Research Paper

Lead, Cadmium and Nickel Contents of Some Medicinal Agents

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Thirty nine brands of pharmaceutical dosage forms (28 tablets, 4 syrups, 6 suspensions and one chewing gum) that are available in United Arab Emirates pharmaceutical markets were investigated for the presence of three heavy metals; lead, cadmium and nickel. Amongst the samples, 13 products were manufactured locally in United Arab Emirates and 26 products were imported from around the world. The samples were prepared by acid digestion procedure and the resultant solutions were analyzed for heavy metals by using a validated graphite furnace atomic absorption spectrometric method. Calibration curves were achieved using different concentration of lead, nickel and cadmium ranged from 0.001 to 0.05 µg/ml. The mean recoveries of metals from the samples were 86.4 to 97%. The %relative standard deviation for the intraassay and interday precision for the metals were <5%. Amongst the 39 samples of pharmaceutical dosage form all exhibited a positive response for lead, cadmium and nickel except three products whose Ni levels were below quantification level. The products contained variable amounts of heavy metals as of 0.0017 to 11.88 µg lead; 0.0011 to 0.5559 µg cadmium and 0.0011 to 2.6428 µg nickel, respectively. Based on maximum recommended daily dose (g) of these products, maximum daily ingested mass of lead was 0.0034 to 11.88 µg/d, 0.0013 to 0.56 µg/d for cadmium and 0.0011 to 2.64 µg/d for nickel, respectively. The results were compared with those of oral permitted daily exposure levels of United State Pharmacopeial National Formulary 2013. All the products were safe to consume and contained lower level of lead, cadmium and nickel than Oral Permitted Daily Exposure levels, except three products which showed higher level of lead than oral permitted daily exposure levels. Hence the raw materials used in manufacturing of these medicinal agents might be responsible for the presence of higher level of lead.

Key words: Lead, cadmium, nickel, medicinal agents, atomic absorption spectrometry

The term "heavy metal" is defined based on their specific gravity, atomic weight, atomic number and chemical properties[1]. Lead, cadmium and nickel are chemical elements with a specific gravity at least 5 times higher than that of water hence they are considered as heavy metals[2,3]. Heavy metals are usually present in nature either as elementary compounds or mineral deposits. During extraction and processing of this metals they comes in contact with atmosphere, soils, water, plants and animals, causes environment pollution and produces toxicity[4]. There are approximately 60 heavy metals known to man, amongst them 23 elements, such as antimony, arsenic, bismuth, cadmium, cerium, chromium, cobalt, copper, gallium, gold, iron, lead, manganese, mercury, nickel, platinum, silver, tellurium, thallium, tin, uranium, vanadium, and zinc considered as heavy metals[5]. However, some metals such as iron and nickel are required in very low concentrations for the survival of all forms of life, hence this metals are considered as essential trace elements[6]. Few metals such as mercury, lead and cadmium are considered as non-essential metals as they do not have any vital or beneficial effect on mammals. They can accumulate in the mammal bodies over period of time and can cause serious illness if ingested in small amounts[7,8]. Hence, these metals are considered as toxic heavy metals.

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History of uses of lead (Pb) mainly for water pipes, pigments, cables and no specific historical uses in medicinal purpose. The toxic implication of Pb in the human body is widely researched. Lynch and Braithwaite[9] compiled information on published cases of heavy metal poisoning and for Pb showed signs and symptoms such as abdominal cramps, nausea, malaise, weight loss, constipation and anaemia as the most common. Exposure is said to be associated with cardiovascular disease, neurological and behavioral effects, impaired renal function, hypertension, impaired dental health, delayed sexual maturity and impaired foetal development[10-12]. Nickel (Ni) historically uses in coins and armor. Ni toxicity is not very common occurrence in human as it is poorly absorbed in the body. However, over exposure of Ni causes a number of adverse effect such as dermatitis, encephalopathy and reduced sperm count[12]. Cadmium (Cd) historically uses in electroplating, pigments and chemicals, various alloys and solder[13]. Overexposure of Cd causes cardiovascular disease, arthritis, osteoporosis, learning disorder, growth impairment, cancer, osteomalacia and pneumonitis[12,14,15].

