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Detection of toxicity in some oral antidiabetic drugs using LIBS and LA-TOF-MS

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ABSTRACT

Majority of the pharmaceutical tablets and capsules available at the medical stores are film-coated for taste masking and for protection against moisture and light. The elemental concentration of the film-coated content should be carefully monitored otherwise it can be toxic. In the present work, the toxicity of some commercial antidiabetic tablets available in Pakistan has been checked by precise quantitative analyses of their elemental content using a novel method. The proposed technique combines calibration free laser induced breakdown spectroscopy (CF-LIBS) and laser ablation time of flight mass spectrometer (LA-TOF-MS) without using aggressive chemicals. The thickness and chemical composition of coating films are analyzed using cross-sectional scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR). It is observed that the film-coating on the German sugar cure cores (GSCC) tablets consist of aluminum (50–100) μm and titanium (500–800) μm. In addition, the thicknesses of Glucophage and Zolid Plus tablets' coatings are found to range from 20–30 μm and composed of titanium, carbon, oxygen, sodium and magnesium. It has been found that a daily dose of three times a day of *GSCC* tablets contains about 600 mg/day of titanium and 150 mg/day of aluminum may considered toxic according to the United States food and drug administration (FDA). The results demonstrated that the core of the *GSCC* tablets mainly composed of calcium (60.7%), magnesium (24.2%), sodium (4.3%), potassium (2.5%), barium (2.4%) and silicon (5.8%) whereas, the core material in the Zolid Plus 850 mg and Glucophage 1000 mg tablets contain metformin ($C_4H_{11}N_5$•HCl) with hydrogen (7.3%), carbon (29.1%), nitrogen (42.4%) and chlorine (21.2%). Inclusive analysis based on the innovated non-destructive methodology that combines CF-LIBS and LA-TOF-MS reveals that it can be used for direct monitoring the toxicity for quality assurance in the pharmaceutical industry of antidiabetic drugs in future.

1. Introduction

Almost 99% of the mass of the human body is composed of O (65%), C (18.5%), H (9.5%), N (3.2%), C (1.5%), P (1%), K (0.4%), S (0.3%), Na (0.2%), Cl (0.2%) and Mg (0.1%) [1]. The other elements in the human body are present in trace amounts. According to the FDA, daily intake macro-nutrient metals such as calcium (1000–1200 mg/day), sodium (1500 mg/day), potassium (4700 mg/day), magnesium (400–420 mg/day), phosphorus (700 mg/day), and chloride (1800–2300 mg/day) is recommended [2, 3] whereas, the daily intake of micronutrient metals such as Al, Ti, Zn, etc., should be less than 100 ppm [4]. It is assumed that the imbalances of these elements, may considered toxic according to FDA and can cause different diseases [4].

Diabetes is a major threat to the global health and it is considered as one of the crucial causes of death in the world [5]. It is characterized by a significant imbalance in the blood glucose concentration which consequently affecting the insulin level. Two types of diabetes are known: type 1 and type 2. Type 1 diabetes is insulin-dependent while type 2 diabetes don't respond to insulin. Many studies claimed that the imbalance of essential metals in the human body is responsible for diabetes [3,5–17]. Due to inequity of certain metals, some reactive oxygen species are produced which might decrease the insulin gene promoter activity in the cells and cause diabetes [7,14,18]. Many interesting studies showed that the micronutrients metals such as aluminum, barium, cadmium, cobalt, copper, rubidium, strontium, molybdenum, selenium, tungsten, tin, chromium, nickel, zinc, manganese, vanadium, lead and arsenic are significantly higher in the people who suffering from diabetes [6,9,12,13,15,19–21]. It is also reported that the

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excessive consumption of micronutrients, like magnesium, in the human body can cause diarrhea and stomach cramps whereas deficiency in potassium, calcium, zinc and sodium might lead to a decrease in insulin glucose transport into the cells [3,8,15,22,23]. A very few studies found lower level of Mn, Cr and Ni in the Type-II diabetes patients. All these studies revealed that only the trace amounts of micronutrients metals are beneficial for the human body [24]. Excessive use of aluminum and titanium in cause health hazards effects on the human body [25–30].

A number of different methods exist to check the quality of the medicine products [31–34], which are mostly complex, time consuming and need specific sample preparation. Instead of conventional methods, LIBS has emerged as an efficient and non-destructive analytical technique for a rapid quality quantification of the paramedical tablets [31–36]. LIBS has been extensively used for the quality control for any material existing in the solid, liquid or gas phase [37–41]. In LIBS method, when a high energy pulsed laser beam is focused on a material to create a plasma plume, various phenomena occur including: surface heating, ablation, vaporization, dissociation, phase change and excitation [42]. Consequently, subsequence processes happened involving: recombination of electrons with the generated electronically excited atoms, atomic ions and neutral atoms which are helpful to determine information about the plasma plume emissions. A qualitative analysis is carried out by spectroscopic consideration of the plasma spectral lines. By associating the wavelengths of the observed spectral lines with the NIST database, the elemental composition of the examined sample can be clearly identified. A compositional analysis gives information about the concentration percentage of each of the elements present as a major or minor constituent in a sample [42–44]. The composition analysis of any solid sample can be determined more accurately by LIBS and a complementary technique like a LA-TOF-MS [45–47].

In the present work, we focus on analysis of some antidiabetic tablets brands in Pakistan, to check for their toxicity using a novel accurate method. We have utilized LIBS in conjunction with the LA-TOF-MS for the qualitative and quantitative analysis of these tablets. The thickness and chemical compositions of the coating layers were studied using the SEM and the FTIR. The compositions and thickness of the coating layers and core of the Glucophage 1000 mg, Zolid Plus 850 mg and *GSCC* tablets were compared.

