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Short communication

Direct analysis in real time – High resolution mass spectrometry as a valuable tool for the pharmaceutical drug development

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ABSTRACT

In this study, direct analysis in real time-mass spectrometry (DART-MS) was assessed for the analysis of various pharmaceutical formulations with intention to summarize possible applications for the routine pharmaceutical development. As DART is an ambient ionization technique, it allows direct analysis of pharmaceutical samples in solid or liquid form without complex sample preparation, which is often the most time-consuming part of the analytical method. This makes the technique suitable for many application fields, including pharmaceutical drug development. DART mass spectra of more than twenty selected tablets and other common pharmaceutical formulations, i.e. injection solutions, ointments and suppositories developed in the pharmaceutical industry during several recent years are presented. Moreover, as thin-layer chromatography (TLC) is still very popular for the monitoring of the reactions in the synthetic chemistry, several substances were analyzed directly from the TLC plates to demonstrate the simplicity of the technique. Pure substance solutions were spotted onto a TLC plate and then analyzed with DART without separation. This was the first DART-MS study of pharmaceutical dosage forms using DART–Orbitrap combination. The duration of sample analysis by the DART-MS technique lasted several seconds, allowing enough time to collect sufficient number of data points for compound identification. The experimental setup provided excellent mass accuracy and high resolution of the mass spectra which allowed unambiguous identification of the compounds of interest. Finally, DART mass spectrometry was also used for the monitoring of the selected impurity distribution in the atorvastatin tablets. These measurements demonstrated DART to be robust ionization technique, which provided easy-to-interpret mass spectra for the broad range of compounds. DART has high-throughput potential for various types of pharmaceutical analyses and therefore eliminates the time for sample cleanup and chromatographic separation.

1. Introduction

Both nuclear magnetic resonance (NMR) and mass spectrometry (MS) share a long tradition in the elucidation and confirmation of the structures of active pharmaceutical ingredients (APIs), impurities and degradation products in pharmaceutical drug development and analysis. Possible bottlenecks of analytical procedures in pharmaceutical analysis are often sample preparation and chromatographic separation [1–3], DART is capable of analyzing the sample at atmospheric pressure, essentially in the open lab environment under ambient conditions. DART mass spectrometry is an analytical technique with the ability to analyze broad range of very different samples without conventional sample preparation and chromatographic separation [4,5] and with minimized matrix effect [6,7], Together with other novel ambient desorption ionization techniques such as desorption electrospray ionization (DESI) and atmospheric-pressure solids analysis probe (ASAP) it has become commercially available in the recent years [8–10]. The DART ion source has been already shown to be efficient for the ionization of APIs in the tablets and other drug formulations [11–16]. DART belongs to the family of soft ionization techniques and thus most of the analyzed samples produce very simple mass spectra corresponding to the molecular ion $[M+H]^+$ [6,11–14]. This phenomenon allows to quickly determine the structure of the APIs that

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are present in the tablet. When DART is coupled to high-resolution mass spectrometry (HRMS) instrument such as Q-TOF or Orbitrap, it might provide additional information to traditional identification approaches used for this purposes in the pharmaceutical development, as well as Fourier transform infrared (FT-IR) spectroscopy [17].

The aim of this work is to demonstrate the possibility of DART in pharmaceutical development. In this study, more than twenty different types of pharmaceutical tablets, ointment, injection solution and suppository with structurally different APIs were tested. Moreover, several APIs were analyzed directly from TLC plates. Pure substance solutions were spotted onto a TLC plate and then analyzed with DART without separation. All of the mentioned samples were introduced directly into the ion source while holding with tweezers in the fixed position and analytes were then desorbed from the surface by the flow of heated gas and ionized. Although imaging possibilities of DART are very limited due to the low spatial resolution, a simple technique of tablet preparation was developed to study the distribution of the selected impurity in the tablet of atorvastatin.

2. Experimental

2.1. Chemicals and reagents

Acetonitrile, methanol of HPLC gradient grade (J.T. Baker, USA) and water purified by Milli-Q system (Millipore, USA) were used for preparation of samples and mobile phases. Phosphoric acid, ammonium formate and diammonium hydrogen phosphate of analytical grade were purchased from Sigma-Aldrich (Prague, Czech Republic). The studied pharmaceutical formulations (for more details see Table 1) were purchased in a local commercial pharmacy chain or developed by Zentiva k.s. (Prague, Czech Republic). APIs for the TLC measurements and atorvastatin tablets were developed by Zentiva k.s. (Prague, Czech Republic).

