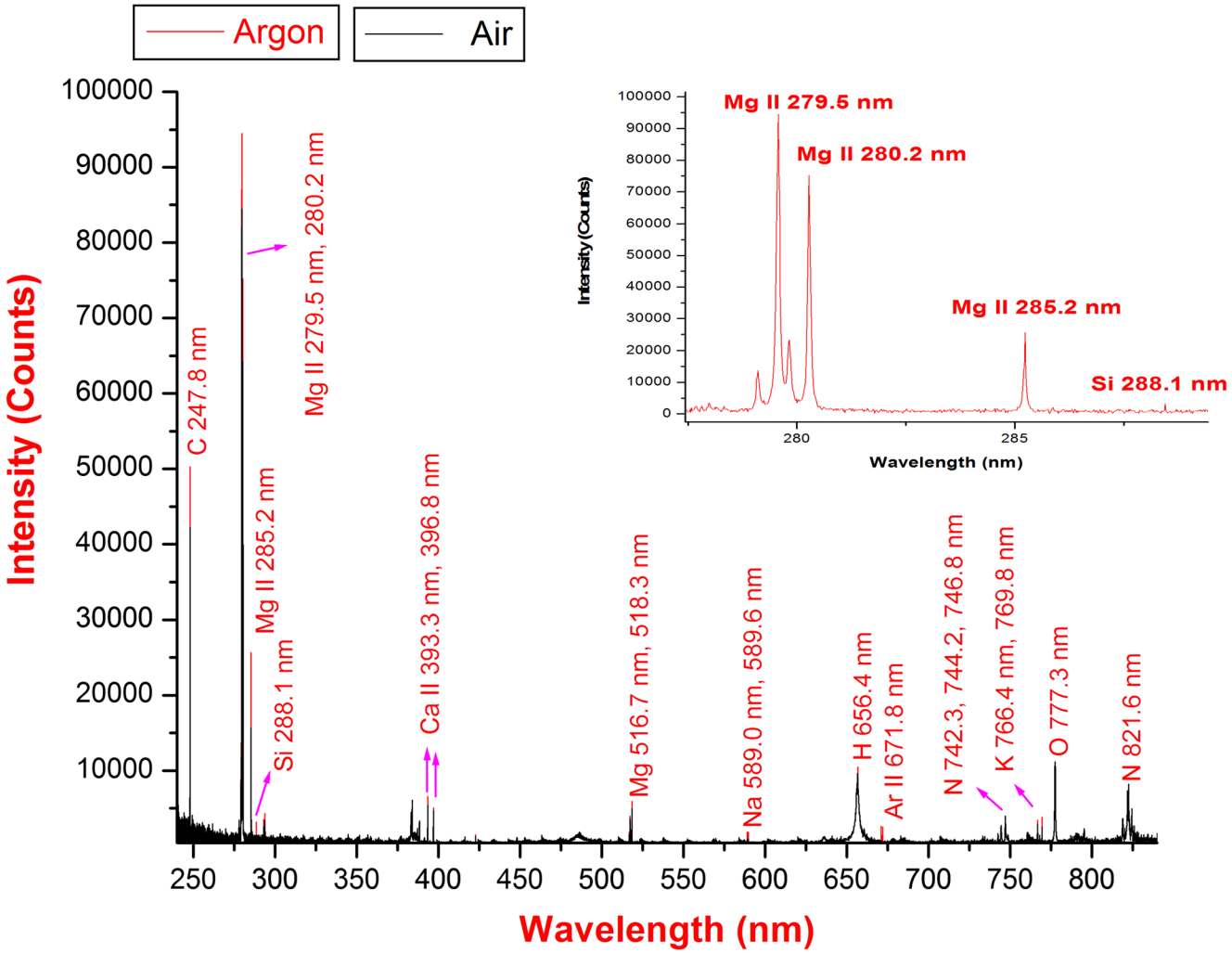

Fig. 2 LIBS spectra of voglibose recorded in air and argon atmosphere

Material and method

The experimental set up for investigation of drug samples is shown in Fig. 1. It consists of Q-switched Nd:YAG high-power pulsed laser (Continuum Surelite III-10) of a pulse width 4 ns (FWHM), deliverable energy up to 950 mJ at 1064 nm with a variable repetition rate of 1–10 Hz [13]. With the second harmonic generator (SHG) crystal of KTP (potassium titanyl phosphate), the frequency of the laser is doubled and we get the laser beam of a wavelength of 532 nm and a maximum deliverable energy of 425 mJ [13]. For recording the LIBS spectra, the laser and the spectrometer is synchronised in such a way that the both of them can be controlled to fire laser pulse for collecting the characteristic emission plasma signal from the sample. The digital delay generator used to synchronise the spectrometer equipped with intensified charge-coupled device (ICCD) and laser because the Nd:YAG laser system works in negative logic and ICCD works in positive logic signal; these signals are inverted in the delay generator. The energy of laser is measured by energy meter (Genetec-e model UP19K-30 H-VM-DO). In the present experiment, the observed signal to background ratio is best at 2-Hz repetition rate and a laser energy of 20 mJ. The plasma is generated on a sample surface; the calculated laser beam power density, i.e. the fluence at focal point, is 5.24×10^{12} W cm^{-2}. The ambient air contains nitrogen around 78% and oxygen about 20% and thus, these atmospheric nitrogen and oxygen may influence the LIBS signal from the laser-induced plasma. The lens to sample distance has been optimised to avoid the atmospheric interference. To get a better signal to noise ratio, the LIBS spectra were accumulated for 50 laser shots and to avoid ablation effect, each laser shot was focused at different points of drug sample by changing the position of the focal points using translation and rotational stage. As the atmospheric interference cannot be removed completely, it is essential to minimise the contribution of nitrogen and oxygen from the air atmosphere. Therefore, the LIBS spectra of pharmaceutical drug samples have also been recorded in the argon atmosphere. The LIBS spectra of drug samples have been

Table 1 Spectral peaks of different elements observed in the LIBS spectra of voglibose

S.N.	Elements	Wavelength (nm)
1	Carbon	247.8
2	Hydrogen	656.4
3	Silicon	250.7, 251.4, 251.6, 252.8, 288.1