2. Experimental

2.1. Sample collection

Samples of the commercial tablets GSCC, Glucophage 1000 mg and Zolid Plus 850 mg were purchased form a local a local pharmacy in Pakistan. The Glucophage 1000 mg (metformin hydrochloride) film coated tablets; manufactured by Merck Serono Ltd., Mfg. Lic. No. 000028, Reg. No. 025488 and Zolid Plus 850 mg (metformin hydrochloride) film coated tablets; manufactured by Getz Pharma (PVT) Ltd., Mfg. Lic. No. 000284, Reg. No. 047480. After verification, it has been found that the GSCC tables which is described as diabetes prevention medication is not made in Germany as written on the medication box. This medication seems to be home made in Pakistan by unauthorized factory with unreal name and origin.

The thicknesses of the coating films on the antidiabetic tablets were estimated using a SEM (JEOL JSM-6510LV). The confirmation of the chemical compositions of the coatings layers was achieved using a Fourier Transforms Infrared Spectrometer (Perkin Elmer 100 FT-IR spectrometer). The LIBS technique was used to determine qualitatively the elemental compositions of major, minor and traces in the coating films and in the tablet cores. The LIBS experimental setup has been discussed in details previously in our earlier papers [48–52]. Briefly, in this setup, a high-power Q-switched Nd:YAG Laser (Brilliant-B, Quantel, France), capable of delivering energy of about 500 mJ at 532 nm, with 5 ns pulse duration and 10 Hz repetition rate was focused to reach a laser irradiance of 5 GW/cm^2 to generate the plasma on the surface of the samples. The optical emission spectra were registered on a set of four spectrometers (model AvaSpec-3648 Avantes, Holland) equipped with CCD 3648 detectors, each having 10 μm slit width and covering the wavelength range of 250–870 nm. The laser energy was measured by an energy meter (Nova–Quantel, France). The target samples were placed in air at an atmospheric pressure. The optical fiber was used to collect the plasma radiation with a collimating lens (0–45° field of view) which was placed normal to the laser beam.

The same antidiabetic tablets samples were quantitatively analyzed using a LA-TOF-MS [42,53]. The entire system was coupled with a turbo molecular pump backed by a mechanical pump to maintain vacuum at about 1×10^{-6} mbar during the experimentation. The laser beam was focused on the sample surface by a quartz lens of 30 cm focal length. The generated ions were detected by a channeltron, operating at a voltage of 1.9–2.3 KV. The ion signals were analyzed by a 500 MHz digital storage oscilloscope (Tektronix) coupled with a personal computer. The ions were generated by laser ablation of the samples using a Q-switched Nd:YAG laser (Brilliant-B, Quantel, France) with fluence in the range of 1–5 J/cm^2.

3. Results and discussion

As discussed earlier, the three brands of film coated antidiabetic tablets available in Pakistan were selected for the comparative analysis. In the GSCC, maximum values of coating thicknesses containing two major elements, aluminum and titanium (the composition was identified by mass spectra of LA-TOF-MS as discussed further in Section 4 below) have been found as compared to the other two brands. The thickness of antidiabetic tablets is measured using SEM and is reconfirmed by depth profiling using the LA-TOF-MS spectra. The chemical compositions of coating layers of antidiabetic tablets are measured using the FTIR. LIBS and LA-TOF-MS were utilized for the complete compositional analysis of antidiabetic tablets.

3.1. Thickness and chemical analysis of coating films

To estimate the thickness of the coating films of the antidiabetic tablets; GSCC, *Glucophage and Zolid plus,* were cut in two pieces of approximately equal diameters. Cross-sessional SEM images were taken for the estimation of the thicknesses of the coating films.

In Fig. 1 (a,b) photographs of the cross-sessional view of the cut pieces of GSCC tablet are presented. Fig. 1(c) shows the cross-sessional SEM image of the front view of the cut piece of GSCC antidiabetic tablet. The image-J software was used to calculate the thickness of the coating layers. The thicknesses of outer coating layers of major elements aluminum and titanium (identified by mass spectra of LA-TOF-MS further below) in GSCC tablet were estimated in the range of 50–100 μm and 500–800 μm, respectively. In the Glucophage and Zolid Plus antidiabetic tablets only single coating layer was observed with the thickness in the range of about 20–30 μm. Similar coating thicknesses in medical tablets are also perceived by many authors [54,55]. To observe the chemical composition of the coating films, the absorption spectra were studied using a FTIR spectrometer. From the absorption spectra, it was noticed that the coating films on the Glucophage and Zolid Plus antidiabetic tablets are composed of Mg, Na, C, O, H and Ti whereas, the coating films in *GSCC* tablets consists of Mg, Al, Ti, O, H and C. Fig. 1(d,e) shows the a typical FTIR spectrum of the coating films of the *GSCC* sugar core cure tablets covering the wavenumber range 400–3200 cm^{-1}. The FTIR spectrum of the outer coating film shows strong bands related to Al-O stretching vibration at 620 cm^{-1}, 661 cm^{-1}, 720 cm^{-1} and 906 cm^{-1} [56]. The absorption peaks in the range 1200–4000 cm^{-1} correspond to commonly observed O—H, H—O—H, C—H, C—O and carboxylate bonds [56], as labeled in Fig. 1(d).