2.2. Sample preparation

No sample preparation was needed for the DART experiments of the tablets. APIs for the measurement from TLC plates were dissolved in acetonitrile. TLC Silica gel $60F_{254}$ aluminum sheets used in this study for TLC experiments were purchased from Merck (Darmstadt, Germany). For the UHPLC and LC–MS measurements of impurity profiling, tablets of atorvastatin were simply homogenized and dissolved in mixture of acetonitrile:water solution (40:60, v/v). Sample extraction for UHPLC analysis was performed on an ultrasonic bath UCC4 (TESON, Slovakia). The solution was centrifuged to get rid of the insoluble excipients. Clear supernatant was then injected to UHPLC and LC–MS system.

2.3. UHPLC instrumentation and methods

All chromatographic experiments were carried out on an Acquity UPLC system with a photodiode array detector (Waters, Prague, Czech Republic). The system was controlled and acquired data were processed by the Empower software (Waters, Prague, Czech Republic). Chromatographic separations were performed on an Ascentis Express C8 column (100 × 2.1 mm, 2.7 μm; Sigma, Czech Republic). The gradient elution employed solvent A and B as mobile phase components. The solvent A was 0.1% phosphoric acid, solvent B was a mixture of acetonitrile:methanol (60:40, v/v). Flow rate of a mobile phase was maintained at 0.4 mL min^{-1} and the column was thermostated at the temperature of 40 °C. The gradient program was set as follows: time/% of solution B: 0/40, 5.2/60, 7.0/80, 7.3/80, 7.5/40 with an equilibration time of 1 min. The injection volume was 1 μL and analytes were monitored at a wavelength of 246 nm.

2.4. LC–HRMS instrumentation and methods

LC–high-resolution mass spectrometry (HRMS) experiments were performed on a LTQ Orbitrap XL Mass Spectrometer (Thermo, San Jose, USA) coupled to an HPLC HTS PAL system (CTC Analytics, Switzerland). LC separation was performed on a Kinetex C18 (150 × 4.60 mm, 2.6 μm, Phenomenex, USA) column using 0.6 mL min^{-1} flow rate and mobile phase consisting of 10 mM ammonium formate (pH 6.3) and acetonitrile (gradient of acetonitrile ranging from 30% to 100% in 18 min). For ionization of eluted analytes APCI ion source operated in the positive mode was employed (vaporizer temperature 400 °C, capillary temperature 300 °C, discharge current 4 μA and tube lens voltage 40 V).

2.5. DART–Orbitrap analysis

DART-Standardized Voltage and Pressure Adjustable (SVPA) ion source with tweezer holder module (IonSense, Saugus, USA) was coupled to Orbitrap Elite mass spectrometer (Thermo Fischer Scientific, Bremen, Germany) through the interface evacuated by the diaphragm pump. This DART modification allowed adjusting the angle of gas supply to the target, while the objects of the analysis were fixed in its positions using tweezer holder module. The DART ion source was operated in the positive ion mode with helium ionizing gas at the pressure of 0.55 MPa. The beam was heated from 50 °C to 500 °C depending on the analyte structure, while the grid electrode voltage was set to 350 V. The parameters of the mass spectrometer were tuned as follows: capillary voltage 50 V, tube lens voltage 100 V, skimmer voltage 18 V and capillary temperature 275 °C. The acquisition rate was set to 2 spectra/s with mass resolving power of 120,000 full-width half maximum (FWHM) for *m/z* 200). Xcalibur software (Thermo Fischer Scientific, Germany) with DART web-based module was used for the instrument operation, data acquisition and processing.

3. Results and discussion

3.1. Identification of the APIs in different pharmaceutical formulations

Mass spectra of all samples were obtained by simply putting the tablet in the ion source of the mass spectrometer, holding with tweezers as depicted in the Fig. 1. The APIs of the studied formulations were identified based on the accurate mass measurements and elemental composition calculation with the error ranging from −0.98 to 3.08 ppm. The optimum desorption temperature for each tablet was carefully determined by rising the temperature of the gas beam from 50 to 500 °C. Similar ion current characteristic curves were achieved for all samples. Typically, almost no signal was present up to temperature 200 °C. At higher temperatures, simple mass spectrum appeared as shown in Fig. 2 for representative compound of prucalopride. The APIs of the studied formulations are summarized in the Table 1 together with relevant details such as structural formula, molecular mass and the most abundant ions that were observed. As summarized in the Table 1, abundant peaks representing molecular ion $[M+H]^+$ were observed for most of the analytes. However, for alcohols and carboxylic acids, $[M–H_2O+H]^+$ ions were detected together with dimers $[2M+H]^+$ and less intensive $[M+H]^+$, which is in the agreement with the theoretical expectations [14,18]. It was shown that it was possible to obtain simple mass spectra for most of the compounds with a broad range of functional groups. Application of

Table 1
Active pharmaceutical ingredients in the analyzed samples.

