Peer-reviewed version available at Atoms 2019, 7, ; doi:10.3390/atoms7030071

Article

Atomic and Molecular Laser-Induced Breakdown Spectroscopy of Selected Pharmaceuticals

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Abstract: Laser-induced breakdown spectroscopy (LIBS) of pharmaceutical drugs that contain paracetamol is investigated in air and argon atmospheres. Characteristic neutral and ionic spectral lines of various elements and molecular signatures of CN violet and C_2 Swan band systems are observed. The relative hardness of all drug samples is measured as well. Principal component analysis, a multivariate method, is applied in data analysis for demarcation purposes of the drug samples. The CN violet and C_2 Swan spectral radiances are investigated for evaluation of possible correlation of the chemical and molecular structures of the pharmaceuticals. Complementary Raman and Fourier-transform-infra-red spectroscopies are used record molecular spectra of the drug samples. The applicationof the above techniques for the drug screening are important for identification and mitigation of drugs that reveal additives that may cause adverse side-effects.

Keywords: Paracetamol; Laser-induced breakdown spectroscopy; Cyanide; Carbon Swan bands; Principal Component analysis, Raman Spectroscopy, Fourier-Transform-infra-red spectroscopy

1. Introduction

Paracetamol (PCM) is a medication that is frequently used for the relief of mild to moderate pain and fever experienced by people of all ages [1]. It is also registered in the model list of essential medicines published by the World Health Organization (WHO) that communicates most important medications for sustenance of human health [2]. However, routine use of PCM may cause complications that could potentially cause liver damage, and simultaneously, a decrease of pain thresholds [2]. The pharmaceuticals would serve their intended purpose only if they are free from impurity or other interference that might be harmful for human health. In addition, various chemical and instrumental methods are regularly introduced in the pharmaceutical drug industry for evaluation of drug contra-indications and effects on the human body [1-2].

At present, various laser-based approaches are available for the elemental analysis of solids, liquids, gases, and heterogeneous biological matrices including drug samples, but fast and cost-effective techniques are vital in manufacturing [3-4]. During the last few decades, laser-induced breakdown spectroscopy (LIBS) has been successful as a reliable, first-choice spectroscopy and analytical technique in various fields of applications [5-9]. The recent studies reveal that LIBS can be an efficient tool for rapid identification and quantification of drug's elemental composition [7-10].

In optical emission spectroscopy reported in this work, viz. LIBS, high peak-irradiance radiation of the order of 100 GW/cm^2 is applied for initiation of breakdown at and near the surface of the target

material. It is a minimally destructive technique for determining the composition of the material in any phase (solids, liquids, and gas) with little or no sample preparation. It offers in-situ, online and real-time operations for the materials that are even remotely located [7-10].

LIBS, in general, is viable for elemental analysis, and conditionally, LIBS is also being used to predict the presence of molecules in the sample [11-16]. The molecular emission is generally more complex than that involving atomic emission. Local plasma conditions as well as plasma cooling duration may take an effective role for changes in measured radiation originating from molecules [7-9]. The present manuscript communicates analysis of drugs such as PCM that are organic in nature. In presence of organic molecules in the sample, the molecular signature of CN violet and C_2 Swan bands could be observed in LIBS spectra [9, 11-14]. The fingerprint of CN and C_2 molecular bands in the LIBS spectra of organic compounds have been examined to correlate the spectral molecular emission from the laser-induced plasma and the molecular structure of an organic compound present in the sample [11-16].

Another spectroscopic technique called Raman and FT-IR Spectroscopy, complementary to LIBS, has also been used for study of molecules present in the drug samples. Raman spectroscopy is a vibrational spectroscopic technique that provides molecular structural information of the materials without any sample preparation [17-18]. The absorption spectrum of drug sample has also been recorded using FT-IR spectroscopy [18].

Hardness of medical pills is usually not mentioned in pharmacopeia specifications [19-22]. However, to produce a quality product, it is essential to decide upper and lower limit of hardness of drugs at the time of manufacturing. Too soft tablets can disintegrate in transport and too hard tablets could cause several complexes in bioavailability, for example, the hardness of chewable tablets should be suitable [22]. There are different approaches to measure the hardness of the drug sample and one of the recent approaches is using LIBS [19-20]. The hardness of sample can be predicted using ionic to atomic line ratio of an element present in LIBS spectra of drugs. In the present manuscript, the relative hardness of drug samples has also been evaluated as well.

In the present work, six different brands of pharmaceutical drug samples have been studied using LIBS in two different environments (air and argon). A statistical approach, namely, Principal component analysis (PCA) [10] has also been applied to classify the drug samples. The present study infers that LIBS could be a more practical approach for the online performance analysis of the drug samples.

2. Results

2.1. LIBS analysis

LIBS spectra of the drugs, summarized in Table 1, have been recorded in ambient atmosphere. The observed atomic and ionic emissions corresponding to the organic elements are C (247.8 nm), Hα (656.3 nm), O (777.4 nm), and N triplet lines (742.46, 744.28, 746.85 nm) are depicted in Fig. 1(a). The spectral lines of inorganic elements such as Na (589.0, 589.5 nm), Mg (279.5(II), 280.2 (II), 285.2, 382.9(II), 383.2(II), 516.7, 517.3, 518.3 nm), Ca (393.3(II), 396.8(II), 397.2(II), 422.6 nm), and Si (250.7, 251.4, 251.6, 252.8, 288.1 nm) have been observed in LIBS spectra of these drugs.