4	Magnesium	279.5, 280.2, 285.2, 382.9, 383.2516.7, 517.3, 518.3
5	Sodium	589.0, 589.6
6	Potassium	766.4, 769.8
7	Calcium	393.3, 396.8, 397.2
8	Nitrogen	742.3, 744.2, 746.8, 818.4, 818.8, 821.6, 824.2
9	Oxygen	777.3, 844.8

recorded over spectral range of 200–900 nm in air and argon environments. As shown in Fig. 1, argon gas has been purged across the sample surface which reduces the interference of ambient atmosphere [14–17]. The emission spectra from plasma were collected by collimating lens which is adjusted at about 45° with respect to the laser beam. The collected signals were fed to the spectrometer (Mechelle ME5000, Andor Technology) through fibre; the spectrometer having spectral resolution of $\lambda/\Delta\lambda \cong 6000$ is equipped with gated intensified charge-coupled device (ICCD); (iStar 334, Andor Technology). The gate delay and gate width have been optimised at 1 and 6 μs respectively with the 10-μm slit width of spectrometer. Andor Solis software along with the NIST Atomic Spectroscopic Database [18] is used for the spectral analysis.

Results and discussion

The LIBS spectra have been recorded under the same experimental conditions for all five samples of different brands in air and argon atmosphere. On the basis of elemental presence in the LIBS spectra of all samples, it can be inferred that all brands are very similar. The LIBS spectra of voglibose ($C_{10}H_{21}NO_7$) drug samples are shown in Fig. 2 which show the elemental signature of carbon (C), hydrogen (H), nitrogen (N) and oxygen (O). In addition to these spectral lines, spectral lines of other elements like magnesium (Mg), silicon (Si), calcium (Ca) and potassium (K) are also observed in the LIBS spectra (Fig. 2). The observed spectral lines of different elements present in the samples are tabulated in Table 1. The intensities of spectral lines at 279.5 and 280.2 nm of Mg are higher as compared to spectral peaks of all other elements present in the LIBS spectra of drug samples of different brands. This infers that Mg is significantly added in all brands. The presence of inorganic elements Na, Mg, Si, K and Ca in drug samples may be passive ingredients or manufacturing impurities. The elemental signature of silicon has been observed only in samples C and D. Five tablets of each sample have been investigated for the study. We have recorded the single-shot LIBS spectrum at different location of each drug and found that the absolute intensity of minerals is almost same at different locations. Thus, we can conclude that the composition of drug is homogenous.