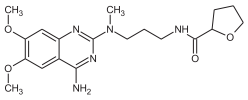
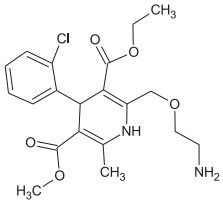
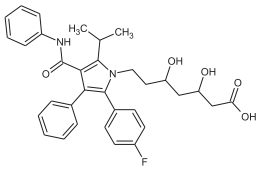
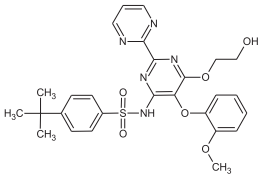
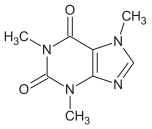
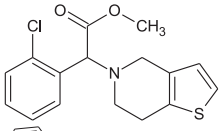
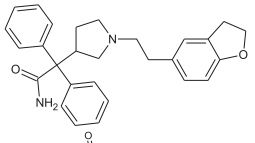
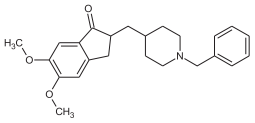
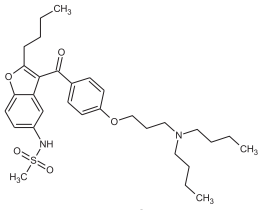
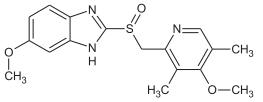
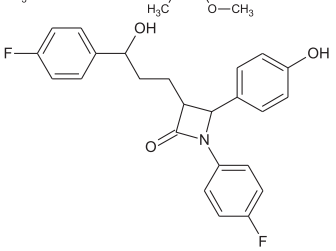
API	Brand	Formulation/sample description	Observed ion	Calculated mass	Observed mass	Error, ppm	Molecular formula	Chemical structure
Alfuzosin	Xatral	Tablet	$[M+H]^+$	390.2136	390.2133	−0.77	$C_{19}H_{27}N_5O_4$	
Amlodipine	In house prototype	Tablet	$[M+H]^+$	409.1525	409.1529	0.98	$C_{20}H_{25}ClN_2O_5$	
Atorvastatin	Sortis	Tablet	$[M-H_2O+H]^+$	541.2497	541.2496	−0.18	$C_{33}H_{35}FN_2O_5$	
			$[M-2H_2O+H]^+$	523.2391	523.2390	−0.19		
Bosentan	In house API	Dissolved in house API for TLC measurement	$[M+H]^+$	552.1911	552.1912	0.18	$C_{27}H_{29}N_5O_6S$	
Caffeine	Saridon	Tablet	$[M+H]^+$	195.0877	195.0883	3.08	$C_8H_{10}N_4O_2$	
Clopidogrel	In house API	Dissolved in house API for TLC measurement	$[M+H]^+$	322.0663	322.0663	0.00	$C_{16}H_{16}ClNO_2S$	
Darifenacin	In house prototype	Tablet	$[M+H]^+$	427.2380	427.2379	−0.23	$C_{28}H_{30}N_2O_2$	
Donepezil	In house prototype	Tablet	$[M+H]^+$	380.2220	380.2220	0.00	$C_{24}H_{29}NO_3$	
Dronedarone	In house prototype	Tablet	$[M+H]^+$	557.3044	557.3043	−0.18	$C_{31}H_{44}N_2O_5S$	
Esomeprazole	In house API	Dissolved in house API for TLC measurement	$[M+H]^+$	346.1220	346.1220	0.00	$C_{17}H_{19}N_3O_3S$	
Ezetimib	Ezetrol	Tablet	$[M+H]^+$	410.1562	410.1561	−0.24	$C_{24}H_{21}F_2NO_3$	
			$[M-H_2O+H]^+$	392.1457	392.1455	−0.51		

Table 1 (*continued*)