Heavy metals in medicinal products may be present as impurities. A list of heavy metals which are likely to be present in a finished pharmaceutical substance can come from catalysts that are deliberately added to the process, from raw materials or reagents that are employed in the manufacturing process and leaching from equipments or vessels that are used in the manufacturing process[16]. Hence, heavy metals may enter the human body via manufacturing, pharmaceutical, industrial, or residential settings[17]. Determination of heavy metals from pharmaceutical dosage form needs a very sensitive and selective analytical technique that can quantify trace level of metals presents as contaminants in the complex matrices. Enormous work published on heavy metal contents of aurvedic medicinal products[9,18-21]. However, a number of authors' reported the determination of Pb in calcium supplemnts[22,23]. Within the UAE, few numbers of pharmaceutical industry locally manufacturing pharmaceutical products and majority of products are imported from around the world. This opted us to evaluate the safety of available medicines in UAE pharmaceutical markets in respect of toxic heavy metal contents. Therefore, the aim of the work was to determine the toxic trace contaminants as Pb, Cd and Ni in pharmaceutical products that are used in high volume in chronic conditions as diabetes, asthma, rheumatoid arthritis, smoking cessation, cholesterol lowering, mineral deficiency and common over-the-counter drugs as analgesic, antipyretics and antihistamines by using a validated graphite furnace atomic absorption spectrometry and to quantitatively compare the heavy metal content obtained through experiment with predetermined oral permissible daily exposure limits published by USP NF 2013[24].

MATERIALS AND METHODS

All the reagents used in this work were of analytical reagent grade unless otherwise stated. The element standard solutions (1 g/l) for cadmium (Cd), lead (Pb) and nickel (Ni) were supplied by MRS Scientific Ltd, Essex (UK). Milli-Q Ultrapure (Type 1) water (Millipore, Bedford, MA, USA) was used for all dilutions of metal analysis. Nitric acid (1% HNO_3) was prepared from 69.5% nitric acid (Scharlau Chemie S.A) and used for preparation of standard 1 µg/ml stock solutions of Cd, Pb and Ni. Ammonium dihydrogen phosphate ($NH_4H_2PO_4$) was supplied by S. D. Fine-Chem Ltd, India. The magnesium nitrate ($Mg(NO_3)_2$) was provided by Surechem products Ltd, UK. Perchloric acid ($HClO_4$) was supplied by Merck Ltd, UK. Whatman ashless filter papers were used for filtration of metal solutions. All glassware was Pyrex grade; polypropylene bottles were provided by Azlon, UK. All glassware and crucibles were socked in 10% nitric acid and washed with distilled water and finally rinsed with Milli-Q Ultrapure (Type 1) water before oven drying at 110°.

Sample preparation:

Thirty-nine brands of pharmaceutical dosage forms that include 28 tablets, 4 syrups, 6 suspensions and one chewing gum were purchased in January 2014 from the pharmacies of UAE. Amongst the samples, 13 products were manufactured locally in UAE and 26 products were imported from Saudi Arabia, Greece, Egypt, Germany, Australia, USA, Jordan, Switzerland, France, Kuwait, Czeck Republic and India. Sample was prepared by dry ashing procedure followed by acid digestion method[6] with a slight modification. The mean product weight of 10-20 sample units (Tablets) or 15 ml solutions (Liquid) for each sample was determined. The weighed product units were ground into a fine powder and aliquots of sample homogenates (2.0-2.5 g powder or 15 ml liquid) were placed in an acid

cleaned porcelain crucible with a cover. The samples were dried in an air oven at 110° for two hours. The dried sample was then charred at 400° to 450° in a muffle furnace (Gallenkamp Muffle Furnace, Model: Tactical 308) until a white/grey ash was obtained. Crucibles were allowed to cool and then the ash was transferred into a volumetric flask treated with conc. HNO_3 (4 ml) and $HClO_4$ (1 ml) and heated on a hotplate at 90° for 1 h. The resultant solution was cooled and filtered through Whatman filter paper and diluted to 50 ml with 1% nitric acid. Magnesium nitrate and ammonium di-hydrogen phosphate were used as a matrix modifier[25] which was added to 1% HNO_3. A blank reagent solution was also prepared using same proportion of solvents in the same way without adding sample homogenates.