The LIBS spectra in air and argon atmosphere are shown in Fig. 2, which show that the intensities of spectral lines of the elements get enhanced in the presence of argon atmosphere as compared to air atmosphere, except the spectral lines corresponding to N and O [14–17]. These variations of the intensity of spectral lines are due to the plasma plume confinement which depends on the pressure of the surrounding gas and hence is related to mass density of gas [15]. The mass density of argon is greater than that of air by which plasma is more confined in argon and hence, the LIBS signal appeared stronger [15–17]. To interpret this effect in a more elaborate manner, we have calculated certain sets of LIBS intensity ratios of constituent elements of drug like C at 247.8 nm, H at 656.4 nm, N at 746.8 nm and O at 777.2 nm and are summarised in Table 2. The trends of intensity ratios are basically related to the reduction of interference of ambient air as well as the confinement of plasma in the presence of argon atmosphere [15–17].

To find out the elemental concentration in the sample, several calibration methods have been proposed [2, 4–9, 19–23]. The spectral interference free emission lines are chosen for intensity calculations. The spectral peak intensities of non-interfering lines, for C at 247.8 nm, H at 656.4 nm, N at 746.8 nm and O at 777.2 nm have been used to obtain the intensity ratios, i.e. H/C, H/N and O/N. There are various

Table 2 Intensity ratios of O/N, H/N and H/C* of voglibose in air and argon atmosphere

S.N.	Sample	O/N (argon)	O/N (air)	H/N (argon)	H/N (air)	H/C (argon)	H/C (air)
1	A (0.3)	6.61 ± 0.16	6.32 ± 0.67	14.32 ± 0.20	12.66 ± 0.39	3.35 ± 0.16	3.73 ± 0.29
2	B (0.2)	8.12 ± 0.44	7.59 ± 0.48	16.38 ± 0.43	13.90 ± 0.75	2.57 ± 0.22	2.79 ± 0.35
3	C (0.3)	9.26 ± 0.24	8.95 ± 0.33	16.83 ± 0.29	15.27 ± 0.50	3.52 ± 0.19	3.89 ± 0.32
4	D (0.2)	9.18 ± 0.66	8.17 ± 0.39	17.64 ± 0.53	14.55 ± 0.40	4.21 ± 0.14	4.72 ± 0.43
5	E (0.3)	9.10 ± 0.46	9.36 ± 0.57	15.95 ± 0.37	15.39 ± 0.77	4.01 ± 0.10	4.04 ± 0.33

*the generating lines taken C at 247.8 nm, H at 656.4 nm, N at 746.8 nm and O at 777.2 nm

