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X-ray powder diffractometry and liquid chromatography studies of sibutramine and its analogues content in herbal dietary supplements

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ABSTRACT

The contemporary societies of the developed countries are prone to use traditional far-east medicines as remedies for all diseases. Some of them, such as obesity, might be classified as civilization diseases. Combating the problem, people try not only several miraculous diets but also herbal infusions (teas) and variety of "herbal" preparations. All these believing that such treatment is healthy and harmless as far as it is "natural". Leaving out of the way the question if herbal medicines can be taken safely without doctors' control the query arises if the common preparations are strictly natural and herbal.

Here we report examples of quality studies of such medicines using both X-ray powder diffraction (XRPD) and liquid chromatography (LC) with various types of detection: ultraviolet (UV), coulometric electrode array (CEAD) and time-of-flight mass spectrometry (TOF-MS). Especially the XRPD assisted with an optical microscopy seems to be useful as a fast screening method of general sample composition of such preparations. First of all it can discriminate between capsules containing pure herbal materials and those with some chemical.

1. Introduction

One of the important problems of the food and pharmaceutical markets in the developed countries is a growing number of so-called dietary supplements and dubious ecological products. The contemporary societies of the rich countries tend to yearn after a simple and healthy life and in this respect different "herbal" products, especially coming from the far-east with a thousand years' medical tradition, are very welcomed. Leaving out of the discussion an indiscriminate use of herbal medicines and its consequence for health the question arises if such herbal products are really natural. The other problem is the open definition of dietary supplements. Many pharmaceutical companies try to extend their market moving as many products as possible to the OTC category and even register some of them as dietary supplements. As far as vitaminic and mineral cocktails could be distinguished as supplementary additives to the not healthy highly transformed food, some preparations claim to be cures for certain ailments and deficiencies. In such cases they should be treated as medicines rather than dietary supplements. To such category one may include very popular in many countries Chinese, Japanese, Mongolian, Indian etc. preparations (capsules and piles) used together with weight control diets. Our interest was directed lately mostly to this category, mainly to establish fast and reliable methods of screening for not specified and sometimes illegal chemical ingredients in these preparations, as well as to analyze quantitatively these substances.

Here we report on our results of the use of the X-ray powder diffractometry as a fast and not destructive method of screening for three compounds: sibutramine hydrochloride (SIB), N-desmethylsibutramine hydrochloride (DSIB) and N,N-didesmethylsibutramine hydrochloride (DDSIB) in popular in Poland and UE anti-obesity herbal preparations: Meizitang, Meizitanc, LiDa Dai Dai Hua Jiao Nang, Super Slim, 3X Slimming Power, White Tea White Lion and Miaozi. SIB is the known and registered pharmaceutical compound being an active ingredient of such legal medicines as: Meridia, Zelixa and Lindaxa used in treatment of rather serious obesity cases. DSIB is known to possess even higher activity than sibutramine itself [1] but is not legal pharmaceutical substance with not established side effects. Both give serious and life-dangerous side-effects. The risks of using these compounds are greater than their benefits. According to the latest results of the Sibutramine Cardiovascular Outcome Trial (SCOUT) European Medicines Agency (EMA) recommended suspension of marketing authorizations for sibutramine [2].

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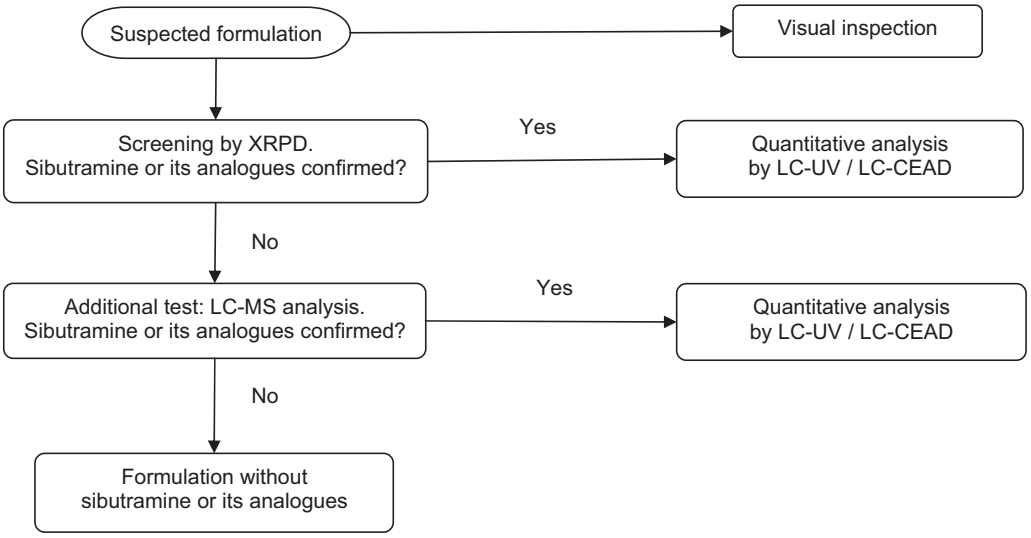