The outer aluminum film was removed by rinsing the samples in

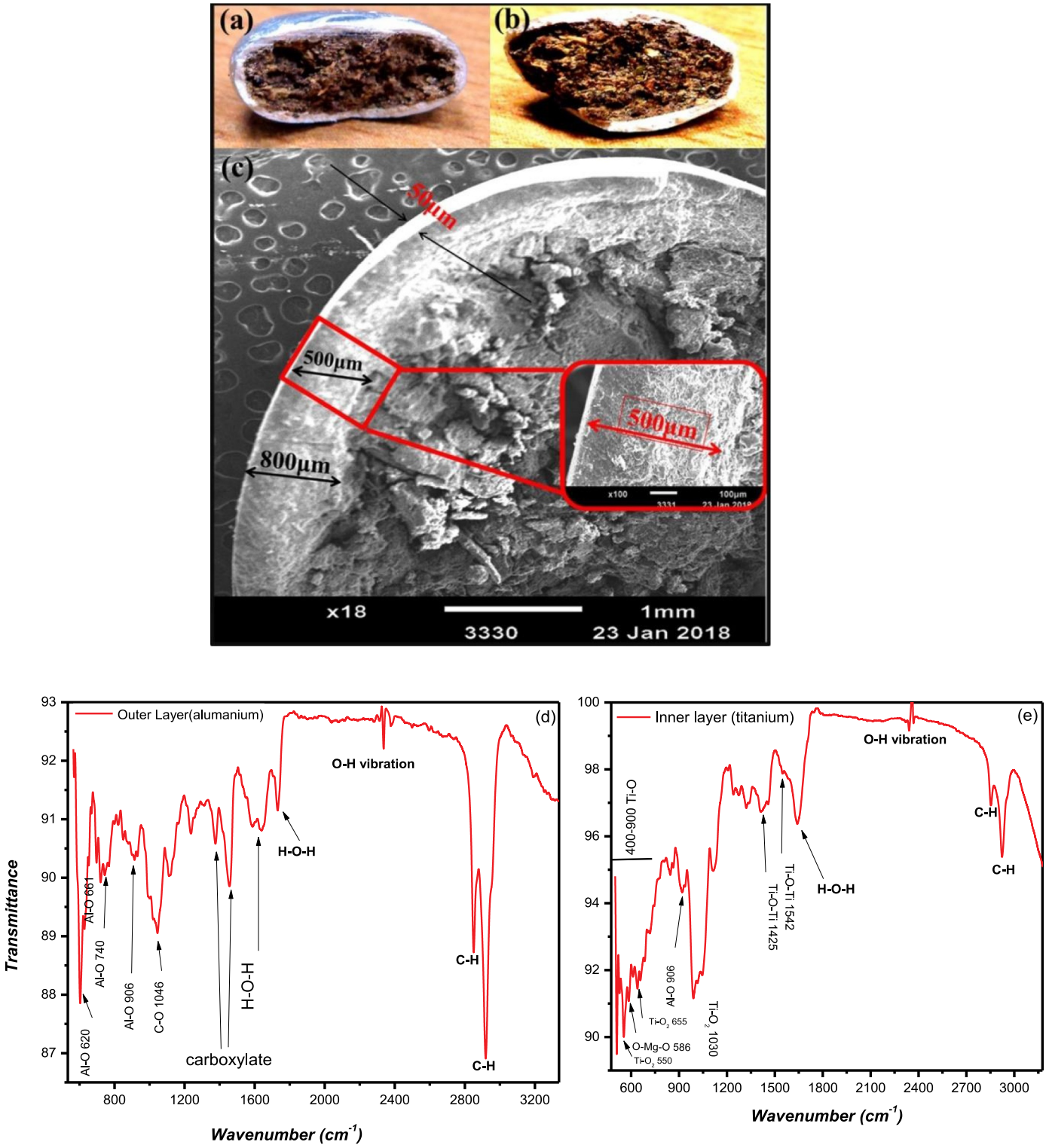

Fig. 1. (a) Cross-sessional view of cut piece of GSCC tablet, (b) enlarge photograph of cut piece, (c) Cross-sessional SEM image of front view of the cut piece operated at Cross-sessional SEM image of front view of the cut piece operated at 25 KeV with an enlarge image of outer layers showing thickness of aluminum and titanium as inset, (d) Fourier transform infrared (FTIR) spectrum (FTIR) of the outer aluminum layer, and (e) FTIR of inner titanium layer of GSCC tablets.

ethanol. Fig. 1(e) shows a typical absorption spectrum of the inner coating film of GSCC antidiabetic tablets. In the second coating layer, strong absorption bands in the region 400–900 cm^{-1} and at 550, 655, 1030, 1425, 1542 cm^{-1} are observed that corresponds to Ti-O-Ti stretching and stretching vibrations [57].

From the above observed results, and by considering the weight of the outer layers of the tablets, it has been found that there is titanium in GSCC, Zolid Plus and Glucophage antidiabetic tablets around 200 mg, 6 mg, 5 mg, respectively, while about 50 mg of aluminum is found in GSCC coating layer only. So that for a recommended daily dose of three times a day of GSCC tablets, daily intake of 600 mg/day of titanium and 150 mg/day of aluminum can cause different diseases and represent toxic doses according to FDA [4].