Standards preparation and calibration curves:
Working standard solutions (1 mg/l) were prepared from stock solutions of standard Pb, Cd and Ni (1 g/l) with 1% nitric acid. Working standard solutions were further diluted with 1% nitric acid to prepare different concentration of metal standard solutions as follows: cadmium: 0.001–0.05 µg/ml; lead: 0.01–0.05 µg/ml and nickel: 0.001–0.05 µg/ml. Calibration curve was established on five to six data points and the absorbance of the metal solution was plotted against the corresponding concentration of the metals. Linear regression of the absorbance of the metals of interests versus the metal concentration was performed for estimation the slope, intercept and correlation coefficient of each calibration curve.

Analytical recovery and precision:
The analytical recovery efficiency was determined by adding measured amounts (5 µg, 10 µg, and 25 µg) of three standard heavy metals (Pb, Ni and Cd) into a selected sample (Paracetamol 500 mg Tablet, UAE). The sample was prepared using the methods of sample preparation with the addition of measured amounts of each of the metals. It was then analyzed by graphite furnace atomic absorption spectrometry (GFAAS) and compared to a control that was also prepared at the same time without added standards. The recovery data was determined by subtracting the values of added standards from the control sample. The experiments were repeated three times. The intraassay precision was assessed by three replicate analyses of standard metal solution at three levels concentration. The interday assay variation was evaluated by analyzing corresponding standard metal solution over a period of four days. A 5 point calibration curve was constructed during each assay run.

Instrumental analysis:
The atomic absorption spectrophotometer AAS 6800 (Shimadzu) with deuterium background correction was used for all metal analysis. The analysis of Cd, Ni and Pb was performed by GFAAS attached with an autosampler ASC-6100. Argon gas was used for flushing the furnace. The standards, blank and sample solutions were analyzed for the elements of interest utilizing with suitable hollow cathode lamps. The lamp current flow (mA) were 8 (Cd), 12 (Ni) and 10 (Pb). The wavelengths (λ_{max}) used for this analysis were 228.8 nm for Cd, 232.0 nm for Ni and 283.3 nm for Pb, respectively. The percentages of different elements in the samples were determined by the corresponding standard calibration curves.

Statistical analysis:
The data results of similar classes of products were compared and subjected to a one-way analysis of variance (ANOVA). Tukey's test ($P<0.05$) was performed to determine the significance of the difference between means.

RESULTS AND DISCUSSION

It has been an ongoing public concern to ensure safety and quality of pharmaceutical products, especially when some of the products are consumed for longer period of times such as oral antidiabetic agents, antilipemic agents, nicotine replacement therapy and calcium supplements. It is also a matter of concern when some of the products are available as over-the-counter such as analgesic-antipyretics, antihistamines and nonsteroidal antiinflammatory agents. In UAE, a number of selected pharmaceutical products are manufactured by a limited number of pharmaceutical industries and majority of pharmaceutical products are imported from around the word. Since pharmaceutical products are always contaminated with certain level of toxic heavy metals during their manufacturing processes, therefore, this work was carried out to find out the safety of local and imported products. Thirty-nine pharmaceutical products were analyzed for quantitation of trace levels of Pb, Cd and Ni by GFAAS amongst them 15 products are prescribed for children. The calibration curves were prepared

by utilizing standard solutions of Pb, Cd and Ni and the curves were linear over the concentration ranges of 0.001 to 0.05 µg/ml. The regression coefficients (r^2) of calibration curves were 0.9998±0.0001 for Pb, 0.9966±0.0001 for Cd and 0.9993±0.0002 for Ni, respectively. The minimum detection limits were 1 ng/ml for Cd, Ni and Pb, respectively. The mean analytical recoveries of metals from the samples were 86.40%-95.64% for Pb, 90.04%-97.00% for Ni and 93.20%-95.84% for Cd and the results are illustrated in Table 1. The %RSD (relative standard deviation) for intraassay precision was 1.23 to 3.33% and for interday assay precision was 3.19-4.97%. The results are exhibited in Table 2.