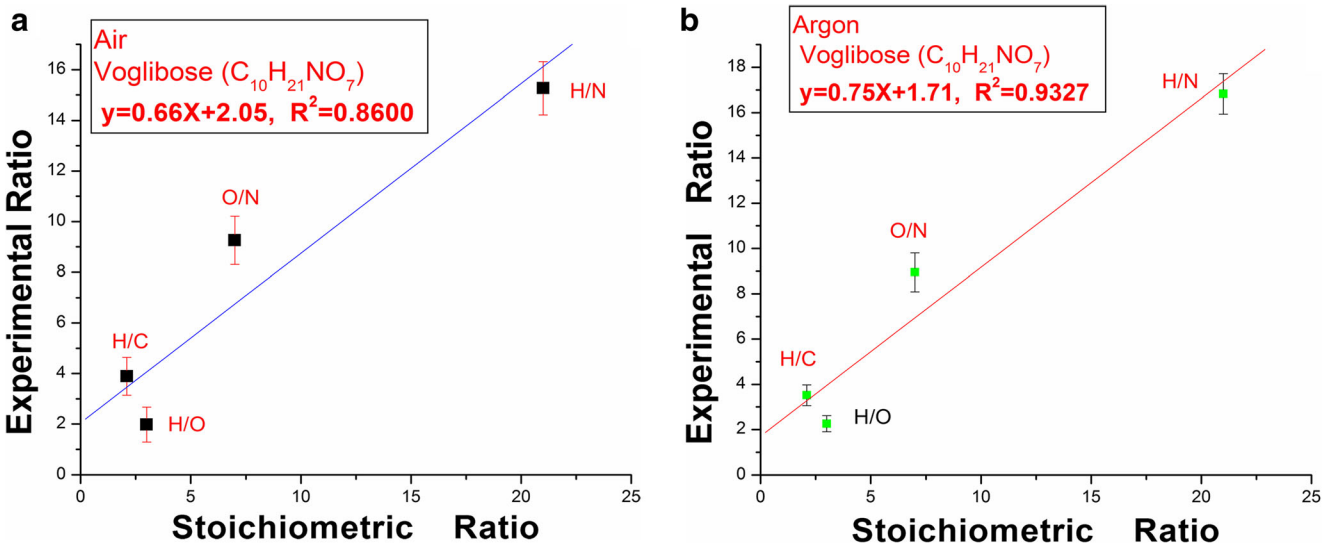

Fig. 3 The ratiometric univariate linear regression plots for **a** air and **b** argon atmospheres

ratios that may be useful to identify organic compounds: the H/C and H/O ratio, which is the most important as it allows the identification and differentiation of organic compounds [17, 21–23]. These organic ratios may be valuable for extracting the formulation of drugs which can be applied significantly in identification of drugs as well as in quality control production [23]. In the present study, the spectral intensity ratios of H/C, H/N and O/N have been calculated in air and argon environments and are tabulated in Table 2. Table 2 shows that H/C ratios obtained in both atmospheres are almost similar. With the help of calculated spectral intensity ratio of drug sample, the univariate regression plots between stoichiometric ratios (ratio of the two organic elements estimated from molecular formula of drug, i.e. voglibose $C_{10}H_{21}NO_7$) and experimental intensity ratios have been drawn for both air and argon atmosphere and are shown in Fig. 3 (a) and (b).

Herein, we demonstrated the application of parametric (linear) correlations for the identification of various drug brands. The above univariate linear regression plots show that the regression coefficient R^2 value is 0.86 for air and 0.93 for argon atmosphere which are very close to each other. Therefore, LIBS spectra recorded in air atmosphere is also as good as in argon atmosphere. Furthermore, it will be cost effective to perform experiment in air. Similar results are obtained for other brands too. The univariate linear regression is generally suitable for the analysis of a limited number of samples. For the analysis of a large number of samples, the statistical method like PLSR provides better results than univariate correlation analysis [24]. In order to relate the ratio analysis to the relative concentration of drug samples, partial least square (PLS) regression models have been developed.