Figures 1, 2 and 3 display molecular spectra corresponding to the CN violet system ($B^2\Sigma^+ - X^2\Sigma^+$) and C_2 Swan band system ($d^3\Pi g - a^3\Pi u$), observed in the LIBS spectra of drugs. The spectra are expected to be formed by recombination of native carbon-carbon and carbon-nitrogen in the laser-induced plasma of drug samples [13-16, 25]. However, another possibility of the appearance of CN features in LIBS spectra may be due to the interaction between atmospheric nitrogen and the laser induced plasma. Therefore, to suppress atmospheric interference, LIBS spectra of drugs have also

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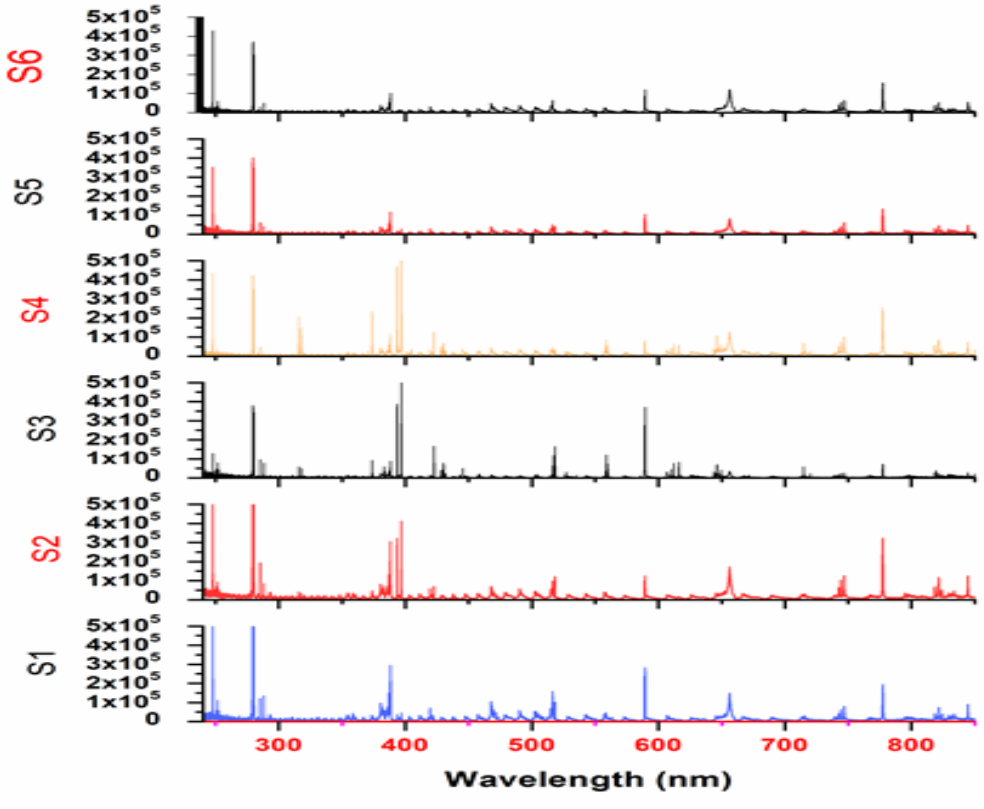
been recorded in argon atmosphere. The experiments reveal CN and C_2 bands in LIBS spectra of drug recorded in argon atmosphere. This confirms that the origin of CN band in the LIBS spectra of the drug is likely due to recombination of native carbon-carbon and carbon-nitrogen in the laser-induced plasma of the drug (Figures 1(b), 2 (b) and 3(a)).

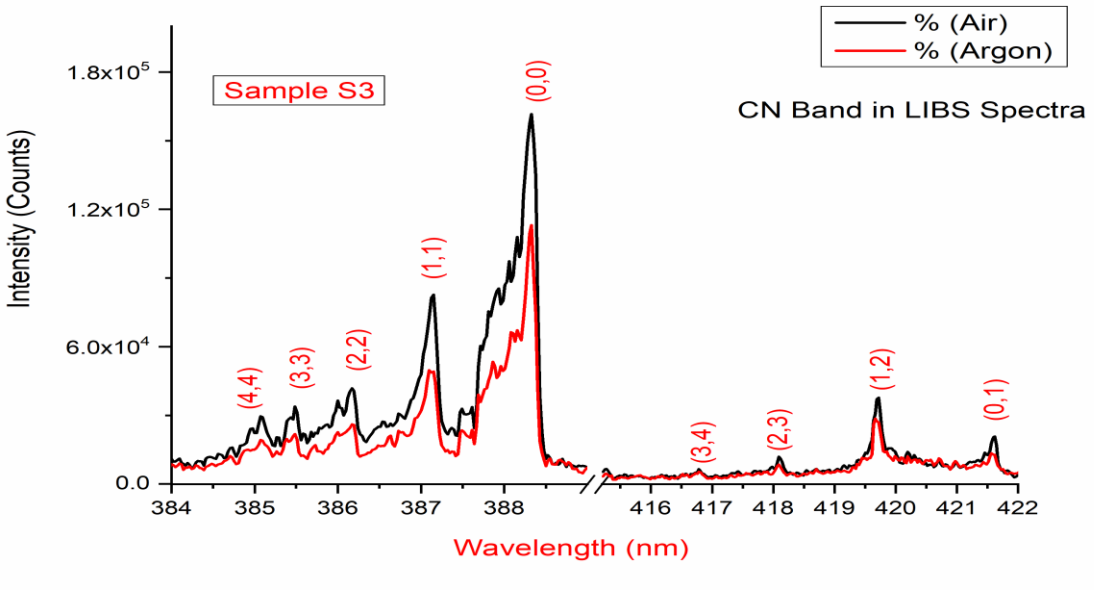
The LIBS spectra of the investigated drugs contain $\Delta v=0$ and $\Delta v=1$ sequence of CN and C_2 band systems. Figure 2(a) shows presence of CN violet band system in argon atmosphere at 388.2, 387.0, 386.1, 385.4, and 385.0 nm corresponding to (0,0), (1,1), (2,2), (3,3) and (4,4) vibrational transitions, respectively, appeared in S1-S5 sample, but these bands are absent in sample S6 [26]. Similarly, Fig. 3(a) reveals that the spectral peaks of C_2 Swan band system are observed in S1-S6 sample at 516.4 nm and 512.8 nm corresponding to (0,0) and (1,1) bands. In addition to (0,0) and (1,1) vibrational bands of C_2, the molecular bands at 471.5, 469.7, 468.4, and 467.8 nm correspond to the (2,1), (3,2), (4,3), (5,4) bands [22].