Six pharmaceutical products under NSAIDs class such as ibuprofen 200 mg, 400 mg, 600 mg and acetylsalicylic acid 81 mg, 100 mg and 400 mg were analyzed for the presence of trace levels of Pb, Ni and Cd and the results are presented in Table 3. Amongst the ibuprofen products, one product was from UAE and others two from Saudi Arabia and Greece, respectively. The lowest level of Pb was found in products of Saudi Arabia (0.032 µg/Tablet) and highest levels recorded in the products of Greece (0.279 µg/Tablet). The mean differences of local and exported products were significant at the 0.05 level. In case of Cd, the recorded levels were in the ranges of 0.0011 to 0.0022 µg/Tablet and product of UAE exhibited significantly (P<0.05) higher levels of Cd than imported products. The levels of Ni in ibuprofen products were in the ranges of below detection limit to 0.0035 µg/Tablet. Greece products showed comparatively higher levels than UAE products and the levels were nondetectable in products of Saudi Arabia.

In case of acetylsalicylic acids products, three products were analyzed; one product was imported from Egypt, one from Germany and one from UAE. The products of Germany exhibited highest level of Pb (1.33 µg/Tablet) and lowest level recorded in UAE products (0.015 µg/Tablet). The mean differences of local and exported products were significant at the 0.05 level. The recorded levels of Cd were in the ranges of 0.0032 µg to 0.0391 µg/Tablet. The mean differences between UAE and Egypt products were insignificant, however products of Germany exhibited significantly higher levels of Cd (P<0.05) than UAE and Egypt's product. In case of Ni, lowest level recorded in UAE products (0.0014 µg/Tablet) and highest level in Germany products (0.1797 µg/Tablet).

The results of maximum daily ingested mass of Pb, Cd and Ni were calculated according to USP NF 2013[24] and compared with oral permissible daily exposure (PDE) limits published by USP NF

TABLE 1: MEAN RECOVERIES OF LEAD, CADMIUM AND NICKEL FROM PARACETAMOL TABLET POWDER

Metal	Amount added to powder (µg)	Amount recovered (µg)*	Mean recovery (%)
Pb	5	4.32±0.21	86.40
	10	9.18±0.34	91.80
	25	23.91±1.11	95.64
Ni	5	4.52±0.24	90.04
	10	9.52±0.38	95.20
	25	24.25±0.38	97.00
Cd	5	4.73±0.14	94.60
	10	9.32±0.49	93.20
	25	23.96±1.03	95.84

*Results are expressed as mean±SD. n=3. SD: Standard deviation, Pb: lead, Cd: cadmium, Ni: nickel

TABLE 2: INTRAASSAY AND INTERDAY PRECISION OF ATOMIC ABSORPTION SPECTROMETRY METHOD FOR THE DETERMINATION OF LEAD, CADMIUM AND NICKEL

Metal	Intra-assay precision			Inter-day precision		
	Concentration taken (µg/ml)	Concentration found (µg/ml)	RSD (%)	Concentration taken (µg/ml)	Concentration found (µg/ml)	RSD (%)
Pb	0.01	0.0090±0.0003	3.33	0.01	0.0081±0.0004	4.94
	0.025	0.0242±0.0007	2.89	0.025	0.0221±0.0011	4.97
	0.05	0.0490±0.0009	1.84	0.05	0.0483±0.0018	3.73
Ni	0.01	0.096±0.0002	2.00	0.01	0.0784±0.0025	3.19
	0.025	0.0243±0.0003	1.23	0.025	0.0235±0.0011	4.68
	0.05	0.0484±0.0011	2.27	0.05	0.0473±0.0018	3.81
Cd	0.01	0.0092±0.0002	2.17	0.01	0.0091±0.0004	4.39
	0.025	0.0260±0.0008	3.07	0.025	0.0226±0.0011	4.87
	0.05	0.0510±0.0014	2.74	0.05	0.0492±0.0024	4.88

Results are expressed as mean±SD, n=3. SD: Standard deviation, RSD: relative standard deviation, Pb: lead, Cd: cadmium, Ni: nickel