Fig. 1. Strategy for identifying adulteration with sibutramine and its analogues in herbal dietary supplements using XRPD and LC–MS and quantitation using LC–UV and LC–CEAD.

Reported methods concerning screening for illegal adulterations with sibutramine in herbal drugs are mainly HPLC–UV [3,4], GC–MS [5,6], LC–MS [7] and LC–MS/MS [4,8–10]. Chandorkar et al. [3] used HPLC–UV for analysis of sibutramine along with only one impurity (5-(2R)-2-aminopropyl)-2-methoxybenzene sulphonamide) in drug formulation. Kim et al. [4] described method for simultaneous determination of the twelve drugs in dietary supplements by LC–PDA. Also they used LC–MS/MS for targeted analysis of SIB and DSIB, however, time analysis was quite long and only one metabolite was determined. LC–MS or GC–MS methods are mainly dedicated for determining SIB and metabolites in human urine [5,6] or in human plasma [7,8]. Different methodologies for finding synthetic drugs in herbal dietary supplements have been established. Some of them are targeted analysis [9] and others are screening ones [4,10]. Most of them are LC–MS methods in different modes. Zou et al. [9] described methodology using LC–MS/MS and LC–TOF-MS for detection of SIB, its two metabolites and one analogue (homosibutramine) in herbal dietary supplements. Chen et al. [10] used LC–ESI-MS/MS coupled with a linearity ion-trap system in the multiple reaction monitoring (MRM) plus enhanced product ion (EPI) mode for testing synthetic drugs used to adulterate botanical dietary supplements. In the 35 of a total of 105 botanical dietary supplements tested they found out several undeclared drugs. To the best of our knowledge, our report for the first time describes the methodology that combine techniques such as X-ray powder diffraction (XRPD) and liquid chromatography (LC) with various types of detection: ultraviolet (UV), coulometric electrode array (CEAD) and time-of-flight mass spectrometry (TOF-MS) to detect sibutramine and its analogues in "herbal" dietary supplements.

The enantioselective behaviors of sibutramine and its two major active metabolites have been of interest from a pharmacokinetic as well as a pharmacodynamic point of view. In pharmaceutical preparations sibutramine is currently used as racemate, however the selective effects of enantiomers on pharmacological consequences have been well characterized, with the *R*(+)-enantiomer being much more potent than the *S*(−)-enantiomer [1]. The chiral resolution of enantiomers in pharmaceutical products [11] and in rat plasma [12,13] has been carried out by LC–MS. Their absolute configuration has been determined by single crystal X-ray analysis in a few studies for structural identification of isolated compounds [14,15].

2. Experimental

2.1. Material studied

Thirteen different samples of LiDa Dai Dai Hua Jiao Nang (Kunming Dali), four of Meizitang (unknown manufacturer), one of Meizitanc (Plant Research and Science Institute), one of Super Slim (unknown manufacturer), one of 3X Slimming Power (Japan), one of White Tea White Lion (Sichuan ZhenHuang Medicine) and four of Miaozi (Bainian Pharmacy, Hong Kong) were analyzed. All twenty-five samples used in our tests were secured by Polish police and custom authorities mostly on the Warsaw airport. All preparations were in the form of capsules of different colours. Capsules contained usually brown to pale beige fine crystalline powder but sometime the powder was white even within the same product.

Reference standards: sibutramine hydrochloride monohydrate (SIB) N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N'-dimethylamine hydrochloride from Zentiva (Prague, Czech Republic), N-monodesmethylsibutramine hydrochloride (DSIB) from Abbott Laboratories (Illinois, USA) and N,N-didesmethylsibutramine hydrochloride (DDSIB) also from Zentiva (Prague, Czech Republic).