If there are no C–C, or C=C bonds in the molecular structure of the sample, then C_2 bands will not be observed in the LIBS spectra of samples [15]. Therefore, to predict the signature of the molecule in the sample, the strongest emission bands of C_2 (0,0) system at 516.4 nm and CN (0,0) system at 388.32 nm are included in calculations, rather than using a carbon line. An analysis of these bands that are recorded with sufficient spectral resolution contains information about the molecule, i.e., it establishes the signature of the molecule present in the sample as described in Table 1.

The variation observed in the spectral intensity of CN and C_2 bands in the LIBS spectra represents the presence of different kinds of molecules in the matrix of pharmaceutical samples. In addition to this, with the help of the reported molecular formula of the drugs, the carbon and nitrogen percentages are calculated and correlated with the CN and C_2 vibrational band intensities present in the LIBS spectra of corresponding drugs (Table 1).



1 (a)



1 (b)

Figure 1. (**a**) LIBS spectra of Drug S1- S6 recorded in ambient atmosphere 240-850 nm;

(b) LIBS Spectra of Sample S3 recorded in argon and ambient atmosphere

Table 1. Sample details along with molecular formula and total weight % of Carbon and Nitrogen

Sample	Compound in sample (Manufacturer)	% of C	% of N
S1	Ibuprofen $C_{13}H_{18}O_2$ (400 mg) and Paracetamol $C_8H_9NO_2$ (325mg)	50.9	30.1
S2	Aceclofenac $C_{16}H_{13}Cl_2NO_4$ (100 mg) Paracetamol $C_8H_9NO_2$ (500 mg)	37.2	50.2
S3	Diclofenac Sodium $C_{14}H_{11}Cl_2NNaO_2$ (50 mg) Paracetamol $C_8H_9NO_2$ (325mg)	23.2	32.3
S4	Paracetamol $C_8H_9NO_2$ (500 mg)	31.7	46.3
S5	Paracetamol $C_8H_9NO_2$ (500 mg)	31.7	46.3
S6	Ibuprofen $C_{13}H_{18}O_2$ (400mg)	30.2	0