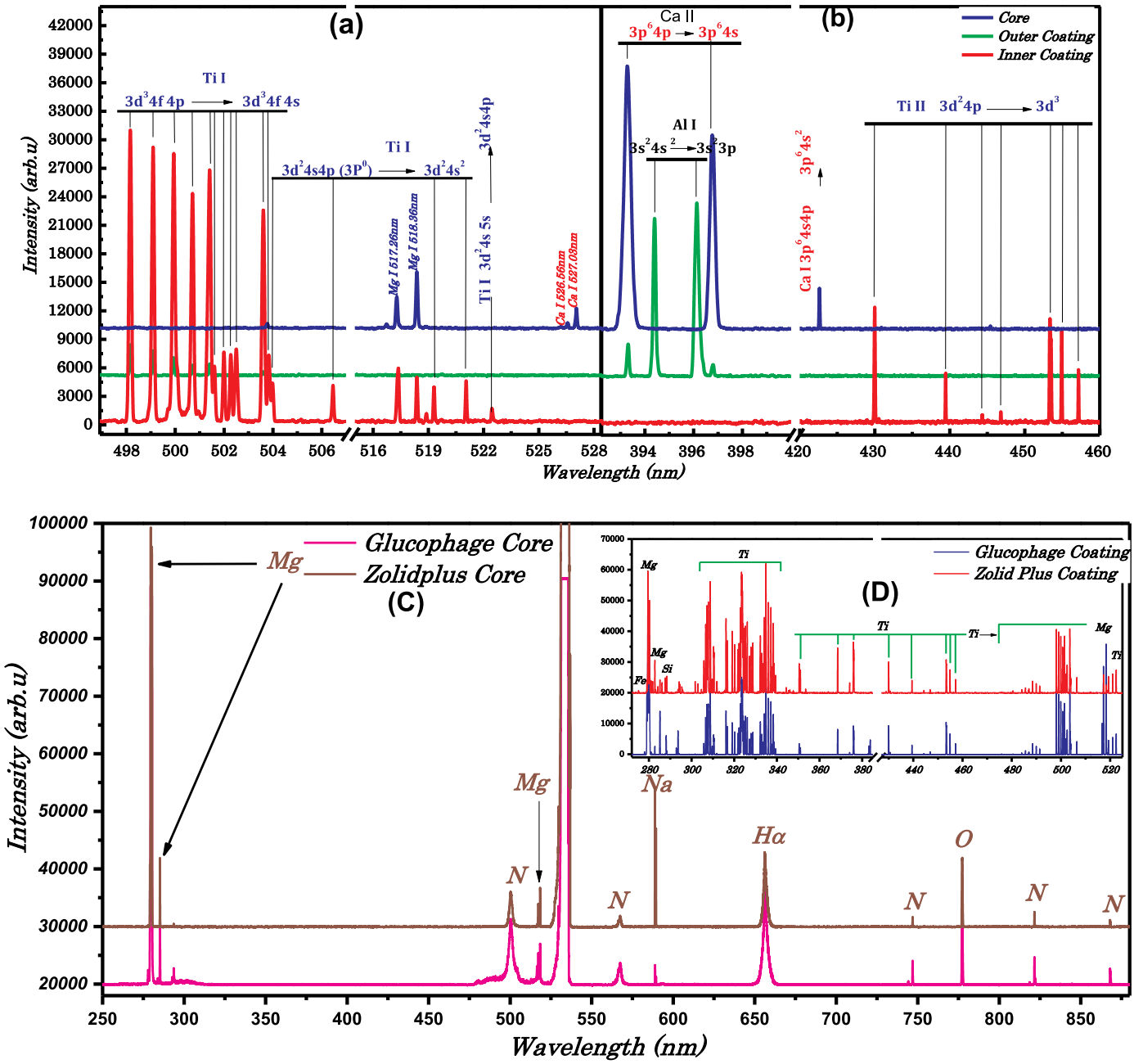

Fig. 2. (a) Optical emission spectra (OES) of outer, inner coating films along with the core of the GSCC tablets covering the wavelength range (495–528) nm, (b) (390–400) nm, (c) OES of coating films of Glucophage 1000 mg and Zolid Plus 850 mg antidiabetic tablets covering the wavelength range (270–530) nm and (d) OES for core materials covering the wavelength range (250–800) nm as inset, respectively.

3.2. Optical emission studies

The qualitative compositional analysis of the antidiabetic tablets is achieved from the optical emission spectra of the laser produced plasma produced on the surfaces of antidiabetic tablets by a Nd:YAG laser (532 nm), fluence about 1–5 J/cm^2 as described previously elsewhere [45–47]. The optical emission spectra of the coating layers as well as the core materials give information about the constituent elements; the major and trace elements present in the samples. In the *GSCC* tablets, two coating layers were observed whereas, in the Glucophage and Zolid Plus antidiabetic only single layer coating layer was observed as studied before using FTIR.

Fig. 2(a, b), represents the optical emission spectra of the outer coating, inner coating and core of the *GSCC* antidiabetic tablet covering the wavelength ranges 495 nm–530 nm and 390 nm–460 nm. All the spectra were recorded under identical experimental conditions such as laser energy, laser fluence and time delay. This spectral region is selected because most of the persistent and strong emission lines of the toxic elements lie in this optical range. In the core of the GSCC tablets, two very strong lines of singly ionized calcium at 393.37 nm and 396.85 nm due to the 4p $^2P_{1/2,\ 3/2}$ → 4 s $^2S_{1/2}$ transitions were observed. In addition, weak emission lines of magnesium at 517.27 nm and 518.36 nm and three calcium lines at 526.56 nm, 527.03 nm and 422.67 nm are observed. In the outer coating layer of the tablet, the observed dominating lines belong to aluminum at 396.15 nm and 394.40 nm due to the 3s^2 4 s $^2S_{1/2}$ → 3s^2 3p $^2P_{1/2,\ 3/2}$ transitions. However, the weak lines of calcium that were dominating in the core spectrum are detected. A couple of titanium emission lines around 500 nm have also been observed. In the inner coating layer, the major observed lines belong to titanium. The multiplet structure shown in

Fig. 2(a) around 500 nm is due to transitions from the $3d^3$ (^4F) 4p $^{3,5}G_{2,3,4,5,6}$ upper levels to the $3d^3$ (^4F) 4 s $^{3,5}F_{1,2,3,4,5}$ levels. Whereas, the structure around 520 nm is due to the $3d^2$ 4s4p → $3d^2$ $4s^2$ transitions. The structure shown in Fig. 2(b) around 450 nm belongs to singly ionized titanium due to the $3d^2$4p → $3d^3$ transitions. The characteristic lines and related transitions of all the detected emission lines have been identified with the help of the NIST data base [58]. Evidently, both of the aluminum and titanium emission lines are absent in the spectra of the core of the tablets. It is clear from the Fig. 2(a, b) that the outer and inner coatings of the *GSCC* tablets contain aluminum and titanium.