2013. The USP NF 2013 recommended permissible daily exposure (PDE) limits of Pb, Cd and Ni in pharmaceutical products are 5, 25 and 500 µg/d, respectively. The maximum daily ingested mass of Pb was higher from products of Greece (1.674 µg Pb) than UAE and Saudi Arabia's products. The maximum daily ingested mass of Pb from acetylsalicylic acids products were 0.015 µg (UAE), 0.048 µg (Egypt) and 10.64 µg (Germany). The maximum daily ingested mass of Cd and Ni was higher from products of Germany than UAE and Egypt's products. After comparison with USP NF 2013[24] it was found that all the products exhibited lower levels of Pb, Cd and Ni than USP NF 2013 recommended level except a product of Germany (acetylsalicylic acid), which contained higher levels of Pb (10.64 µg) than PDE levels of USP NF 2013. However, the maximum recommended daily dose for Germany's product was higher (3.2 g) than UAE (0.081 g) and Egypt's product (0.2 g).

Five solid dosage forms (paracetamol 500 mg) were studied under this class; two products were manufactured in UAE, two exported from Saudi Arabia and one from Australia (Table 4). The recorded level of Pb in paracetamol tablets were in the ranges of 0.062 µg to 0.234 µg/Tablet. The highest level recorded in one of the products of Saudi Arabia and one of the UAE products exhibited lowest level of Pb. The mean differences of local and exported products were significant at the 0.05 level. The maximum daily ingested mass of Pb from paracetamol tablets were 1.128 µg (UAE), 0.496 µg (UAE), 1.872 µg (Saudi Arabia), 1.384 µg (Australia) and 1.56 µg (Saudi Arabia). After comparison with oral PDE limits published by USP NF 2013[24], it was found that all the products of analgesic and antipyretics exhibited lower levels of Pb than USP NF 2013 recommended level.

The recorded levels of Cd in solid dosages forms of analgesics were in the ranges of 0.0023 µg to 0.0381 µg. In comparison, between local and exported products, the mean differences of UAE and Australia's products were significant at the 0.05 level except two products of Saudi Arabia, where the mean differences were insignificant (P<0.05). The maximum daily ingested masses of Cd from these products were in the ranges of 0.0184 to 0.3048 µg. The results were compared with oral PDE limits of USP NF 2013[24] and all the products showed lower levels of Cd than USP NF 2013 recommended level (25 µg/d).

For Ni, lowest level recorded in one of the UAE and Saudi Arabia's product and the mean differences were not significantly (P<0.05) different. The other product of Saudi Arabia exhibited higher level of Ni than Australia and UAE's product and the mean differences

TABLE 3: LEAD, CADMIUM AND NICKEL CONTENTS OF SOME NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Manufacturing country	Active ingredient	Daily dose (g)*	Pb concentration found (µg/tablet)	Maximum daily ingested mass of Pb (µg)	Cd concentration found (µg/tablet)	Maximum daily ingested mass of Cd (µg)	Ni concentration found (µg/tablet)	Maximum daily ingested mass of Ni (µg)
Saudi Arabia	Ibuprofen	2.4	0.032±0.004	0.384	0.0011±0.0002	0.0132	BDL#	BDL#
UAE	Ibuprofen	2.4	0.099±0.002	0.396	0.0022±0.0003	0.0088	0.0022±0.0001	0.0088
Greece	Ibuprofen	2.4	0.279±0.01	1.674	0.0013±0.0001	0.0078	0.0035±0.0001	0.021
UAE	Aspirin	0.081	0.015±0.001	0.015	0.0032±0.0001	0.0032	0.0014±0.0000	0.0014
Egypt	Acetyl-salicylic acid	0.2	0.024±0.002	0.048	0.0012±0.0000	0.0024	0.0037±0.0001	0.0074
Germany	Acetyl-salicylic acid	3.2	1.33±1.15	10.64	0.0391±0.0013	0.3128	0.1797±0.0032	1.4376

*Maximum recommended daily dose. #BDL: Below detection level, results are mean±SD, n=3, SD: standard deviation, Pb: lead, Cd: cadmium, Ni: nickel