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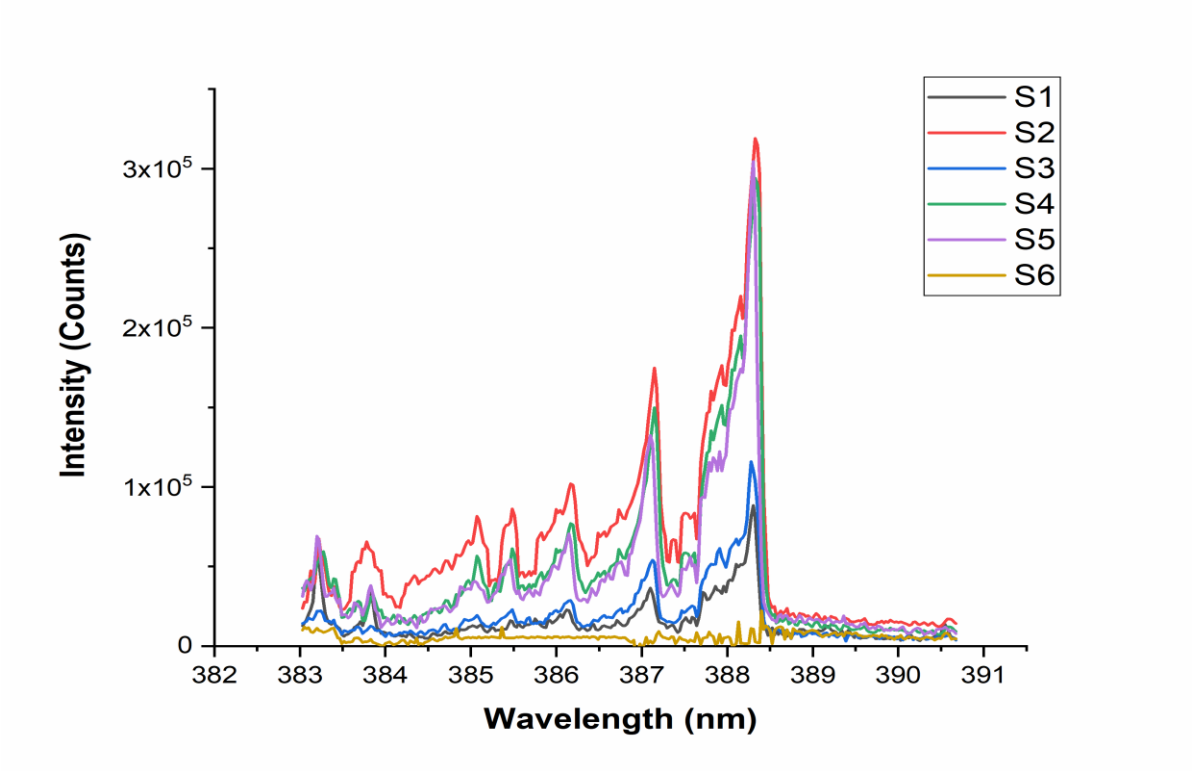
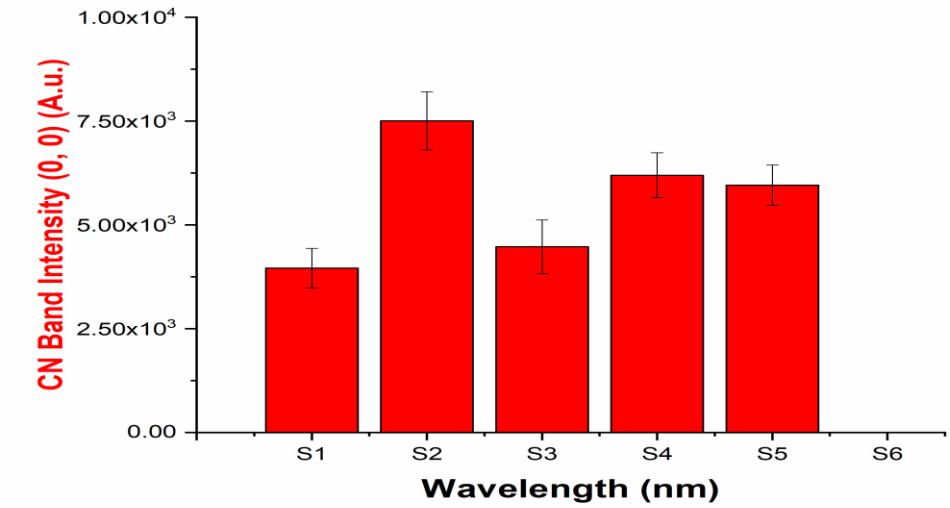
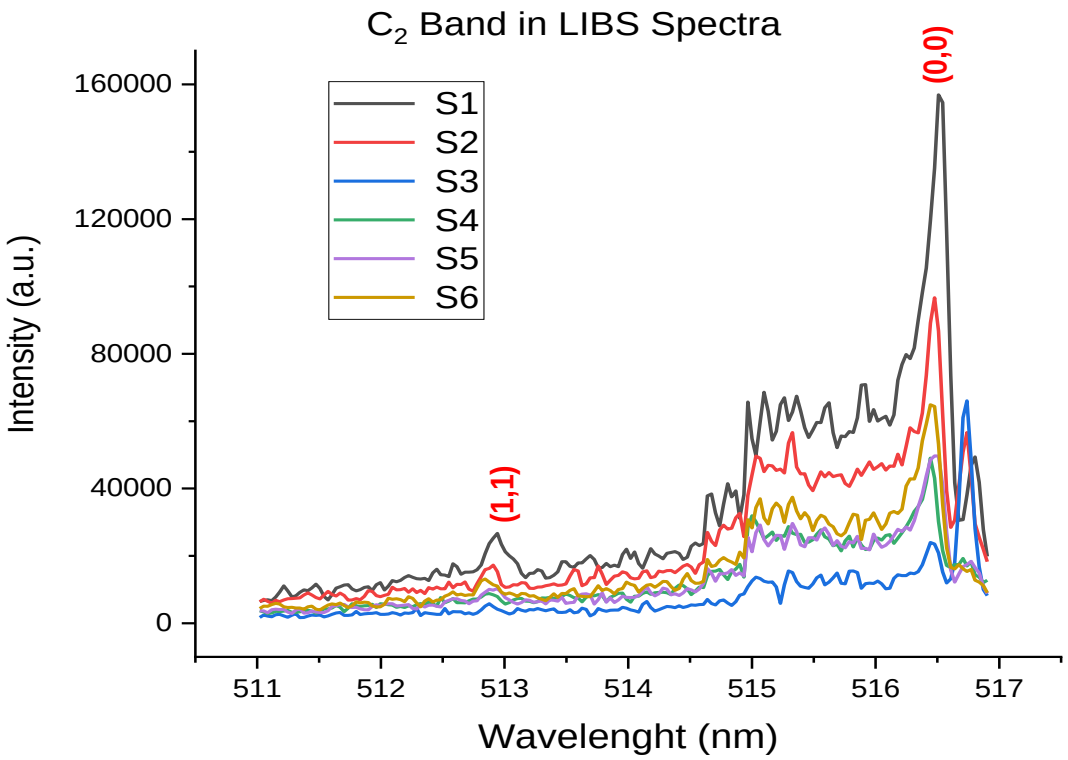


2 (**a**)