In order to compare the compositions of the film coated antidiabetic tablets, we also quantitatively analyzed the branded Glucophage 1000 mg and Zolid Plus 850 mg tablets. The emission spectra of the inner core material are shown in Fig. 2(c,d) covering the wavelength range from 250 to 870 nm. In the spectra, the emission lines of oxygen, nitrogen, hydrogen and few lines of magnesium are evident. The core of the antidiabetic tablets consists of metformin hydrochloride and for the treatment of diabetes, the molecular formula of $C_4H_{11}N_5 \cdot HCl$ and molecular weight of 165.63 g/mole which is used for the treatment of diabetes [59]. Fig. 2(c,d), (inset) represents the optical emission spectra of the coating films of Glucophage 1000 mg and Zolid Plus 850 mg antidiabetic tablets covering the wavelength range 270–530 nm. The emission spectra show the same titanium emission lines as observed in the *GSCC* tablets. The hypromellose and polyethylene glycol are the main constituents of the coating films, but only spectral emission lines of titanium, magnesium, iron, silicon and sodium are observed. As it is an organic compound, therefore it is difficult to calculate the compositions of all the elements. The compositions of these tablets are determined using a LA-TOF-MS, as discussed in detail in the last section.

3.3. Measurement of plasma temperature

Since the core material in the *GSCC* tablets mainly consists of calcium, magnesium, sodium potassium and barium therefore, calibration-free LIBS technique (CF-LIBS) was used to calculate the compositions of the ingredients. In this technique, the plasma temperature and electron number density is required to determine the compositions of the detected elements. However, in order to use CF-LIBS, two conditions have to be fulfilled: (i) the plasma is optically thin and (ii) the plasma is in local thermodynamic equilibrium (LTE). The optically thin plasma condition was validated using the observed intensity ratios of various spectral lines with the ratios obtained using spectroscopic parameters [37–39]. Assuming that the plasma follows LTE, the plasma temperature was considered from the emission intensities of the optically thin plasma emission lines of neutral Ca using the Boltzmann plot method. To acquire more accurate plasma temperature, the spectral line intensities of Ca were corrected for self-absorption. After the self-absorption correction, the Boltzmann plot was drawn and the plasma temperature was estimated using neutral calcium lines listed in the Table. 1. The spectroscopic data of the lines used in Boltzmann plot were taken from NIST database [58]. As errors are bound to be present in the determination of the plasma temperature by the Boltzmann plot method therefore, the electron temperature is determined with uncertainty of about ± 10% error, which mainly comes from the transition probabilities and emission line intensities.

Fig. 3(a), demonstrates a Boltzmann plot drawn using the neutral Ca lines listed in Table-1. The dots are the experimental data point and the line, which passes through the points, is a linear regression fit. The plasma temperature is estimated from the slope of the line as (9000 ± 900) K. The calculated plasma temperature is then used for the elemental compositions of different elements present in the core of the *GSCC* antidiabetic tablets.

3.4. Determination of electron number density

In order to estimate the electron number density, we have selected the Stark-broadened profile of the hydrogen H_α line at 656.28 nm. The Stark width $\Delta\lambda_{FWHM}$ of the line is determined by de-convoluting the observed line profile as a Voigt profile, which takes into account the instrumental width, the Doppler width and the Stark width. The line profile of the hydrogen H_α line is reproduced in Fig. 3(b), showing the experimental data point and the Voigt fit. The FWHM is determined as (1.49 ± 0.05) nm. The electron density is calculated using the following relation [37–39]:

$$N_e = \left(\frac{\Delta\lambda_{FWHM}}{1.098}\right)^{1.473} \times 10^{17} cm^{-3} \quad (1)$$

The electron number density is deduced as (1.6 ± 0.2) × 10^{17} cm^{-3}.

To check the local thermodynamic equilibrium (LTE), the criteria of minimum electron density, proposed by McWhirter, that the collisional processes are dominating over the radiative processes, has been validated. The lower limit for the electron density is calculated using the relation [60]

$$N_e > 1.6 \times 10^{12} \times \Delta E^3 \times T^{1/2} \quad (2)$$

Here ΔE is the highest energy difference between the upper and the lower energy level in (eV) and T is the plasma temperature (K). The lower limit for electron density, calculated from the emission lines of calcium and magnesium, was in the range of 10^{15} cm^{-3} whereas, the number density calculated using the H_α line was in the range of 10^{17} cm^{-3}. Thus, rel. (2) is validated which indicates that the plasma can be considered close to LTE and the optical emission spectrum is associated to the compositional analysis.

3.5. CF-LIBS for quantitative analysis

Compositional analysis was performed after confirming the optical thin and LTE conditions [61,62]. For this purpose, online calibration free method was utilized for the compositional analysis of major minor and trance elements present in the GSCC antidiabetic tablets. In this technique, the optically thin spectral lines are used to estimate the atomic concentrations using the simple Boltzmann equation [37,38,62].

Table 1
Spectroscopic parameters of the emission lines of Ca I used to calculate the plasma temperature, taken from NIST database [58].