Methanol from Labscan (Dublin, Ireland), formic acid from Park Scientific Limited (Northampton, UK), ammonium formate and ammonium acetate from Fluka – all of them of purity suitable for LC, doubly distilled water additionally purified in the Nanopure Diamond Deionization System from Barnstead (Dubuque, IA, USA) were used throughout.

2.2. Equipment and conditions

2.2.1. XRPD

The powder samples after eventual grinding in an agate mortar were placed in sample holders and then on an X-ray diffractometer. In all cases a Bruker-AXS D8 Advance powder diffractometer (Karlsruhe, Germany) was used to collect diffractograms. The parallel CuKα X-ray beam coming from a Göbel mirror and the θ–θ scan mode were applied. The data were collected in 2θ range from 3 to 60° with 0.02°/s scan rate. The collected diffractograms were then treated with standard smoothing and background subtracting procedures.

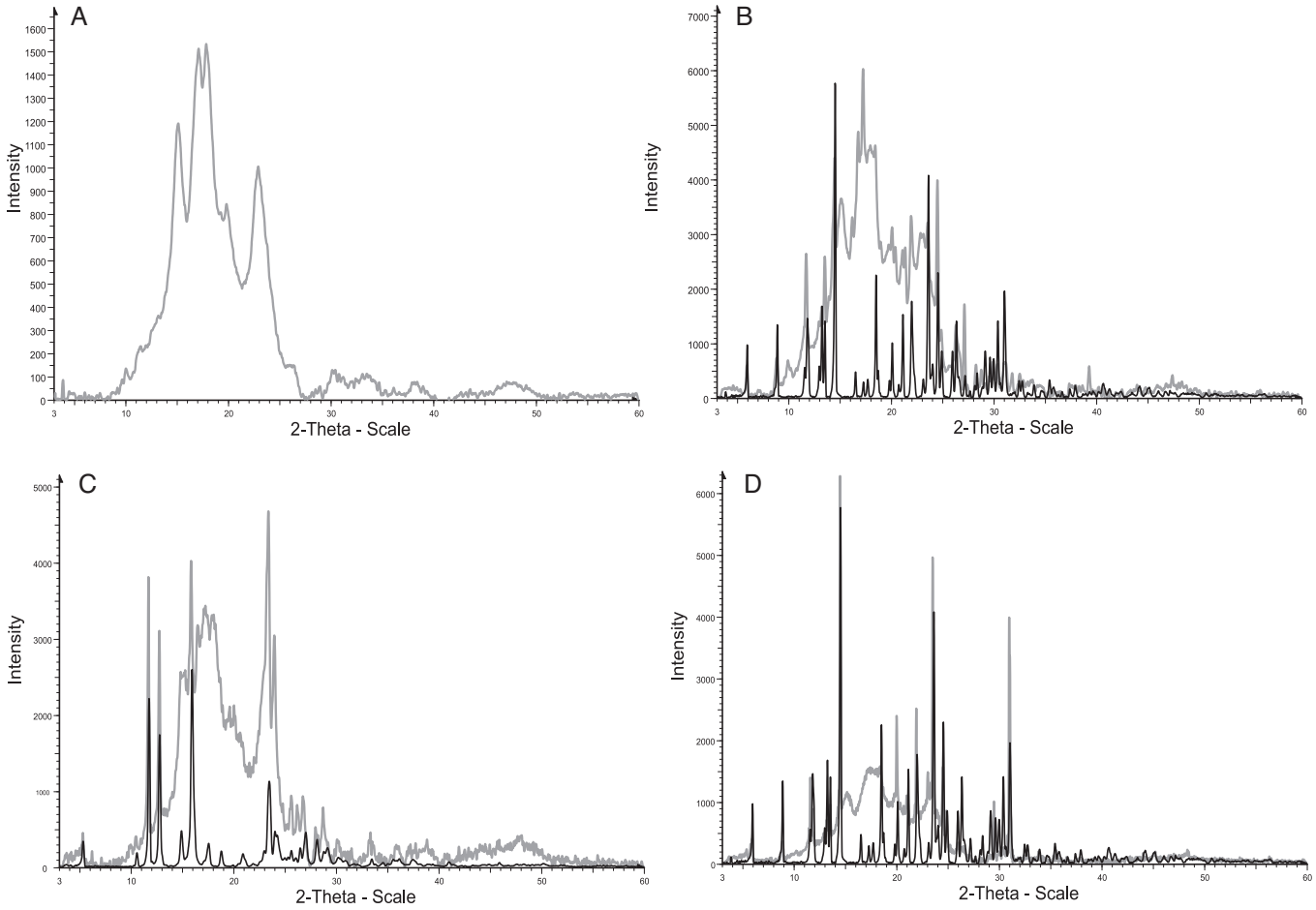

Fig. 2. The comparison of diffraction patterns of herbal LiDa (A), LiDa with SIB – grey and SIB standard – black (B), LiDa with DSIB – grey and DSIB standard – black (C), Meizitang with SIB – grey and SIB standard – black (D).