TABLE 4: LEAD, CADMIUM AND NICKEL CONTENTS OF SOME ANALGESICS-ANTIPYRETIC AGENTS

Manufacturing country	Active ingredient	Daily dose (g)*	Pb concentration found (µg/tablet)	Maximum daily ingested mass of Pb (µg)	Cd concentration found (µg/tablet)	Maximum daily ingested mass of Cd (µg)	Ni concentration found (µg/tablet)	Maximum daily ingested mass of Ni (µg)
UAE	Paracetamol	4	0.141±0.002	1.128	0.0381±0.004	0.3048	0.0014±0.0001	0.0112
UAE	Paracetamol	4	0.062±0.003	0.496	0.0160±0.0015	0.128	0.0128±0.0001	0.1024
Saudi Arabia	Paracetamol	4	0.234±0.012	1.872	0.0028±0.0002	0.0224	0.0014±0.0000	0.0112
Australia	Paracetamol	4	0.173±0.009	1.384	0.0260±0.003	0.208	0.2601±0.0004	2.0808
Saudi Arabia	Paracetamol	4	0.195±0.002	1.56	0.0023±0.0005	0.0184	0.3213±0.0002	2.5704

*Maximum recommended daily dose, results are mean±SD, n=3, SD: standard deviation, Pb: lead, Cd: cadmium, Ni: nickel

amongst these products were significantly (P<0.05) different. The results were compared with oral PDE limits of USP NF 2013[24] and all the products showed lower levels of Ni than USP NF 2013 recommended level (500 µg/d).

Three liquid products of analgesic, one syrup (UAE) and two suspensions (UAE and Australia) showed positive response for Pb, Cd and Ni (Table 5). Higher level of Pb, Cd and Ni were recorded in syrup than suspension and local product showed higher levels of Pb and Cd than exported one except Ni, where the product of Australia contained higher level of Ni than local products. Statistically, the mean differences for recorded levels of Pb, Cd and Ni were significantly different (P<0.05) amongst the studied products. However, the mean differences of between suspension (Australia) and syrup (UAE) were not significantly (P<0.05) different. After comparison with the oral PDE levels of USP NF 2013[24], the recorded levels of Pb, Cd and Ni were below the permissible levels.

Two products of loratidine 10 mg, one manufactured locally and the other one was imported from USA, was studied and compared their Pb levels (Table 6). The products of UAE exhibited lower level of Pb (0.095 µg) and Cd (0.0013 µg) than USA products that contained 0.792 µg Pb and 0.0017 µg Cd, respectively. However, the recorded level of Ni was higher in UAE products (0.0145 µg) than the product of USA (0.0011 µg). The calculated maximum daily ingested masses of Pb, Cd and Ni from these products were compared with the PDE levels of USP NF 2013[24] and both the products exhibited lower and safe levels of Pb, Cd and Ni than oral PDE levels set by USP NF 2013.

Four cetirizine HCl 10 mg products were also studied; amongst them, one product was manufactured in UAE and the other three products were exported from Saudi Arabia, Jordan and Switzerland, respectively. The product of Saudi Arabia exhibited significantly (P<0.05) lower level of Pb (0.013 µg) than other products. However, the mean differences of local and imported products were significantly different. The maximum daily ingested masses of Pb from these products were in the ranges of 0.013 to 0.038 µg and were lower levels of Pb than USP NF 2013[24] published PDE levels.

The recorded levels of Cd in these products were in the ranges of 0.0014 to 0.0019 µg and the mean differences were not significantly different (P<0.05) amongst the four cetirizine HCl products. In case of Ni, recorded level was below detection limit for UAE products, and the mean differences between other products were significantly different (P<0.05). The calculated maximum daily ingested masses of Ni from these products were in the ranges of 0.0015 to 0.0033 µg and were in safe level in comparison with USP NF 2013[24] published oral PDE levels.