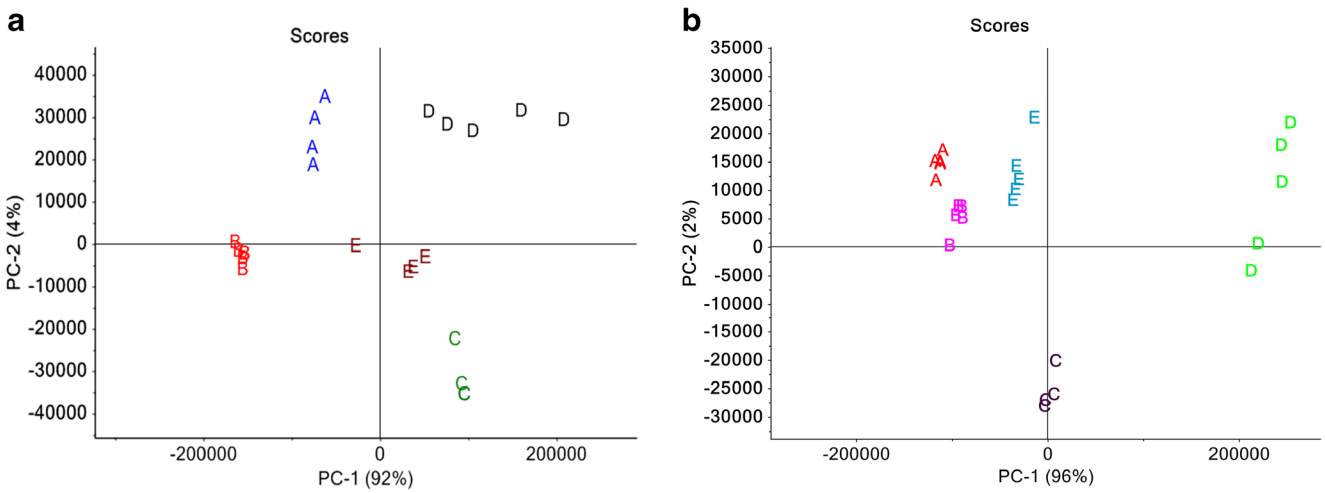

Fig. 4 Two-dimensional score plot of PCA **a** in air **b** in argon

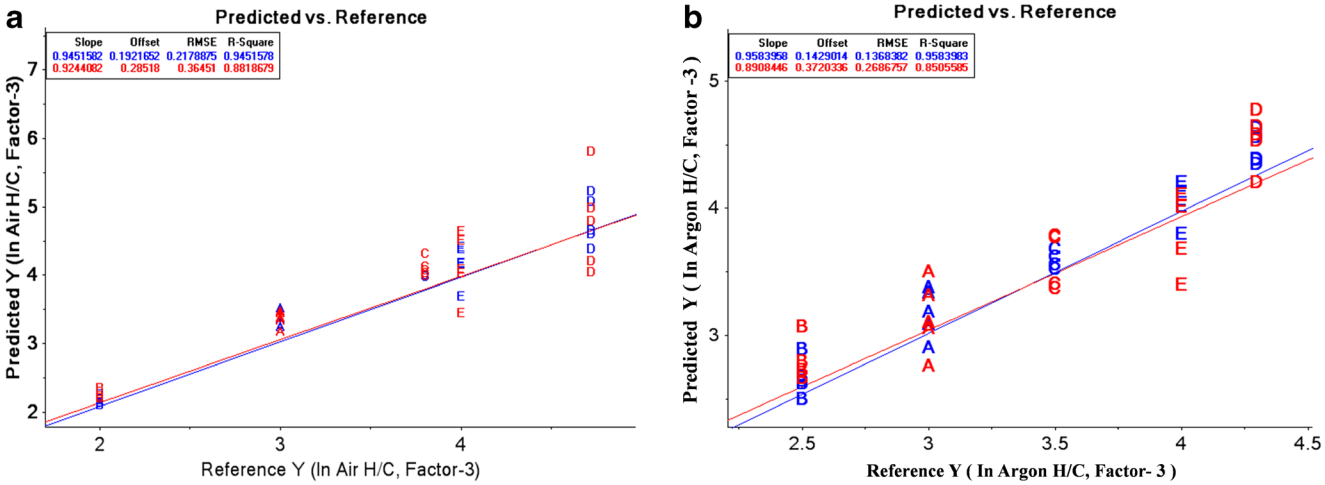

Fig. 5 PLSR analysis of drug sample A–E in **a** air and **b** argon atmospheres using H/C ratio

Statistical methods for the analysis of LIBS spectral data for the discrimination and quantification of different drug samples

Principle component analysis

The Unscrambler-X software (CAMO India Pvt. Ltd.) has been used for performing the multivariate analysis of the LIBS spectral data. PCA is an exploratory data analysis (EDA) tool which allows the arranging of samples into different clusters [11, 12]. Two matrices (30 × 30,456) of the LIBS spectral data for drug samples in air and argon atmosphere have been prepared for multivariate analysis. It is clear from Fig. 4 (a) and (b) that the samples are classified 96% (92% by PC1 and 4% by PC2) in air and 98% (96% by PC1 and 2% by PC2) in argon atmosphere. It is depicted in Fig. 4 (a), (b) that the pharmaceutical drug samples of different brands are classified into five groups with PCA plot. Although, the elemental constituents present in all samples are almost same yet these samples get clustered in different groups. This analysis gives an advantage for the classification of drugs by multivariate analysis coupled with LIBS.