2.2.2. LC–MS

A mass spectrometer MicrOTOF-QII from Bruker Daltonik (Bremen, Germany) was used to obtain the mass spectra, when peak identifications were required. The following settings were used: electrospray ionization (ESI) in the positive ion mode. Dry gas flow rate was set to 9.0l min^{-1} and the dry heater at 190 °C. The capillary voltage was set to 4500 V and end plate offset to −500 V. MS data were recorded in the full scan mode (from 50 to 800 *m*/*z*).

2.2.3. LC–UV and LC–CEAD

A LC Ultimate 3000 system (Dionex, Germering, Germany) consisting of: a pump, a degasser, an autosampler, a column heater, a pulse damper, a UV detector or a CEAD detector was used throughout this work. A CEAD is a CoulArray 5600A (ESA, Chelmsford, MA, USA) detector, equipped with porous graphite working electrodes (up to 16 electrodes maintained at individual constant potentials), a palladium electrode (reference electrode) and a platinum wire (auxiliary electrode). Data processing was carried out with CoulArray for Windows 2.05 (ESA) and Chromeleon 6.8 software (Dionex). An optimization of chromatographic separation was achieved using DryLab 2000 Plus Software (Molnar Institute, Berlin, Germany).

The analysis was performed in an isocratic mode on a Hypersil Gold C18 analytical column (150 mm × 4.6 mm; 5 μm particle size; Thermo Fisher Scientific, Waltham, MA, USA). The mobile phase in LC–UV method contained ammonium formate (pH 3.7 adjusted with 96% formic acid; 50 mM) – methanol (40:60, v/v). In LC–CEAD the mobile phase consisted of ammonium formate (pH 6.4; 25 mM) – methanol (35:65, v/v). The mobile phases were passed through filters (0.22 μm, nylon) and degassed with a Sonifier 250/450 (Branson Ultrasonics, Dunbury, CT, USA) before use. The electrodes potentials, in LC–CEAD, were set to 750 mV and 900 mV for SIB and DSIB, respectively. The column was maintained at 25 °C in a column block heater. A flow rate was set at 0.7 ml min^{-1}.

2.3. Standard solutions

Stock standard solutions of all the studied substances were prepared by diluting approximately 10 mg of each substance in 10 ml of the mobile phase. From these solutions, a mixture containing 500 μg ml^{-1} of all the studied substances was prepared and it was further successively diluted with the mobile phase to obtain required concentrations. All solutions were stored in a cool, dark place when not in use.

2.4. Sample solutions

Since there was no information about the content of sibutramine hydrochloride and/or its analogues in analyzed samples, the homogenized content of capsules was weighed into a 50 ml volumetric flask and dissolved with the mobile phase for LC–UV method. Following shaking for 15 min and being placed in an ultrasonic bath for 10 min, samples were filtered through syringe PTFE 0.45 μm filters, then first milliliters of the filtrates were discarded. Stock solutions were preanalyzed by LC–UV to estimate

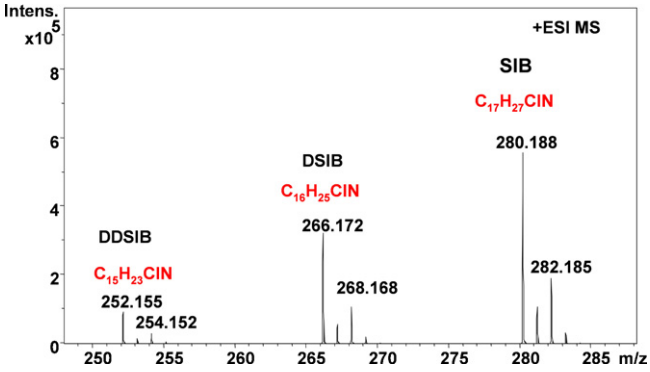

Fig. 3. Mass spectra recorded for identification of peak from the solution containing mixture of SIB, DSIB and DDSIB.

the substance concentration and then were further diluted with the mobile phase to the final concentration of ca. 25 μg ml^{-1} and 2 μg ml^{-1} of all the studied substances for LC–UV and LC–CEAD method, respectively.