Three liquid products of antihistamines such as diphenhydramine 7 mg (UAE) and diphenhydramine 13 mg (UAE) and loratadine 5 mg (USA) were studied and these products exhibited higher level of Pb than Cd and Ni level (Table 5). In comparison between two products of UAE, diphenhydramine 7 mg contained higher level of Pb but lower level of Cd and Ni than diphenhydramine 13 mg. Loratidine 5 mg also exhibited positive response for Pb, Cd and

TABLE 5: LEAD, CADMIUM AND NICKEL CONTENT OF SOME LIQUID PHARMACEUTICAL PRODUCTS

Manu facturing country	Active ingredient	Daily dose for children (g)*	Pb concentration found (µg/5ml)	Maximum daily ingested mass of Pb (µg)	Cd concentration found (µg/5ml)	Maximum daily ingested mass of Cd (µg)	Ni concentration found (µg/5ml)	Maximum daily ingested mass of Ni (µg)
Saudi Arabia	Ibuprofen	0.8	0.0333±0.0001	0.2664	0.0017±0.0001	0.0136	0.0083±0.0001	0.1088
Kuwait	Ibuprofen	0.8	0.0551±0.0002	0.4408	0.0016±0.0001	0.0128	0.0766±0.0023	0.6128
England	Ibuprofen	0.9	0.0666±0.0005	0.5994	0.0022±0.0001	0.0198	BDL#	BDL#
UAE	Ibuprofen	0.8	2.0411±0.0567	16.33	0.0025±0.0000	0.02	0.0433±0.0004	0.3464
UAE	Paracetamol	0.24	0.0633±0.0021	0.1266	0.0018±0.0003	0.0036	0.0027±0.0006	0.0054
Australia	Paracetamol	0.24	0.0017±0.0003	0.0034	0.0011 0.0000	0.0022	0.0367±0.0002	0.0734
UAE	Paracetamol	0.5	0.0083±0.0002	0.0166	0.0012±0.0001	0.0024	0.0045±0.0001	0.009
UAE	Diphenhy-dramine	0.028	0.0783±0.0010	0.3132	0.0019±0.0005	0.0076	0.0011±0.0000	0.0044
UAE	Diphenhydr-amine HCl	0.027	0.0683±0.0007	0.1366	0.0022±0.0005	0.0044	0.0018±0.0001	0.0036
USA	Loratadine	0.01	0.0351±0.0012	0.0702	0.0015±0.0000	0.003	0.0099±0.0000	0.0198

*Maximum recommended daily dose for children if prescribed, #BDL: Below detection level, results are mean±SD, n=3, SD: standard deviation, Pb: lead, Cd: cadmium, Ni: nickel

TABLE 6: LEAD, CADMIUM AND NICKEL CONTENTS OF SOME ANTIHISTAMINE AGENTS

Manufacturing country	Active ingredient	Daily dose (g)*	Pb concentration found (µg/tablet)	Maximum daily ingested mass of Pb (µg)	Cd concentration found (µg/tablet)	Maximum daily ingested mass of Cd (µg)	Ni concentration found (µg/tablet)	Maximum daily ingested mass of Ni (µg)
USA	Loratadine	0.01	0.792±0.13	0.792	0.0017±0.0003	0.0017	0.0011±0.0000	0.0011
UAE	Loratadine	0.01	0.095±0.002	0.095	0.0013±0.0002	0.0013	0.0145±0.0003	0.0145
UAE	Cetirizine HCl	0.01	0.028±0.002	0.028	0.0014±0.0003	0.0014	BDL#	BDL#
Saudi Arabia	Cetirizine HCl	0.01	0.013±0.004	0.013	0.0016±0.0002	0.0016	0.0026±0.0000	0.0026
Jordan	Cetirizine HCl	0.01	0.034±0.004	0.034	0.0019±0.0005	0.0019	0.0033±0.0001	0.0033
Switzerland	Cetirizine HCl	0.01	0.038±0.002	0.038	0.0018±0.0004	0.0018	0.0015±0.0000	0.0015

*Maximum recommended daily dose, #Below detection level, results are mean±SD, *n*=3, SD: standard deviation, Pb: lead, Cd: cadmium, Ni: nickel

Ni. However, the maximum daily ingested masses of Pb, Cd and Ni from these products were below than those of oral PDE levels of USP NF 2013[24].