Wavelength (nm)	Transition Upper level		Lower level	*Transition Probability(10^7 s^{-1})*	*Energies E_k(eV)*	g_k
Ca I						
616.21	$3p^64s5s\ ^3S_1$	→	$3p^64s4p\ ^3P_2$	4.77	31,539.495	3
518.88	$3p^64s5d\ ^1D_2$	→	$3p^64s4p\ ^1P_1$	4.00	42,919.053	5
527.03	$3p^63d4p\ ^3P_2$	→	$3p^63d4s\ ^3D_3$	5.00	39,340.080	5
558.87	$3p^63d4p\ ^3D_3$	→	$3p^63d4s\ ^3D_3$	4.90	38,259.124	7
612.22	$3p^64s5s\ ^3S_1$	→	$3p^64s4p\ ^3P_1$	2.87	31,539.495	3
422.67	$p^63d4p\ ^3F_4$	→	$3p^63d4s\ ^3D_3$	21.8	23,653.304	3
643.90	$3p^63d4p\ ^3F_4$	→	$3p^63d4s\ ^3D_3$	5.30	35,896.889	9

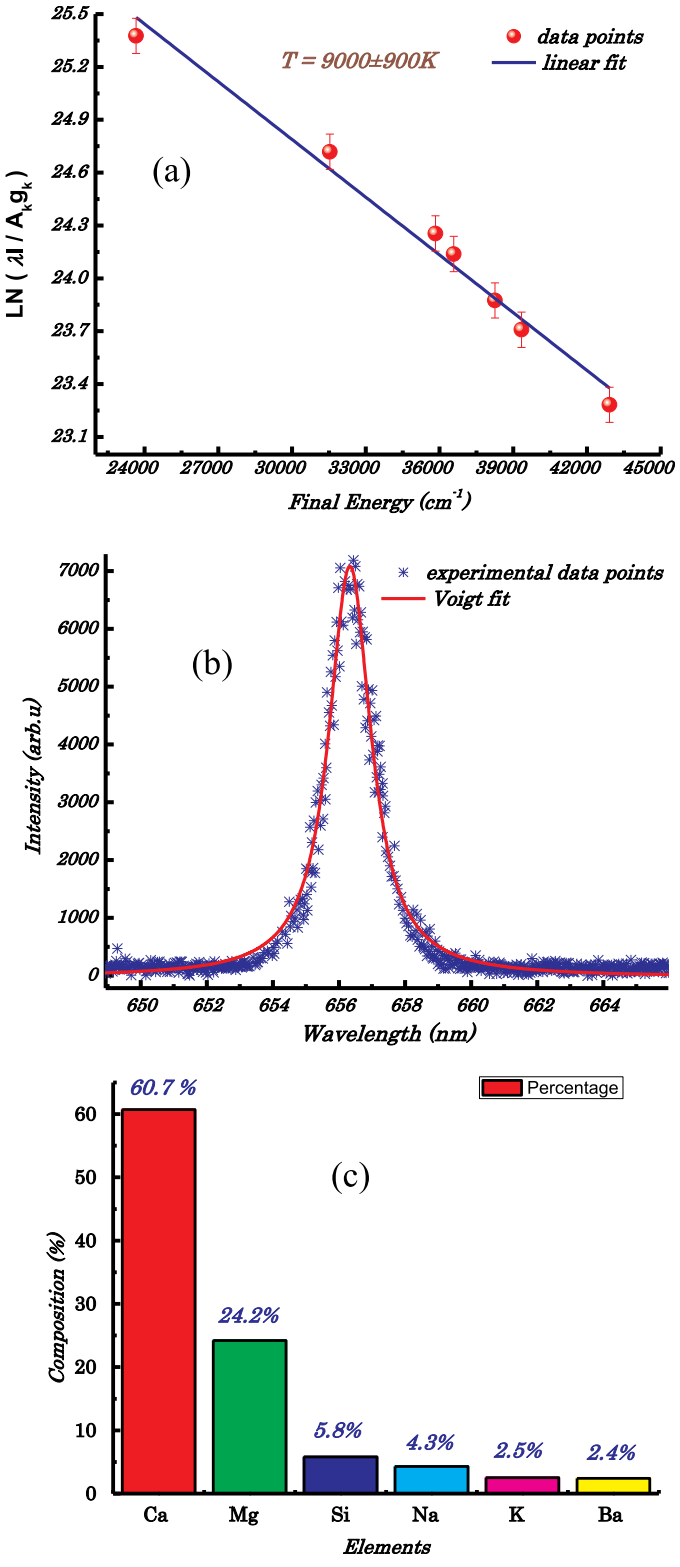

Fig. 3. (a) Boltzmann plot based on the neutral Ca I lines. The plasma temperature is calculated from the slop of the line. (b) line profile of the hydrogen H_α line at 656.28 nm along with the Voigt fit to determine the full width at half maximum. (c) bar graph showing the percentage compositions of the detected element in the core of the GSCC antidiabetic tablets.

$$C^z = I_k \frac{U^z(T)}{F A_k g_k} e^{\left(\frac{E_k}{kT}\right)} \quad (3)$$

Where, F factor is related to the ablated mass, C^z is the composition of neutral atom, I_k is the integrated line intensity, g_k is the statistical weight of the upper level, A_k is the transition probability, $U(T)$ is the partition function, E_k is the energy of the upper level, T is the electron temperature and k is the Boltzmann constant. All the spectroscopic parameters used for the compositional analysis were taken from the NIST database [58]. To calculate the contribution of the ionized species, the Saha Boltzmann equation was utilized [63]. The total composition of an element was calculated by taking into account its contributions of neutral as well as ionizes species. After taking a number of spectra, an average elemental composition is calculated for each element. In Fig. 3(c), a bar graph represents the percentage compositions of the detected element in the core of the GSCC antidiabetic tablets. It is evident from the figure that calcium and magnesium have major contributions in the core of the GSCC tablets with the composition of about 60% and 24%. The compositions of the other elements such as sodium, potassium, silicon and barium are estimated as 4.3%, 2.5%, 5.8% and 2.4%.