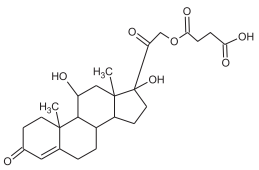
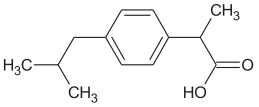
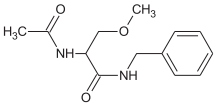
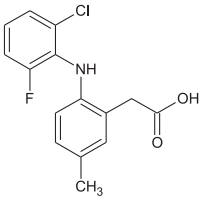
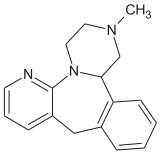
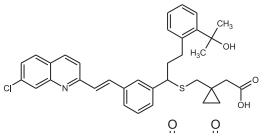
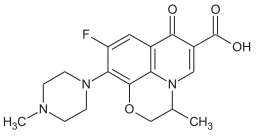
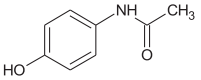
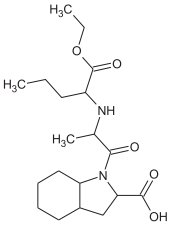
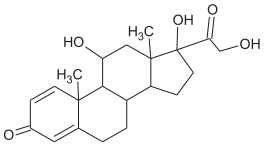
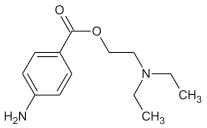
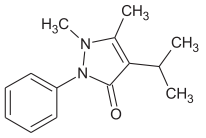
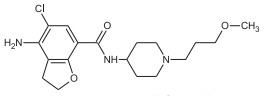
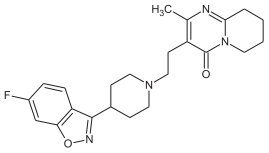
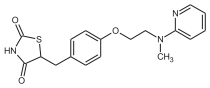
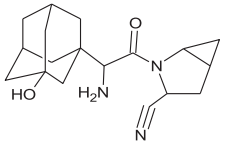
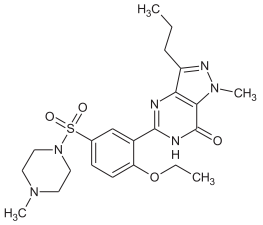
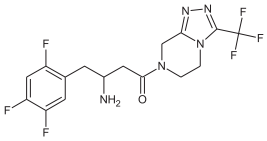
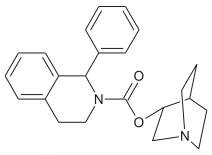
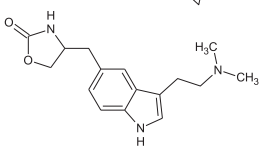
API	Brand	Formulation/sample description	Observed ion	Calculated mass	Observed mass	Error, ppm	Molecular formula	Chemical structure
Hydrocortison	Hidrocortizon	Injection solution	$[M+H]^+$	463.2326	463.2322	−0.86	$C_{25}H_{34}O_8$	
Ibuprofen	Nurofen/ Ibalgin	Dissolved in house API for TLC measurement, gel, ointment	$[M+H]^+$	207.1380	207.1380	0.00	$C_{13}H_{18}O_2$	
			$[M-CH_2O_2+H]^+$	161.1325	161.1326	−0.62		
Lacosamide	Vimpat	Tablet	$[M+H]^+$	251.1390	251.1389	−0.40	$C_{13}H_{18}N_2O_3$	
			$[2M+H]^+$	501.2708	501.2708	0.00		
Lumiracoxib	Prexige	Tablet	$[M+H]^+$	294.0692	294.0692	0.00	$C_{15}H_{13}ClFNO_2$	
			$[M-H_2O+H]^+$	276.0586	276.0587	0.36		
			$[2M-2H_2O+H]^+$	551.1099	551.1102	0.54		
Mirtazapin	In house API	Dissolved in house API for TLC measurement	$[M+H]^+$	266.1652	266.1651	-0.38	$C_{17}H_{19}N_3$	
Montelukast	Singulair	Tablet	$[M+H]^+$	586.2177	586.2177	0.00	$C_{35}H_{36}ClNO_3S$	
Ofloxacin	In house API	Dissolved in house API for TLC measurement	$[M+H]^+$	362.1511	362.1511	0.00	$C_{18}H_{20}FN_3O_4$	
			$[2M+H]^+$	723.2948	723.2949	0.14		
Paracetamol	Paralen/ Saridon	Suppository, Tablet	$[M+H]^+$	152.0706	152.0710	2.63	$C_8H_9NO_2$	
Perindropil	In house prototype	Tablet	$[M+H]^+$	369.2384	369.2388	1.08	$C_{19}H_{32}N_2O_5$	
Prednisolon	Predni H Tablinen	Tablet	$[M+H]^+$	361.2010	361.2008	−0.55	$C_{21}H_{28}O_5$	
			$[M-H_2O+H]^+$	343.1904	343.1903	−0.29		
			$[M-C_2H_4O_2+H]^+$	301.1798	301.1797	−0.33		

Table 1 (*continued*)