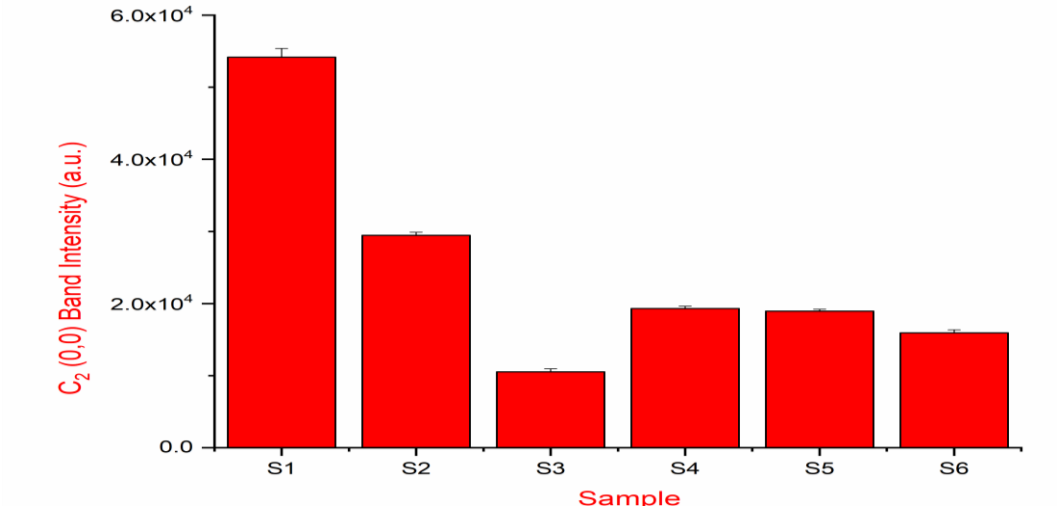


2 (b)

Figure 2. (a) LIBS spectra of the drugs showing the presence of vibrational band of CN molecule; **(b)** Intensities of (0,0) band of CN band present in LIBS spectra of drugs



3 (**a**)



3 (**b**)

Figure 3. (a) LIBS spectra of the drugs showing the presence of vibrational band of C_2 molecule; **(b)** Intensities of (0,0) band of C2 band present in LIBS spectra of drugs.

2.2. Relative hardness of the tested drugs

Using LIBS, the relative hardness of the drugs (tablets) is measured. Hardness of the material can be evaluated from the intensity ratio of the 373.6-nm ionic line of Ca II and of the neutral 422.6-nm line of Ca I. The higher the ratio, the harder the sample [19]. Alternatively, the intensity ratio of the ionic spectral lines Mg II at 279.5 nm, and of the neutral lines Mg I at 285.2 nm can also be used to

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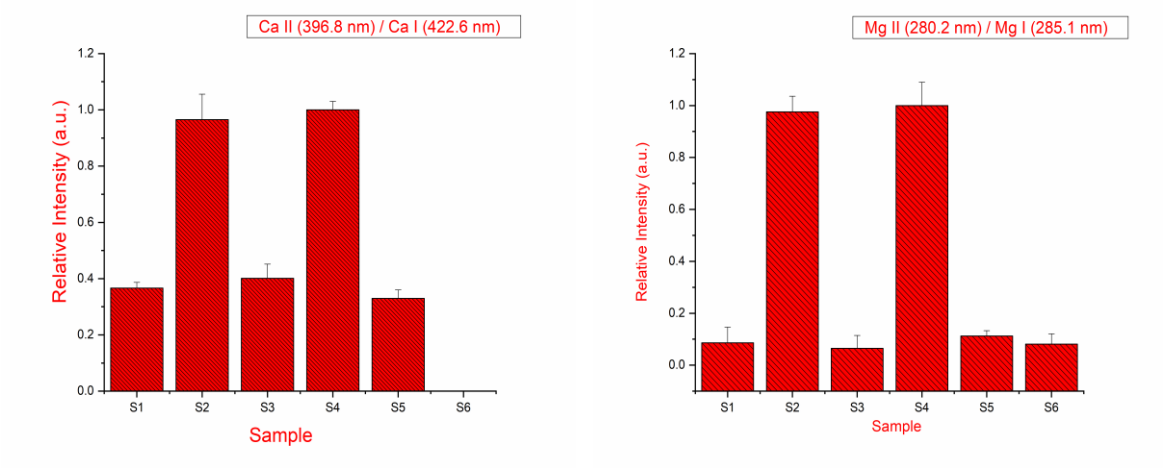
146 determine the hardness of the tablet [20]. The emission line intensity alone cannot be used to
147 determine the hardness of the tablet because matrix effects and change of experimental parameters
148 with sample [19-20].

149 The interference-free emission line of calcium has been taken for the calculation of intensity ratio.
150 The measurement is repeated for the ratio of ionic lines, to neutral lines of magnesium observed in
151 LIBS spectra of the drugs belonging to different brands and the results are shown in Fig. 4 (a) & 4 (b).
152 It is observed that the ratio changes with respect to the sample and calculated data suggest that
153 sample S2 & S4 is harder in comparison to all other samples. Therefore, the density of the drugs in
154 terms of the hardness of the drug has been calculated. This methodology can be significant for
155 monitoring the uniform density of the tablet at the time of manufacturing and batch performance
156 analysis of the drug.

157



(**a**) (**b**)

158 **Figure 4. (a)** Intensity ratio of spectral lines Ca (II) 396.8 nm and Ca (I) 422.6 nm;

159 **(b)** Intensity ratio of spectral lines Mg (II) 279.5 nm and Mg (I) 285.2 nm.