4. Ionic studies using LA-TOF-MS

LA-TOF-MS spectra are used for the quantitative determination of ingredients in the antidiabetic tablets. In order to verify the results obtained from the optical emission studies, the elemental compositions of the antidiabetic tablets were also determined using the LA-TOF-MS [53]. The thickness of the coating layers was calculated by depth profiling and the compositions of the core of the tablets were calculated using the integrated signal intensities in the mass spectra. In Fig. 4(a), the LA-TOF-MS spectrum of the GSCC tablets with the depth profiling recorded using a Q-switched Nd: YAG laser (6 mJ at 532 nm, 5 ns pulse width). The entire system was maintained at about 10^{-6} Torr vacuum during the experimentation. The laser beam was focused by a quartz lens of 30 cm focal length, which was placed in front of the entrance window of the vacuum chamber. A calibration curve for the ionic mass ($\sqrt{m}$) versus Flight Time (T) fit, with $R^2 = 0.99$, is reproduced as an inset in the figure. A number of mass spectra were recorded at different number of laser shots, varying from 1 to 50. It is observed that at 6 mJ laser pulse energy, only the aluminum and carbon peaks appear with very high intensity. Subsequently, with more laser shots, the intensity of the aluminum peak decreases whereas the intensities of carbon and oxygen peaks remain unaltered. For more clarifications, in Fig. 4(b), the variations in the signal intensities of C, O, Al and Ti as a function of the number of laser shots are represented. This figure reveals that with increasing the number of laser shots, only the intensity of the titanium signal shows an increasing trend, Al signal intensity decreases whereas the intensities of the O and C signals remain constant.

By reaching 50 laser shots, the aluminum emission signal disappears whereas only the titanium peak remains with good intensity. It can be inferred that the aluminum layer of thickness $\hat{\approx}$ 50–100 μm (measured with cross-sectional SEM as described before), is completely removed after 50 laser shots. It is concluded that each average laser pulse energy of 6 mJ ablates a about 1–2 μm of the coating layer of aluminum. The qualitative analysis obtained from the LA-TOF-MS spectra also validates our optical emission results obtained from the LIBS technique

In Fig. 4(c), the time of flight mass spectrum of the core of the GSCC antidiabetic tablets is revealed. The time of flight mass spectrum is recorded at the optimized values of accelerating voltage at 1.2 KV and channeltron voltage at 1.8 KV. All the observed elements in the optical emission spectrum are also detected in the mass spectrum with almost the same compositions. The mass spectrum of the core of the GSCC tablets revealed the major contents of calcium, magnesium, potassium, sodium, and barium. It is revealed from Fig. 4(c) that calcium and magnesium have major contributions in the core of the GSCC tablets with the composition of about 60% and 24%, respectively. The compositions of the other elements such as sodium, potassium, silicon and barium are estimated as 4.3%, 2.5%, 5.8% and 2.4%, respectively.