API	Brand	Formulation/sample description	Observed ion	Calculated mass	Observed mass	Error, ppm	Molecular formula	Chemical structure
Procaine	In house prototype	Tablet	$[M+H]^+$	237.1598	237.1597	−0.42	$C_{13}H_{20}N_2O_2$	
Propyphenazone	Saridon	Tablet	$[M+H]^+$	231.1492	231.1499	3.03	$C_{14}H_{18}N_2O$	
Prucalopride	In house prototype	Tablet	$[M+H]^+$	368.1735	368.1738	0.81	$C_{18}H_{26}ClN_3O_3$	
Risperidon	Rispen	Tablet	$[M+H]^+$	411.2191	411.2192	0.24	$C_{23}H_{27}FN_4O_2$	
Rosiglitazone	Avandia	Tablet	$[M+H]^+$	358.1220	358.1218	-0.56	$C_{18}H_{19}N_3O_3S$	
Saxagliptin	Onglyza	Tablet	$[M+H]^+$	316.2020	316.2020	0.00	$C_{18}H_{25}N_3O_2$	
Sildenafil	Viagra	Tablet	$[M+H]^+$	475.2122	475.2125	0.63	$C_{22}H_{30}N_6O_4S$	
Sitagliptin	Januvia	Tablet	$[2\,M+H]^+$ $[M+H]^+$	949.4171 408.1254	949.4179 408.1250	0.84 −0.98	$C_{16}H_{15}F_6N_5O$	
Solifenacin	Zevesin	Tablet	$[M-NH_3+H]^+$ $[M+H]^+$	391.0988 363.2067	391.0985 363.2068	−0.78 0.28	$C_{23}H_{26}N_2O_2$	
Zolmitriptan	Zomig	Tablet	$[M+H]^+$	288.1707	288.1705	−0.69	$C_{16}H_{21}N_3O_2$	

DART is not limited to the single API in the formulation. Tablet samples containing two APIs perindropil and amlodipine and three APIs such as caffeine, paracetamol and propyphenazone were also unambiguously identified without any problem. The mass spectrum of the triple combination is shown in Fig. 3.

Among the others common formulations, injection solution of hydrocortison, gel and ointment containing ibuprofen and suppository with paracetamol were tested. Measurement of these formulations also resulted in the fast and simple identification of APIs. In the case of gel, ointment and suppository, very low temperature (50 °C) had to be applied to prevent burning and melting of the formulation itself. The injection solution was identified by putting the liquid on the TLC plate in front of the mass spectrometer after partial evaporation. In these more complex

samples, API signal was often mixed with the high-abundant excipients, such as polyethyleneglycol in the case of hydrocortisone.

As previously stated, TLC chromatography is still very popular when monitoring the progress of the reactions in synthetic chemistry. The advantages of coupling TLC and DART mass spectrometry include the possibility of detection of all components in the sample including those retained in the starting zone, with almost no limitations in the choice of eluent [19]. However, assigning chemical structures to the TLC spots is not an easy task and needs further sample handling. DART ion source is ideal solution to obtain high-resolution mass spectra of the compounds directly from standard TLC plates [20], without any further sample preparation [21,22]. To test this option for drug development purposes, six pure APIs were dissolved in the acetonitrile and then spotted on a standard silica TLC plate (see Table 1 for the list of the compounds). For the subsequent mass spectral analysis, these spots were visualized under the UV light and circled with a pencil. TLC plates were then directly placed into the ion source of the mass spectrometer while holding with tweezers. All of the tested APIs provided simple spectra with the most abundant $[M+H]^+$ ions. Based on the results achieved, this technique has a potential to become one of the tools for the routine monitoring of the components in crude organic reaction mixtures which leads (not only) to the molecule of the API.

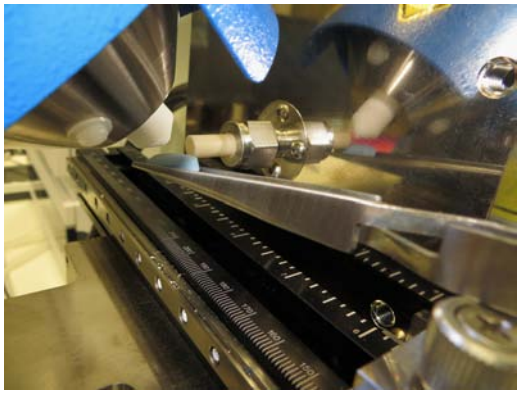


Fig. 1. Experimental setup for the measurement of the tablet with DART mass spectrometry.

3.2. Determination and distribution of impurity D in atorvastatin tablets

Complete understanding of the degradation mechanism in drug product is critical in pharmaceutical development as the drug stability and degradation products could have significant impact on the formulation, analytical method development, packaging, storage conditions and shelf-life determination [23,24]. During development of the drug containing atorvastatin as an API, the impurities were detected in the amount above the specification limit [24,25]. Using UHPLC and high-resolution MS analysis, one of the impurities was identified and confirmed as the epoxide impurity, also known as impurity D (CAS 148146-51-4, $C_{26}H_{22}FNO_4$, monoisotopic mass: 431.1532) according to relevant USP Pharmacopoeia (see the Fig. 4**,** showing the chromatogram, mass spectrum and structural formula of the impurity). Stress degradation behavior of atorvastatin showed that impurity D was formed under oxidative and photolytic stress conditions. Oxidative degradation of atorvastatin has been already well described and has been found to be caused by oxidation of the pyrrole ring [26]. The most probable mechanism of the reaction is intermediate endoperoxide formation with subsequent rearrangement and nucleophilic attack by the 5-hydroxy group of the heptanoic fragment. Oxidation reaction leads to four main degradation products including impurity D [27].