160 **2.3.** Principal Component Analysis (PCA)

161 The LIBS spectra of the samples S1-S6 are shown in Fig. 1 (a). Qualitatively, it is clear from Fig.1
162 (a) that there could be slight variations in the spectral signature and thus elemental composition
163 among all the drug samples. However, even for slight variations in the composition of the drug
164 samples, the discrepancy among the six types of the drug is investigated with PCA of LIBS spectral
165 datasets. The principal component scatter-plot has been drawn using LIBS spectral datasets of S1-S6
166 recorded in argon atmosphere to represent the three-dimensional PCA. The graph represents one
167 point in the Figure 5 for each spectrum in term of principle components (PCs). PCA gives the visual
168 representation of the data set through projection. One can extract important information from the
169 variables (in form of principal components) of the dataset. The uncorrelated variables in PCA are
170 known as principal components [27]. The library set of LIBS spectra have been represented in the
171 form of the matrix of order 1.5 million (60*24806) for six drug sample of different brands. Using
172 Unscrambler-X software [10], the matrices are transformed into principle components (PCs)
173 representations. Weighted linear combinations of variables are found to describe major trends in the
174 data. The representations in PCA are displayed in score plots, viz. in terms of PCs of different in
175 dimensions including (PC-1, PC-2 & PC-3).

176 Figure 5 depicts three different PCs (PC-1, PC-2, & PC-3) to elucidate the variations of the spectra
177 as well as their scores for discrimination of the samples. In the experiments, ten LIBS spectra were

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recorded for each brand of the sample and these data are included for the PCA analysis. Apparent clustering of each brand sample can be noticed in Figure 5 that shows obvious differences between six groups of drug samples. The sample of S1 (blue data), S2 (red data), S3 (dark green data), S4 (black data), S5 (light green data) and S6 (brown data) in Fig. 5 are color-coded. The samples S4 and S5 are closely clustered to each other which indicates that both the sample may have common compositions. This is also mentioned in Table 1 that S4 and S5 have almost similar compositions. The discrimination observed in PCA score plots for data recorded in ambient air is close to that in the argon atmosphere. The analysis shows that information extracted from PCA allows significant classification of the drugs in-spite of having nearly similar compositions.

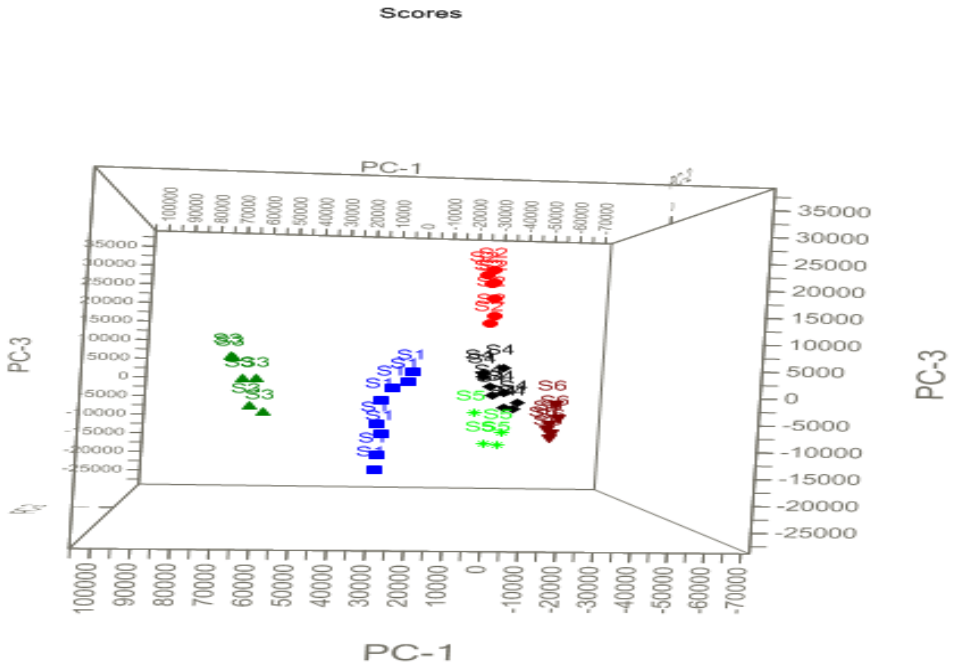

Figure 5. *Principle Component Scatter (PCA) plot of the drugs in three dimensional*

2.4. Raman Spectroscopy

Raman spectra of drugs have been recorded for identification and verification of molecular composition present in the drug. The PCA plot in Figure 5 reveals that sample S3 is highly discriminated from the other samples, and therefore, we have firstly taken sample S1 and S3 for Raman analysis. The observed peaks in Raman spectra of sample 1 and sample 3 are tabulated in Table 2 and depicted in Figures 6 (a) and 6 (b).

Analysis with Raman characteristic group frequencies [18], the peaks at 3049 cm^{-1} could be identified as associated with C-H stretching mode, 1647 cm^{-1} and 1611 cm^{-1} are associated with C=O stretch. The vibrational mode with peak at 1566 cm^{-1} is associated with N-H bending and the mode with peak at 1115 cm^{-1} is associated with aromatic ring breathing. The vibrational mode with peaks at 801 cm^{-1} and 750 cm^{-1} are found to associate with C-H bending (para) and C-N stretching mode, respectively. The vibrational modes around 2800-3000 cm^{-1} are associated with alkyl C-H bands. With the present resolution, most of the vibrational modes observed in Raman spectra of these samples are common (see Table 2) which confirms the similar functional group of the samples.