After a complete compositional analysis of the GSCC tablets,

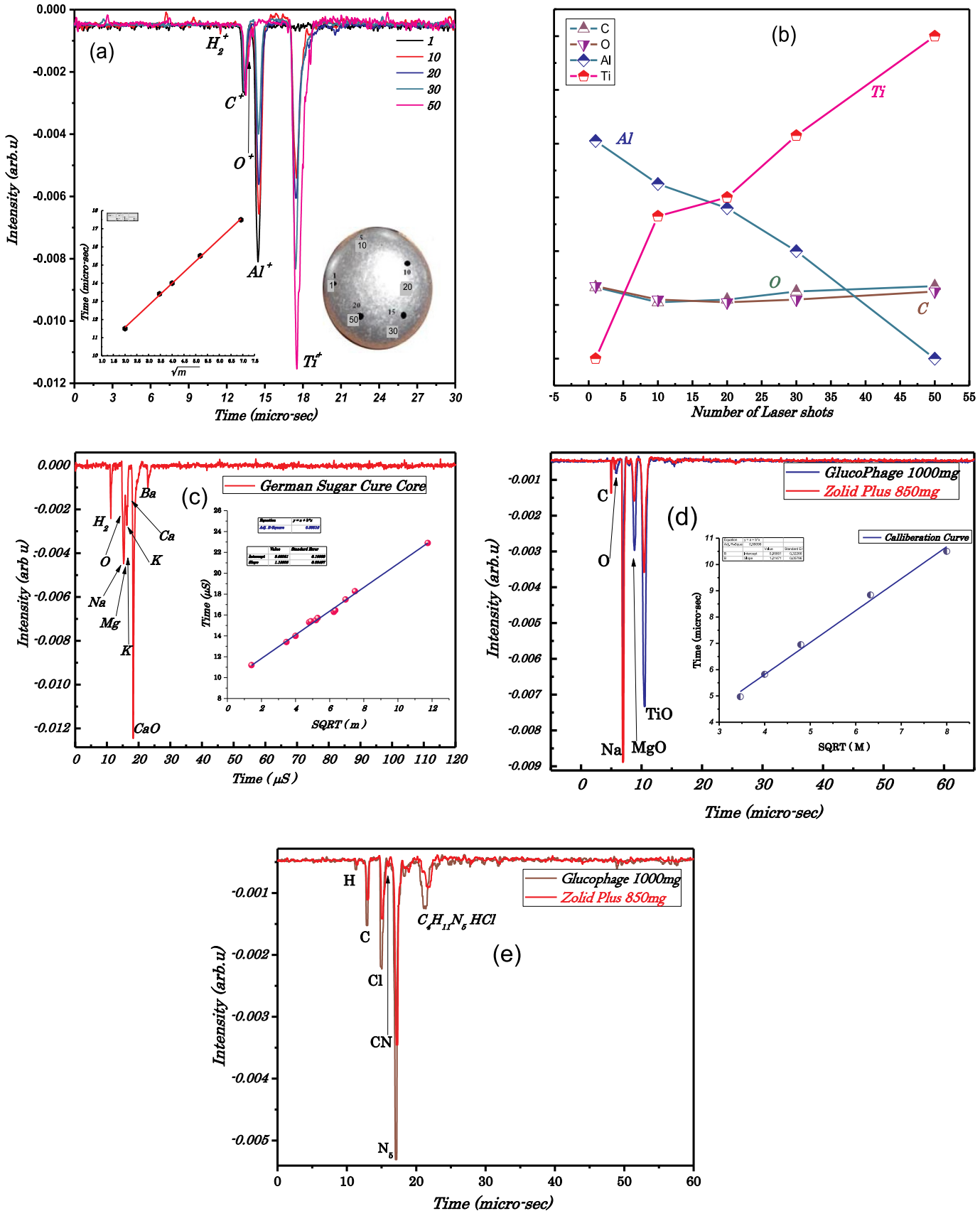

Fig. 4. (a) Time of flight mass spectrum (TOF-MS) of the GSCC tablets at different laser shots, (b) variation of the intensity of the ion signal with the number of laser shots. The operating channeltron Voltage V_{ch} = 1.8 KV and 10^{-6} mbar vacuum, (c) TOF-MS of the core of the GSCC tablets taken at channeltron Voltage V_{ch} = 1.8 KV and 10^{-6} mbar vacuum, (d) TOF-MS of the coating films of the Glucophage 1000 mg and Zolid Plus 850 mg tablets, the channeltron operating Voltage V_{ch} = 1.9 K and at 10^{-6} mbar vacuum, (e) TOF-MS of the inside of the Glucophage 1000 mg and the Zolid Plus 850 mg tablets, the channeltron Voltage V_{ch} = 2.0 KV and 10^{-6} mbar vacuum.

Glucophage 1000 mg and Zolid Plus 850 mg were also quantitatively analyzed using the same linear time of flight mass spectrometer at the optimized conditions. The time of flight mass spectra of the coating layers were obtained at an accelerated voltage V_{ac} = 1.6 KV, channeltron voltage V_{ch} = 1.9 KV and the system was kept at 1×10^{-6} mbar vacuum.

Fig. 4(d), characterizes the time of flight mass spectra of the coating layers in Glucophage 1000 mg and Zolid Plus 850 mg antidiabetic tablets. The mass spectra showed that the outer layers of the Glucopgae 1000 mg and Zolid Plus 850 mg are mainly composed of carbon, oxygen, sodium, magnesium and titanium, sodium and magnesium. As the thickness of these layers are very thin, in the range 20–30 micrometers as described before, therefore, these coating films are completely removed after some laser shots. It is observed that the contents of O, MgO and TiO are much higher in the Glucophage 1000 mg as compared to that in the Zolid Plus 850 mg tablets.

In Fig. 4(e), the LA-TOF-MS spectra of the core material of the Glucophage 1000 mg and Zolid Plus 850 mg tablets are demonstrated. The figure reveals that the cores of the studied tablets are mainly composed of C, H, N and Cl with the compositions about hydrogen (7 ± 3)% carbon (29 ± 5)%, nitrogen (42 ± 7)% and chlorine (22 ± 5)%. One peak around time of flight of 20μs was also detected that belongs to pure metformin hydrochloride labeled as C4H11N5•HCl. The white colored metformin hydrochloride is commonly used for the treatment of diabetes that is an indication of the quality drugs. Composition of metformin hydrochloride is high in Glucophage 1000 mg as compared to the Zolid Plus 850 mg tablets.

5. Conclusion

The compositional analysis of locally available antidiabetic tablets was performed by means of a novel method that combines CF-LIBS and LA-TOF-MS to monitor the toxicity of these drugs. The compositions of the cores and coatings along with the thickness of coating films of the GSCC, Zolid Plus 850 mg and Glucophage 1000 mg antidiabetic tablets were also compared. The thickness and chemical composition have been verified using SEM and FTIR spectroscopy. It is observed that the thickness of the coating film in GSCC tablets is about 500–800 μm (Al and Ti) whereas, the thicknesses of the coating film in Zolid Plus and Glucophage tablets are tenths of micrometers (Ti, Ca, and Mg). The coating layers of GSCC antidiabetic tablets mainly composed of aluminum followed by titanium whereas, the coatings of Zolid Plus and Glucophage tablets mainly composed of TiO along with CaO, MgO. The core of the GSCC tablet is composed of calcium, magnesium, sodium, potassium, barium, silicon with varying compositions whereas, the core material in Zolid Plus 850 mg and Glucophage 1000 mg tablets is found to be C4H11N5•HCl. All the elements detected in the core of Zolid Plus 850 mg and Glucophage 1000 mg tablets were not observed in the GSCC tablets. It has been concluded that a daily dose of 3 times a day of GSCC tablets may contain around 600 mg of titanium and 150 mg of aluminum which consider toxic according to FDA. This study demonstrates that LIBS complementary with LA-TOF-MS represents a powerful method which can indicate the toxicity of medication and be used for quality control in the pharmaceutical industry without using aggressive chemicals.

Novelty statement

- Ø In this contribution for the very first time analytical analysis of Pakistani Antidiabetic Tables is performed using LIBS and LA-TOF-MS.
- Ø Work Present in this research paper is original and is not submitted for publication in any other journal

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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