3. Results and discussion

3.1. Strategy for the detection of sibutramine and its analogues in herbal dietary supplements

The flow chart in Fig. 1 provides the strategy for the detection of sibutramine and its analogues in "herbal" dietary supplements.

3.1.1. XRPD

Especially the XRPD seems to be useful as a fast and non-destructive screening method of general sample composition of such preparations. First of all it can discriminate between capsules containing pure herbal materials and those with some chemical additives. Herbal samples (Fig. 2a) are characterized by very broad, not characteristic maximum, or maxima in the range of 2θ angle from ca. 9 to 28°. In this range samples containing different types of starch or starch and cellulose mixtures give diffraction patterns. If a sample is a mixture of a natural material and a crystalline chemical additive the resulting X-ray pattern will be a superposition of these broad diffraction maxima and a characteristic sharp diffraction pattern from the additive. In Fig. 2b we present an example of a diffraction pattern obtained for "not herbal" LiDa. Very similar examples can be found for Meizitang (Fig. 2d). Taking into account the relative intensities of sharp maxima and broad background in Meizitang and LiDa one can conclude that the ratio of chemical ingredient and natural (herbal) material in Meizitang is higher than in LiDa.

The question arises, what type of chemical additive might be present in such preparations. A natural guess will be one of the pharmaceutically active ingredients used today or in the past in medicines applied in the obesity treatment – namely: fenfluramine, fentermine or sibutramine. All of them belong to the group of "anorectic" compounds, which main biological action is increasing the brain concentration of neurotransmiters, mostly serotonine and noradrenaline and as a result giving a satiety feeling [16].

In Fig. 2b and d on the diffraction patterns of "not herbal" preparations the diffraction patterns of SIB were superimposed. One can easily see that all sharp peaks present in the patterns of LiDa or Meizitang can be ascribed to SIB.

As far as the most frequent additive found in similar "dietary supplements" is sibutramine hydrochloride, from time to time in LiDa preparations we found an additive of completely different diffraction pattern (Fig. 2c). Deeper analysis showed that it was

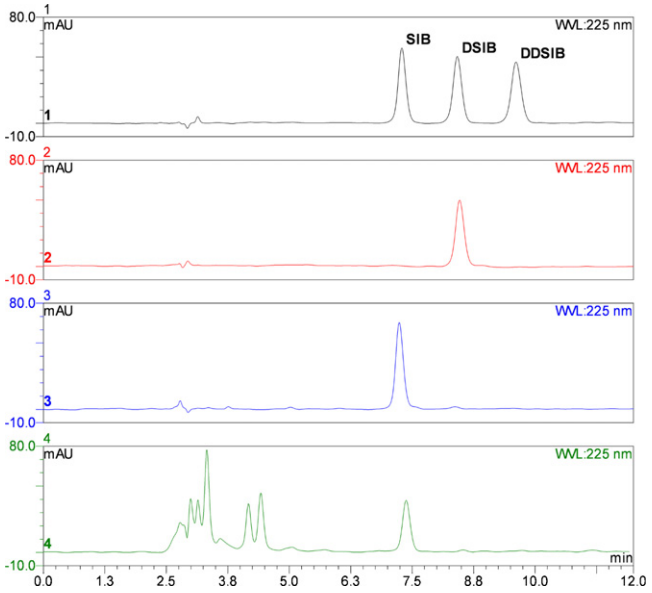

Fig. 4. Chromatograms LC–UV recorded from the solution containing mixture of SIB, DSIB and DDSIB (1), LiDa with DSIB (2), LiDa with SIB (3) and Miaozi with SIB (4).

N-desmethylsibutramine hydrochloride. In Fig. 2c on the diffraction pattern of such LiDa powder a diffraction pattern of DSIB is superimposed. DSIB is a chemical compound of similar biological activity as sibutramine itself but has even higher potency. It is however not registered pharmaceutical substance of not documented side effects. In this respect such ingredient should be present neither in medicines nor dietary supplements.

A little bit different looked samples of Miaozi – even the broad maximum in the range 9–28° looked differently, as of herbal origin or, if at all, a little bit enriched with certain chemical additive. A further qualititative analysis was done using LC–MS.