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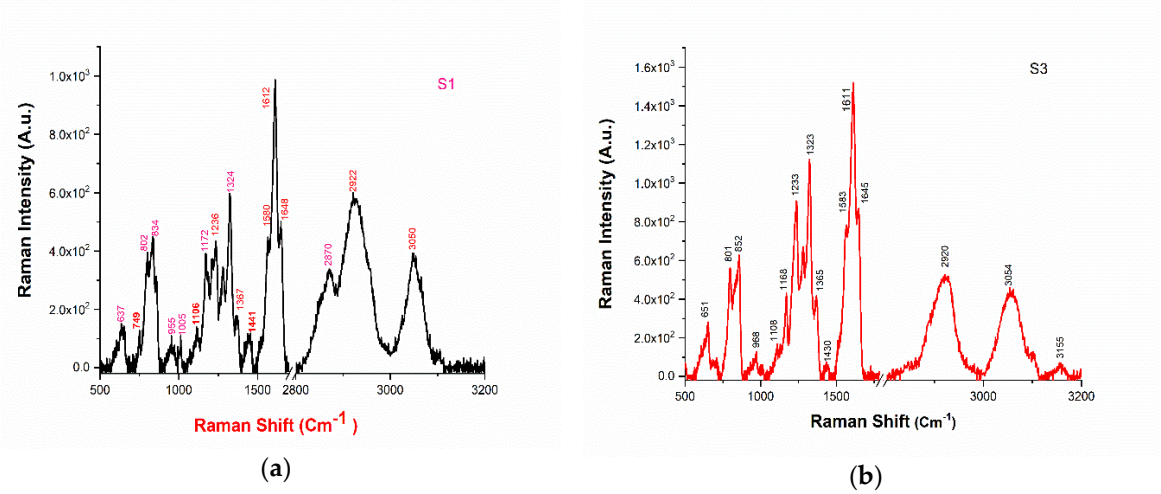

Figure 6. (**a**) Raman Spectra of sample S1; (**b**) Raman Spectra of sample S3.

Table 2. Observed vibrational modes in the Raman spectra of Sample S1 & S3

Sample S1 Raman Shift (cm^{-1})	Sample S3 Raman Shift (cm^{-1})	Result
749	------	C-N stretch
802	801	C-H Bend, para
1116	------	Aromatic ring breathing
1213	1211	C-O Stretch
1236	1230	C-O Stretch
1367	1365	CH_3 bend
1441	--------	O-H bend
1580	1583	N-H Bend
1612	1611	C=O stretch
1648	1645	C=O stretch+ N-H deformation
2927	2920	Saturated C-H
3050	3055	Aromatic C-H

2.5. FT-IR Spectroscopic Analysis

The FT-IR spectrum of sample S1 and S3 are shown in Figures 7(a) and 7(b). The distinctive vibrational peaks at 3320-3335 cm^{-1} were assigned to NH stretching. Vibrational peaks at 1650-1730 cm^{-1} and 1575-1560 cm^{-1} were attributed to C=O stretching, and C=C stretching, respectively. Absorption bands at 2955 cm^{-1} represents C-H stretching whereas 1422, & 1380 cm^{-1} were assigned to C-H bending, and vibrational peaks at 780 cm^{-1} represent fingerprint stretching of C-Cl. Furthermore, Raman peaks at wavenumber 1712, 935 and 780 cm^{-1} are not observed in FT-IR spectra of sample S1. The presence of these additional vibrational peaks represents the signature of additional functional group, i.e., diclofenac sodium in sample S3 [28].

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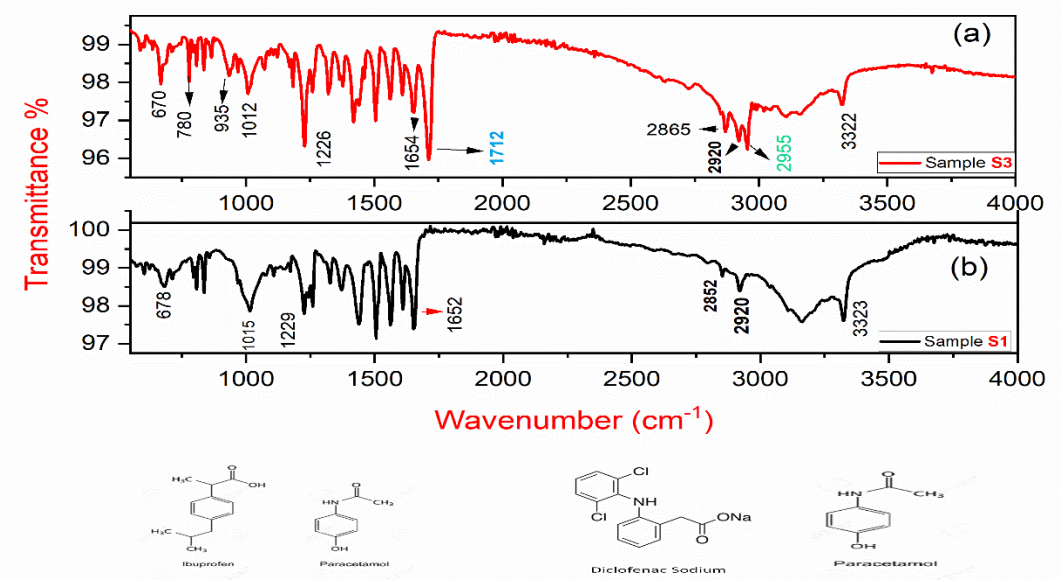

Figure 7. (**a**) FT-IR Spectra of sample S3; (**b**) FT-IR Spectra of sample S1.

Thus, our present molecular study infers that molecular study from LIBS technique confirms the presence of different molecules in sample S1-S6, which stems from complementary analysis for Raman and FT-IR spectroscopy. One can conclude that LIBS allows one to study elemental as well as molecular compositions.