Investigation of impurity D formation was performed using eight batches of atorvastatin crystal form I tablets (each 2 batches contained 10, 20, 40 and 80 mg of atorvastatin per tablet) prepared by dry granulation method, compressed using rotary tablet press and coated with non-functional hypromellose coating. Seven batches (numbered 1–7) of tablets were packed into aluminum/aluminum blisters in oxygen atmosphere, while one (number 8)

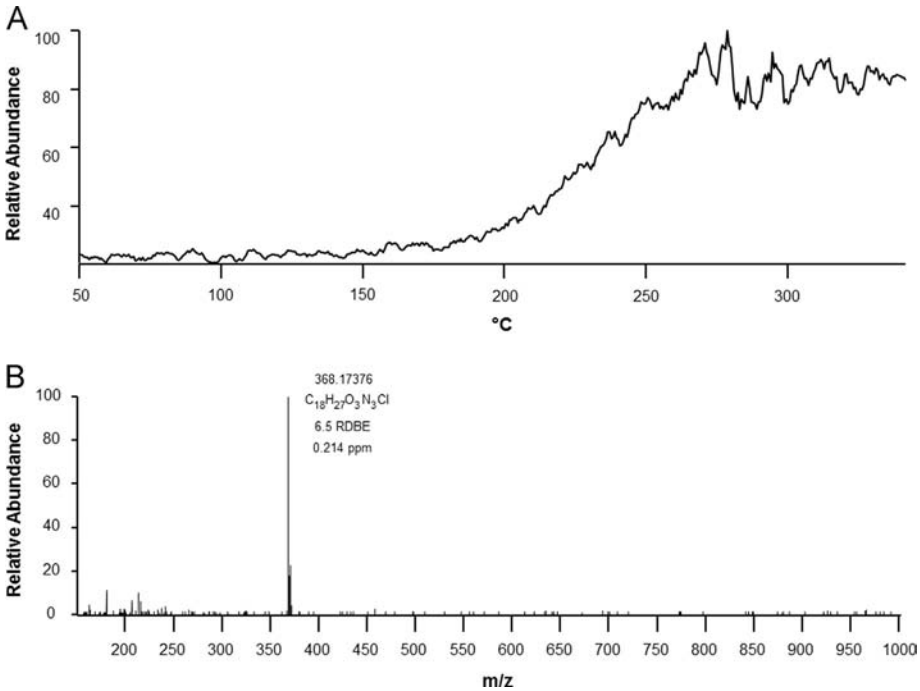


Fig. 2. Desorption characteristics for the prucalopride API. (A) – Influence of the desorption temperature on the relative response (TIC) of prucalopride compound, (B) – mass spectrum of prucalopride at 300 °C. RDBE=Ring Double Bond Equivalents. TIC=Total Ion Current.

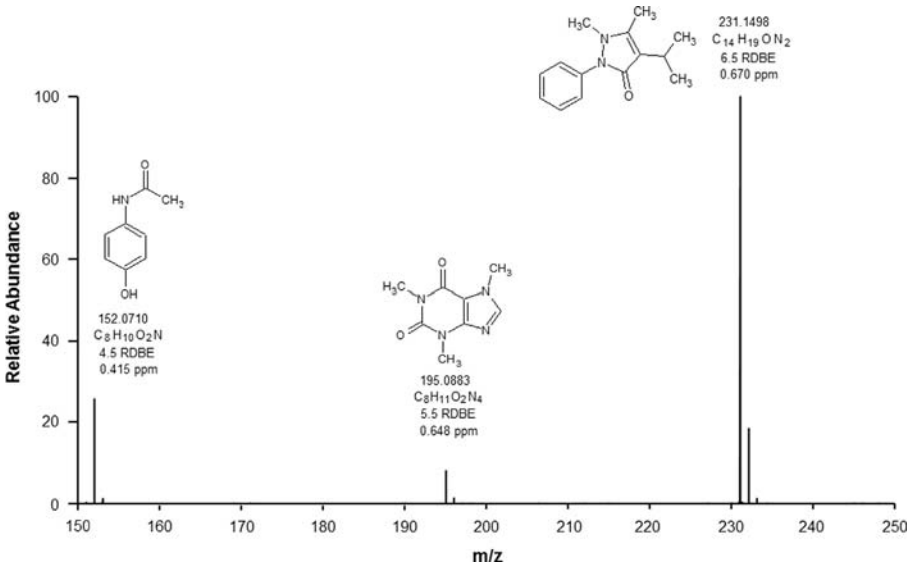


Fig. 3. Mass spectrum of the tablet containing three active ingredients. RDBE=Ring Double Bond Equivalents.