In all samples, where SIB or DSIB were identified, quantitative analysis was performed by LC–UV/LC–CEAD.

3.1.2. LC–MS

In some cases (e.g. Miaozi samples), where SIB or its analogues were not confirmed by XRPD, LC–MS was used. The advantages of LC–MS include its high specificity, sensitivity and ability to identify the unknowns even in small amounts. Especially the use of TOF-MS, which allows accurate mass measurements and hence the assessment of empirical formulas of unknown molecules is very useful in counterfeit products analysis.

Stock solutions of SIB, DSIB, DDSIB standards were used for identification purposes. Due to different *m*/*z* ratio and characteristic isotope profile for sibutramine and its analogues containing chlorine (Fig. 3) the analysis is quite easy and obvious. Hence the LC–MS analysis of Miaozi samples identified the presence of SIB and its quantity was measured by LC–UV/LC–CEAD.

In some preparations also additional compounds were found. Some of them were identified as alloin and phenolphthalein.

3.2. Quantitative analysis of sibutramine content by LC–UV and LC–CEAD

3.2.1. Selection of the chromatographic conditions

In order to obtain optimal chromatographic separation and the best peak shape, water–methanol mobile phases containing ammonium formate or ammonium acetate were evaluated. For both, LC–UV and LC–CEAD, methods the best response was obtained with a Hypersil Gold C18 analytical column (150 mm × 4.6 mm, 5 μm

Table 1
Retention time, repeatability and relative retention time of investigated compounds by LC–UV and LC–CEAD (10 μg ml^{-1} and 100 ng ml^{-1} each of them, respectively).

Compound	Retension time (min) ± $tS_{\bar{x}}$, $p = 0.05$	R.S.D (%)	RRT*	Resolution	Asymmetry	Plates
LC–UV						
SIB	7.17 ± 0.03	0.14	1.00	3.64	1.04	10100
DSIB	8.27 ± 0.03	0.17	1.15	3.42	1.01	10569
DDSIB	9.44 ± 0.03	0.14	1.31	–	1.00	10808
LC–CEAD						
SIB	11.84 ± 0.14	0.45	1.00	–	1.05	9820
DSIB	7.39 ± 0.17	0.92	0.63	11.09	1.05	8580

* Relative retention time.

Table 2
Linear regression data, LOD and LOQ of investigated compounds by LC–UV and LC–CEAD.

Compound	Range (μg ml^{-1})	Equation	r^2	Standard error of the slope	Standard error of the intercept	LOD (μg ml^{-1})	LOQ (μg ml^{-1})
LC–UV							
SIB	0.500–200	$y = 0.4470x - 0.1036$	0.9999	0.1810	0.0457	0.500	1.500
DSIB	0.500–200	$y = 0.4381x - 0.0625$	0.9999	0.3118	0.0787	0.500	1.500
DDSIB	0.500–200	$y = 0.4219x + 0.6804$	0.9989	1.1529	0.2910	0.500	1.500
LC–CEAD							
SIB	0.025–2.5	$y = 0.0332x - 0.0001$	0.9996	0.0003	0.0001	0.0075	0.025
DSIB	0.100–2.5	$y = 0.0022x - 0.0001$	0.9992	0.0001	0.0001	0.100	0.300

particle size; Thermo) and the mobile phase containing ammonium formate buffer – methanol. The content of methanol and ammonium formate in the mobile phase and pH value of ammonium formate solution were optimized with the help of the DryLab 2000 Plus software. The examined ammonium formate solutions were 12.5, 25 and 50 mM and methanol content ranged from 45 to 75%. The pH values of ammonium formate solution ranged from 2.7 to 6.4. The maximum intensities and short retention times with good separation for all the examined substances were observed at pH 3.7 and 6.4, for LC–UV method and LC–CEAD method, respectively.

The following chromatographic conditions were chosen as optimal: in the LC–UV method (Fig. 4) a mixture of ammonium formate (pH 3.7 adjusted with 96% formic acid; 50 mM) – methanol (40:60, v/v), and in the LC–CEAD method (Fig. 5) a mixture of ammonium formate (pH 6.4; 25 mM) – methanol (35:65, v/v).