3. Materials and Methods

In LIBS set-up as described elsewhere [10], the high peak-power and frequency-doubled 532 nm, nanosecond pulses from a Nd:YAG laser device have been used to generate plasma at the sample surface. The laser beam is focused onto the sample surface using a convex lens of 15 cm focal length. The repetition rate of laser pulses is kept at 2 Hz with 15 mJ per pulse of laser energy. The emitted signals from the cooling plasma have been recorded. The spectra show neutral and ionic atomic lines together with molecular bands [7, 9]. For resolving the atomic spectral emissions from the ablated sample, the emissions from plasma are dispersed with a Mechelle spectrometer (spectral range 200 nm to 900 nm, $\lambda/\Delta\lambda \approx 6000$; Mechelle ME5000, Andor Technology).

The LIBS spectra are represented in terms of intensity versus wavelength. Calibration of the spectrometer for accuracy is important in LIBS analysis. In the present study, wavelength and intensity calibrations of the Mechelle spectrograph, equipped with intensified charge coupled device (ICCD), utilize National Institute of Science and Technology (NIST) certified standard lamps. Two different types of standard lamps were used: (i) Hg-Ar (HG-1, Ocean Optics) lamp for wavelength calibration and (ii) deuterium-tungsten-halogen lamp (DH-2000-BAL, Ocean optics) for intensity calibration.

The spectrometer is equipped with an ICCD (iStar 734, Andor technology) and the obtained spectra are recorded with Andor Solis software. The identification of lines is performed by matching the spectral lines and relative intensities using the NIST atomic spectroscopy database [23]. The gate delay and the gate width of the spectrometer are kept at 1μs and 2μs, respectively, for optimization of signal to noise and signal to background ratios.

In Raman spectroscopy for the molecular analysis of the sample, Raman microscopy measurements have been performed with a Raman spectrometer (RIAR-532 Research India, having resolution 6 cm^{-1}). The Raman spectra was analyzed with reported data from G. Socrates *et al.* (2011) [18] and Zanyar Movasaghi *et al.* (2007) [24].

Fourier transform infrared (FT-IR) spectra were recorded using the spectrometer Spectrum-65, (Perkin Elmer) with frequency range of 500-4000 cm^{-1}. The FT-IR spectroscopic analysis of each drug sample has been carried out to evaluate the structure information with help of literature [28-29].

In the present study, different brands of sample named as S1, S2, S3, S4, S5, and S6 have been taken and the details of which are tabulated in Table 1. LIBS spectra have been recorded for 50 accumulations to produce one single, average LIBS spectrum. For each sample, 10 spectra have been recorded. On the basis of spectral intensity variation of the ingredients of the drug, PCA has been applied to the LIBS spectral dataset of drug samples [10].

4. Discussion and conclusions

The simultaneous monitoring of atomic as well as molecular variations in drugs at the time of manufacturing can be quite challenging. This work introduces a new approach for drug compositional analysis, namely a combination of analytical methods including LIBS, Raman- and FT-IR spectroscopy. The study conditionally enables one to engage in simultaneous study of atomic and molecular compositions of pharmaceuticals using LIBS. The spectral signature of organic and inorganic elements can be detected with LIBS. The results reveal that the matrix of the pharmaceutical sample is composed of organic and inorganic materials. In addition to this, vibrational bands of C_2 Swan and CN violet band systems are also observed. The CN and C_2 band spectral intensity in LIBS spectra allows one to infer presence of organic compounds/molecules in each sample [30]. In addition, complementary analysis of drugs is performed with Raman spectroscopy to determine the molecular composition of the drug. The observed spectral signatures in Raman spectra are correlated with CN and C_2 bands intensity that are observed in the LIBS spectra.

Hardness testing may be important for manufacturing pharmaceuticals. This work computed the relative hardness of the investigated drugs. The chemometrics analysis using PCA of the recorded LIBS data suggests applications as a rapid and selective technique for classification of selected pharmaceutical materials. Therefore, LIBS can be an effective tool for the study of composition variations in the form of trace elements, active and inactive ingredients, and molecules contained in the drug.

The presented results successfully demonstrate that LIBS is useful for elemental and molecular analysis. On the basis of our present work, one can say that LIBS along with chemometrics has good potential for the development and implementation of instruments for in-situ and on-line analysis of multiple elements and molecular analysis of drugs [30].

Acknowledgments:

One of the authors, Pravin Kumar Tiwari, is thankful to Kuldeep Kumar Patel from Research India for providing Raman experimental facility, and to Dr. Praveen Kumar Shahi, Assistant Prof. Physics Department SPM degree college, University of Allahabad, Allahabad and Prof. S. B. Rai, Physics Department, Banaras Hindu University, Varanasi for FT-IR experimental support. Pravin Kumar Tiwari also thanks for support by the Board of Research in Nuclear Sciences, India, by providing Senior Research Fellowship support for the work, Sanction No. 39/14/30/2016-BRNS/34434, 24.01.17.

Author Contributions

Pravin Kumar Tiwari (PKT) analyzed the samples following collection of experimental data, and he prepared the initial draft of this article. Dr. Nilesh Kumar Rai contributed in the analysis of Raman data and apprehended in critical review of the manuscript. Dr. Rohit Kumar also focused on visualization of the outcomes, and he conducted the experiments jointly with PKT. Prof. Christian Gerhard Parigger suggested various approaches for the experimental studies and communicated substantially in the creation of the manuscript in its current form. Prof. Awadhesh Kumar Rai (A.K.R.) motivated the work together with different approaches of drug analysis, and he provided expert advice in the interpretation and data analysis, moreover, Prof A.K.R. provided significant support for this work.

Role of Funding Source

This research received no external funding.

Conflicts of Interest

There are no conflicts of interest.

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