PLSR algorithm for measurement of relative concentrations of organic elements in the drug samples

C.Y. George et al. [25] has shown that multivariate calibration can be performed correctly even when spectra are only partially resolved and this is a common phenomenon in the LIBS spectra of the complex system/organic samples. Without knowing the actual concentration of the matrix, the ratio-based empirical approach on the LIBS data, PLSR calibration has been carried out, and this approach can be applied to get ratios of elements in the unknown matrix. PLSR has been

Table 3 Intensity ratios of H/C, H/N and O/N* of voglibose using PLSR regression

S.N.	Brand (mg)	Air		Argon		Air		Argon	
		Experimental H/C	Predicted H/C	Experimental H/C	Predicted H/C	Experimental O/N	Predicted O/N	Experimental O/N	Predicted O/N
1	A (0.2)	3.73 ± 0.29	3.16 ± 0.26	3.35 ± 0.16	3.08 ± 0.18	6.61 ± 0.67	6.15 ± 0.65	6.32 ± 0.16	6.65 ± 0.69
2	A (0.3)	3.73 ± 0.29	3.29 ± 0.28	3.35 ± 0.16	3.06 ± 0.19	6.61 ± 0.67	6.45 ± 0.68	6.32 ± 0.16	6.86 ± 0.68
3	B (0.2)	2.79 ± 0.35	2.08 ± 0.30	2.57 ± 0.22	2.55 ± 0.20	8.12 ± 0.48	8.40 ± 0.58	7.59 ± 0.44	7.76 ± 0.63
4	B (0.2)	2.79 ± 0.35	2.13 ± 0.24	2.57 ± 0.22	2.54 ± 0.24	8.12 ± 0.48	8.50 ± 0.55	7.59 ± 0.44	7.46 ± 0.59
5	C (0.3)	3.89 ± 0.32	3.88 ± 0.30	3.52 ± 0.19	3.71 ± 0.23	9.26 ± 0.33	9.30 ± 0.64	8.95 ± 0.24	8.27 ± 0.73
6	C (0.3)	3.89 ± 0.32	3.85 ± 0.25	3.52 ± 0.19	3.40 ± 0.25	9.26 ± 0.33	9.40 ± 0.57	8.95 ± 0.24	9.08 ± 0.61
7	D (0.2)	4.72 ± 0.43	4.53 ± 0.26	4.21 ± 0.14	4.56 ± 0.30	9.18 ± 0.39	9.10 ± 0.62	8.17 ± 0.66	8.29 ± 0.65
8	D (0.2)	4.72 ± 0.43	4.34 ± 0.33	4.21 ± 0.14	4.08 ± 0.26	9.18 ± 0.39	9.01 ± 0.65	8.17 ± 0.66	8.81 ± 0.75
9	E (0.3)	4.04 ± 0.33	4.00 ± 0.35	4.01 ± 0.10	3.78 ± 0.25	9.10 ± 0.57	9.10 ± 0.60	9.36 ± 0.46	9.25 ± 0.64
10	E (0.3)	4.04 ± 0.33	3.26 ± 0.25	4.01 ± 0.10	3.98 ± 0.24	9.10 ± 0.57	9.10 ± 0.60	9.36 ± 0.46	9.11 ± 0.62

*the generating lines taken C at 247.8 nm, H at 656.4 nm, N at 746.8 nm and O at 777.2 nm