In the LC–CEAD method the dependence of peak current intensities of studied compounds from the potential of working electrodes was investigated. Proper selection of applied electrode potentials is critical for accurate measurements. To establish suitable detection potential, the hydrodynamic voltammetric curves of analyzed compounds were recorded in the potential range from +600 to +950 mV *vs.* palladium reference electrode using chromatographic conditions mentioned above. An advantage of coulometric electrode array detection is that hydrodynamic voltammograms can be done on-line and that peak heights of all analyzed compounds increased with an increase of potential. For further experiments, the potential of the porous graphite electrode was set to +750 mV for SIB and to +900 mV for DSIB, respectively (Fig. 5). For DDSIB no signal was observed in the investigated range.

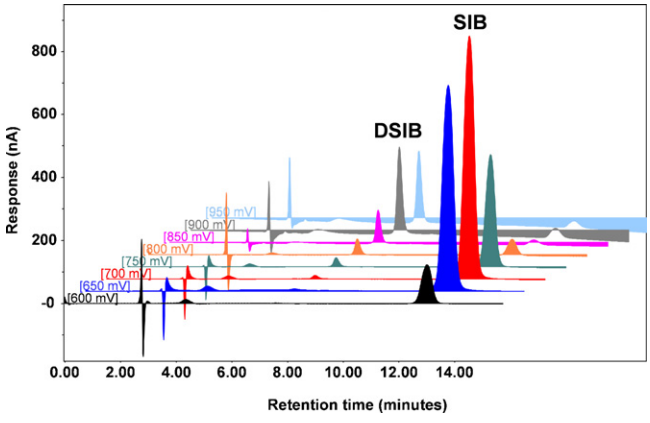

Fig. 5. Chromatograms LC–CEAD recorded from the solution containing mixture of SIB and DSIB at concentration 2 μg ml^{-1}.

The effect of different flow rates (from 0.6 to 1.0 ml min^{-1}) and column temperature (from 20 to 30 °C) on peak resolution was studied. The flow rate was set to 0.7 ml min^{-1}, the injection volume was 20 μl and experiments were done at 25 °C.

3.2.2. Validation of the LC–UV and LC–CEAD methods

The quantitative aspects of the proposed methods were examined according to ICH guidelines [17]. The statistical evaluation for all analyzed substances was calculated using Chromeleon Validation ICH software. The data concerning method validation are summarized in Tables 1–3. Peak areas were evaluated in the whole validation.

3.2.2.1. Linearity. The linearity was estimated by analyzing mixture standards of all studied substances. In the LC–UV method ten concentrations of analyzed substances ranging from 0.5 to 200 μg ml^{-1} were used to obtain calibration curves. In LC–CEAD

Table 3
Precision, repeatability and recovery of sibutramine and its analogues determination by LC–UV and LC–CEAD ($n = 3$).

Compound	Added	Found mean ± $tS_{\bar{x}}$, $p = 0.05$	Recovery (%)	R.S.D (%)
LC–UV (μg ml^{-1})				
SIB	9.70	9.54 ± 0.22	98.35	0.91
	24.26	24.02 ± 0.40	99.01	0.66
	97.03	99.27 ± 1.58	102.31	0.64
DSIB	9.98	9.84 ± 0.53	98.60	2.18
	24.48	24.42 ± 0.58	99.75	0.97
	99.80	100.53 ± 0.51	102.73	0.21
DDSIB	9.78	9.52 ± 0.33	97.34	1.41
	24.45	24.26 ± 0.05	99.22	0.09
	97.80	95.39 ± 0.77	97.53	0.32
LC–CEAD (ng ml^{-1})				
SIB	10.20	10.23 ± 0.04	100.29	0.17
	51.00	50.35 ± 0.30	98.73	0.24
	102.00	101.81 ± 0.58	99.81	0.23
DSIB	98.70	101.21 ± 1.73	102.54	0.69
	246.80	247.12 ± 1.31	100.13	0.21
	493.50	512.27 ± 1.97	103.80	0.15

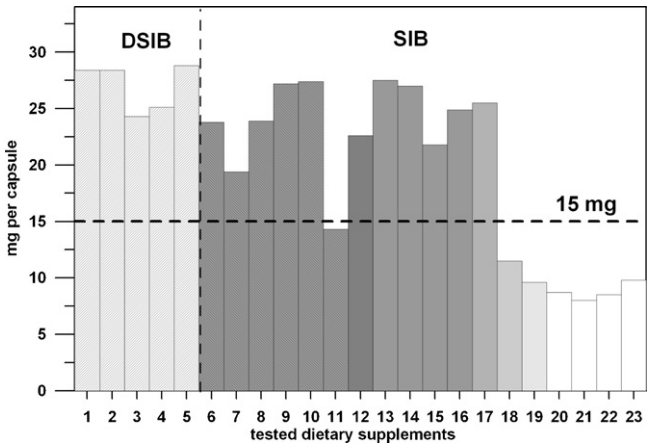

Fig. 6. Contents of SIB or DSIB in various batches of the tested dietary supplements: LiDa (1–11); Meizitanc (12); Meizitang (13–16); Super Slim (17); 3X Slimming Power (18); White Lion (19) and Miaozi (20–23).

method the linearity was estimated in the range from 0.025 to 2.5 μg ml^{-1} (for SIB) and from 0.100 to 2.5 μg ml^{-1} (for DSIB) (Table 2).