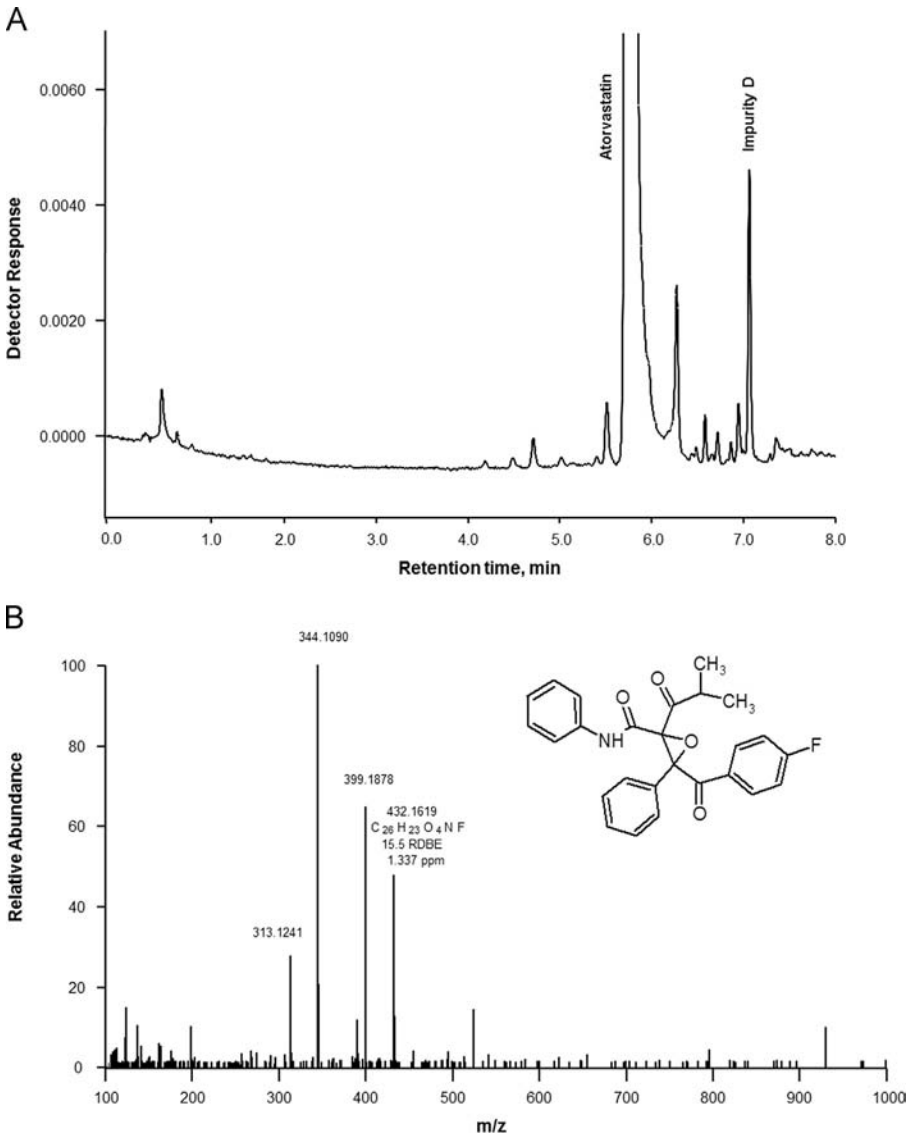


Fig. 4. UHPLC chromatogram (A), mass spectrum and structural formula (B) of the impurity D detected in atorvastatin. RDBE=Ring Double Bond Equivalents.

Table 2
Atorvastatin assay, impurity D level and sum of impurities in tablets after 6 months stability study at 40 °C/75% RH determined by UHPLC method. The relative standard deviations (RSD) were determined from six parallel measurements. RSD for atorvastatin assay were < 1.2% and for impurity D content were < 2.5%.

	40 °C, 75%RH	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8[a]
Atorvastatin assay [mg]	Initial conditions	10.4	19.9	10	40.3	19.8	79.5	39.6	81.9
	After 6 months	10.3	20	9.9	40.3	19.7	79.6	39.6	82.2
Impurity D level [%]	Initial conditions	0.05	0.05	0.06	< 0.05	0.06	0.06	0.06	< 0.05
	After 6 months	0.22	0.19	0.24	0.14	0.2	0.18	0.14	0.05
Sum of impurities level [%]	Initial conditions	0.18	0.18	0.33	0.14	0.26	0.32	0.28	0.15
	After 6 months	0.79	0.8	0.88	0.73	0.92	0.74	0.81	0.38

[a] Packed in nitrogen atmosphere.