employed here as a multivariate method to construct the ratio-based calibration model for drug samples. To draw the calibration model from elemental ratios, typical wavelength regions containing the majority of the emission lines of corresponding elements are chosen. A total of 30 spectra, i.e. six spectra of each five samples, have been recorded. Out of 30 spectra, 20 spectra are chosen for training set which serve as the known sample (reference) to prepare the PLSR model. The rest of the ten spectra are chosen as test sets which serve as the unknown sample. This method works on the principle of the PLS calibration, which is widely used for the analysis of large data [24, 26]. To build the PLS calibration models, we have selected the spectral range of that element whose ratios are chosen for PLSR analysis. The performance of model is assessed by the value of regression coefficient R^2 and root-mean-square error (RMSE). For a good correlation, the R^2 values should be almost equal to one while RMSE should close to zero. The regression coefficient represents a direct linear relationship between the LIBS spectra and the elemental ratios. The best calibration model can be drawn if the predicted values are equal to the reference values [24–26]. Using these calibration models, test sets are predicted. Once the PLS model is accurately developed for a matrix, then we can evaluate the calibration set for several other matrixes [24–27]. For the prediction of the test samples, a ratio-based library data set is constructed. Finally, the calibration curve is drawn as shown in Fig. 5, calibration in blue line and validation in red line. The validation line deviates very little from the calibration line, which infers that the calibration is close to the validation. The model cannot be trusted if there are large differences between the calibration and the validation. Figures 5(a) and (b) describe the PLS regression model for H/C ratio of voglibose recorded in air and argon atmosphere, respectively.

From Fig. 5 (a) and (b), it is clear that there is a good agreement between the reference values and the predicted values. Similarly, the PLSR models for O/N, H/N. have also been drawn. Among these ratios, H/C ratio-based model shows better accuracy and reliability because of the lower value of RMSE and with higher (close to unity) R^2 value as compared to other ratios. Using the above developed PSLR model, we have predicted the intensity ratios of test (unknown) samples. The predictions, using H/C and O/N ratios with deviation, for all brands are tabulated in Table 3.

It is clear from Table 3 that the calculated values are very close to the predicted values. In addition, the values of H/C ratio for all samples have less deviation in predicted values as compared to other ratios, e.g. H/N and O/N. Our study reveals that the multivariate data processing methods (PCA and PLS) lead to more fruitful results than univariate approach. The present methodology could be used for the inspection and recognition of authenticity of drug sample for improving the internal quality control to carry out confirmation of packed and elaborated drugs in the industry and official organisations (customs, police, the British Pharmacopoeia (BP), the United States Pharmacopeia (USP), the Indian Pharmacopoeia (IP), etc.) [23, 28].

Conclusion

The ratio-based classification and regression of pharmaceutical samples show that LIBS along with statistical analysis has the capability of fast online assessment of identification and classification of pharmaceutical drugs of different dosages and brands. Calibration models are developed to predict relative intensity ratios of different elements. Our study claims that H/C ratio analysis can be applied for rapid measurement of relative concentrations as well as identification of dose strength. It is found that H/C ratios are almost constant in the LIBS spectra recorded in air and argon atmosphere; thus, it will be cost-effective to perform experiment in air. LIBS can be used to identify the counterfeit in generic pharmaceutical drugs. Thus, the proposed methodology can be implemented for online, in-situ monitoring of active ingredients in pharmaceutical drug samples.

Acknowledgements The authors are thankful to Prof. A N Dwivedi, Department of English, University of Allahabad, to Dr. A K Pathak, Department of Physics, Ewing Christian College, University of Allahabad and to Dr. Abhimanyu Kumar Singh and Dr. G S Maurya, Department of Physics, the University of Allahabad for their valuable suggestions and support. One of the authors, Pravin Kumar Tiwari, is thankful to the University Grant Commission, New Delhi, India, for providing the UGC DPhil fellowship.

Funding information We are not having any financial assistance for this study from any funding bodies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval I would like to inform that the Departmental Programme Committee (DPC), Department of Physics, Faculty of Science, University of Allahabad, and the Research Degree Committee (RDC), University of Allahabad, have approved the topic *Study of Pharmaceutical Sample using Spectroscopic techniques* for DPhil research work. This is also approved by the Registrar, University of Allahabad. The manuscript *Rapid analysis of pharmaceutical drugs using LIBS coupled with multivariate analysis* is a part of the abovesaid DPhil degree work. This proves the ethical approval for our study is not required.

Informed consent We, Pravin Kumar Tiwari, Shikha Awasthi, Rohit Kumar, Raj Kumar Anand, Pradeep Kumar Rai and Awadhesh Kumar Rai, authors of the article *Rapid analysis of pharmaceutical drugs using LIBS coupled with multivariate analysis* declare that no individual rights are infringed during this study. In our study, we did only compositional analysis of medicine in our laboratory; thus, the medicine (voglibose) has not been used for any clinical purpose.

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