3.2.2.2. Detection and quantitation limits. The detection limit (LOD) and quantitation limit (LOQ) were defined as signal-to-noise ratios of 3:1 and 10:1, respectively. Determination of the signal-to-noise ratio (S/N) was performed comparing measured signals from samples of known low concentrations of an analyte with those of blank samples and establishing the minimum concentration at which the analyte can be reliably detected. For the all analyzed substances, their limits of detection and quantitation were significantly lower using the coulometric detection. For SIB LOD and LOQ were 0.0075 μg ml^{-1} and 0.025 μg ml^{-1} for the coulometric detection whereas for the UV detection LOD and LOQ were equal to 0.5 μg ml^{-1} and 1.5 μg ml^{-1}, respectively.

The limits of detection and quantitation for all analyzed substances are presented in Table 2.

3.2.2.3. Precision and accuracy. Repeatability was assessed using three concentrations covering the specified range for the procedure. The precisions were calculated from three consecutive injections for each concentration and the observed RSD ranged from 0.15 to 2.18% (Table 3). Intermediate precision was calculated for two days. The accuracy of the recovery for SIB and its analogues was evaluated for three concentrations. The mean recoveries for all samples for each run were in the range of 97.3–103.8% (Table 3).

3.2.2.4. Range. The calibration curves for response of all studied substances were performed. Responses obtained in the examined range were expressed by a linear equation $y = ax + b$ with good r^2 correlation coefficients, not less than 0.9989 (Table 2).

3.2.2.5. Robustness. Methods' robustness was evaluated during the method development. Methods are robust for column temperature ±5 °C, flow rate ±15%, ammonium formate content ±5 mM, pH of ammonium formate solution ±0.2 for LC–UV method and ±0.05 for LC–CEAD method. For all parameter variations the minimum *Rs* value between critical pair of peaks was greater than 1.5.

3.2.3. Determination of active substances in herbal dietary supplements by LC–UV and LC–CEAD

Most of analyzed herbal medicines (23 from 25) contained SIB or DSIB instead of pure herbal components (Fig. 6). It was found that 16 preparations contained SIB or DSIB in the concentration much higher than maximal allowed SIB dose per day (15 mg).

4. Conclusion

The strategy proposed in this study for the detection of sibutramine and its analogues in "herbal" dietary supplements seems to be correct. It was found that 23 from 25 analyzed herbal medicines contained SIB or DSIB instead of pure herbal components. XRPD easily discriminated fake and original samples by visual examination of diffraction patterns, which serve as fingerprints of manufacturers. LC–MS due to its high specificity, sensitivity and ability to identify the unknowns even in small amounts was very useful in counterfeit products examination when XRPD analysis gave negative results. And the LC–UV and LC–CEAD methods developed in our study proved to be fast, reliable and easy methods for the quantitative analysis of SIB, DSIB and DDSIB in "herbal" preparations.

The results of this study demonstrate a real dramatic problem concerning the safety of administration dietary supplements and herbal products. 92% (23 from 25) of the analyzed preparations declared as "natural and herbal" did not comply with declaration, because they contained synthetic chemicals instead of pure herbal components and thus can cause damage to health. What is worse 64% (16 preparations) contained SIB or DSIB in the concentration much higher than maximal allowed SIB dose per day (15 mg). Combating this huge dose of chemical substances in a capsule with daily dose proposed on the box (usually 2–3 per day) and with many side effects, it comes to the conclusion that administration Chinese, Japanese, Mongolian, Indian etc. preparations of unknown or doubtful origin is really dangerous for human health and even life. These products not only have poor quality but also are illegal adulterated with synthetic compounds. Thus the governments of developed countries should pay special attention to the situation on the dietary supplements market and any distribution of products of unknown origin or dubious quality should be strictly forbidden.

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