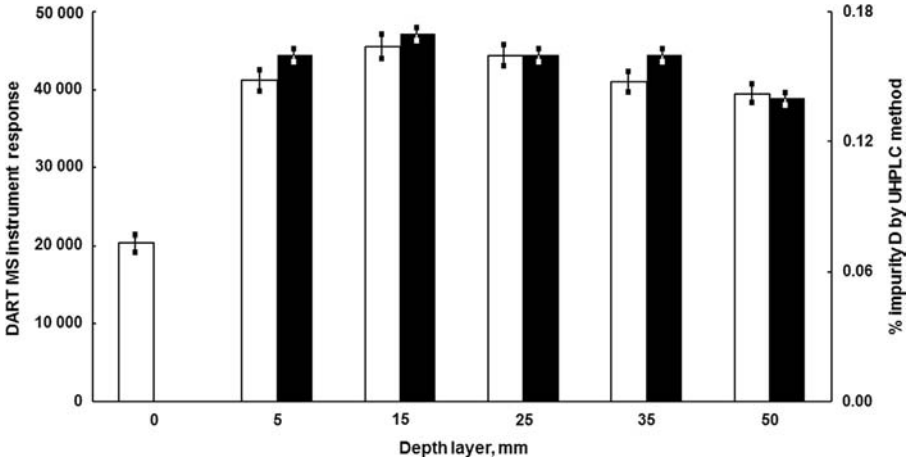


Fig. 5. Distribution of the impurity in the tablet of atorvastatin. White column – DART mass spectrometry, black column – UHPLC determination. The 95% confidence intervals (■ – ■) were determined from six parallel measurements.

was packed into same blisters under nitrogen atmosphere. The tablets were then placed in the stability chambers at 40 °C/75% relative humidity (RH). Impurity D concentration level was measured together with atorvastatin assay and sum of the impurities after 6 months using previously described UHPLC method. The results are shown in Table 2. It is clearly visible that the presence of oxygen resulted in impurity D formation while this phenomenon has not been observed in the absence of oxygen in blister cavities (batch 8). Thus presence of oxygen has been confirmed as a main instability factor. At this point of pharmaceutical development, DART can be employed to determine whether the impurity of interest is formed only under the coating of the tablet or if the oxygen can penetrate to the greater depths and thus DART can help to completely understand the degradation mechanism.

As previously stated, there are poor imaging possibilities of the DART technique due to the low spatial resolution. On the other hand, rough estimation can be done in the following way. The tablet that contains the impurity D was firstly analyzed using DART as all other samples described in the Section 3.1., which was defined as a measurement at the depth 0. To get an idea about the distribution of the impurity deeper in the tablet, several layers were removed from the tablet by scratching the surface using a common razor blade. It means that the analysis of the depth 0 represented the DART measurement of the intact tablet and further depths (i.e., 5, 15, 25, 35 and 50 mm) corresponded to the analysis of the same tablet with 5–50 mm of the tablet mass removed. The impurity was identified as $[M+H]^+$ ion with an accurate mass of $m/z=432.1619$ which corresponded to the elemental composition $C_{26}H_{23}FNO_4$. Final distribution of the impurity is depicted in the Fig. 5 as a function of the intensity of the selected ion vs. the depth of layer in the tablet. As can be seen from these plots, no remarkable fluctuations in the impurity intensity were observed and thus its concentration and presence seems to be uniform within the whole tablet. Relatively low content of the impurity at surface (depth 0) was probably caused by the tablet coating made of hypromellose. All analyses were repeated for three different tablets from two independent batches with similar results (relative standard deviation of the ion intensity was ranging from 6.0 to 8.3%). It was demonstrated that DART can be used for rough estimation of the impurity distribution in the tablet and help to understand completely the origin and consequences of the degradation process. These results were verified using UHPLC analysis with the following sample preparation approach. Five layers (5, 15, 25, 35 and 50 mm) of tablet were made by scratching the tablet using a razor blade. Powder from each layer was weighed and dissolved in the appropriate volume of extraction solvent to obtain the same concentration of atorvastatin. UHPLC results confirmed uniformity of the impurity D within the whole tablet (Fig. 5).

4. Conclusion

In the article presented herein, DART mass spectrometry was found to be an excellent technique for quick and easy identification of a broad range of APIs in pharmaceutical formulations, including structurally very different molecules. This incorporates tablets containing up to three APIs, ointments, gels and injection solution. Furthermore, DART was used as an effective method for the direct analysis of a wide variety of organic compounds directly from the TLC plates. This can significantly fasten and simplify monitoring of the organic synthesis reaction leading to the final molecule of interest. Although DART is not mentioned as imaging technique like MALDI or DESI, rough distribution of the compound

of interest could be determined as was demonstrated in the case of impurity D in atorvastatin tablets. DART has already showed a large potential in many application fields, including pharmaceuticals analysis, mainly for its ease of use, speed and simplicity. High-throughput capabilities and simple method development can be genuinely beneficial in the competitive field of drug development.

Acknowledgments

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