Calcium supplements either contained mineral calcium from non-food sources as oyster shell which often described as refined and natural sources or chelated calcium (calcium lactate or calcium gluconate). Therefore, the primary "natural" sources of calcium for nutritional supplements all contain lead as well as the risk of exposure to lead from over-the-counter calcium supplements has been well recognized[23]. Six products of calcium supplements were studied; three were exported from USA, one from Switzerland, one from India and the other one from Czech Republic (Table 7). There were no local products available to compare with the exported one. All the calcium supplements contained vitamin D except product of Switzerland which contained vitamin C. However, all the products exhibited higher level of Pb than Cd and Ni. In case of Pb, the recorded level was in the ranges of 0.123 µg to 11.88 µg and the product of Switzerland exhibited significantly (P<0.05) higher level of Pb than other exported products. Amongst the three USA products, one of the products showed higher level (1.64 µg) of Pb than others (0.123-0.217 µg) and the mean differences were significantly different. In comparison with product of India (1.20 µg Pb) and USA (1.64 µg Pb), the mean differences were not significantly different (P<0.05). The recorded label of Cd in calcium supplements were in the ranges of 0.0256 µg (USA) to 0.5559 µg (Czech Republic). The mean differences amongst six products were not significantly different (P<0.05). The recorded level of Ni was in the ranges of 0.1200 µg (USA) to 2.6428 µg (India), however the mean differences of recorded Ni values of all the products were insignificant (P<0.05). The maximum daily ingested mass of Pb, Cd and Ni from these products were compared with the USP NF 2013[24] published oral PDE values and found Pb exposure from the product of Switzerland (11.88 µg) was two times higher than other exported products. The others products exhibited lower values than USP NF 2013 PDE levels. In case of maximum daily ingested mass values for Cd and Ni, all the products exhibited lower levels than the oral PDE levels published by USP NF 2013[24].

Three products of metformin HCl 1 g, two products were imported from France and Kuwait, respectively and the other one was manufactured in UAE showed positive response for Pb, Cd and Ni (Table 8). The recorded level of Pb was 0.297 µg (France), 0.225 µg (UAE) and 0.184 µg (Kuwait), respectively. However, there were no significant differences (P<0.05) between the mean values of France and UAE. The recorded levels of Cd and Ni in these products were in the ranges of 0.0024 to 0.0349 µg and 0.0122 to 0.0876 µg, respectively. The mean differences for Cd level between France and Kuwait were not significantly different (P<0.05); however the mean differences for Ni amongst the three products were significantly different (P<0.05). The maximum daily ingested masses of Pb from these products were higher than Cd and Ni. However, the results data were compared with USP NF 2013[24] published PDE levels for Pb, Cd and Ni, and all the products showed lower level of these elements than USP NF 2013 recommended value.

Two antilipemic agents (atorvastatin 20 mg), one products exported from USA and the other one from Germany were studied for evaluation of their trace levels of Pb, Cd and Ni content (Table 8). The recorded levels of Pb, Cd and Ni for the product of USA were 0.095, 0.0199 and 0.0331 µg, respectively. The product of Germany contained 0.059 µg Pb, 0.0082 µg Cd and 0.0424 µg Ni, respectively. However, the product of

TABLE 7: LEAD, CADMIUM AND NICKEL CONTENTS OF SOME CALCIUM SUPPLEMENTS

Manufacturing country	Active ingredient	Daily dose (g)*	Pb concentration found (µg/tablet)	Maximum daily ingested mass of Pb (µg)	Cd concentration found (µg/tablet)	Maximum daily ingested mass of Cd (µg)	Ni concentration found (µg/tablet)	Maximum daily ingested mass of Ni (µg)
USA	Calcium carbonate	0.6	0.217±0.008	0.217	0.0256±0.0023	0.0256	0.0591±0.0001	0.0591
Switzerland	Calcium lactate gluconate, Calcium carbonate, Vitamin C	2.33	11.88±1.34	11.89	0.1891±0.0011	0.1891	0.2921±0.0052	0.2921
USA	Calcium carbonate	1	1.64±0.011	1.64	0.1472±0.0012	0.1472	0.2241±0.0021	0.2241
USA	Calcium carbonate	1.2	0.123±0.001	0.123	0.0525±0.0002	0.0525	0.1200±0.0012	0.12
Czech republic	Calcium carbonate	1.2	0.482±0.008	0.482	0.5559±0.0054	0.5559	0.1622±0.0014	0.1622
India	Calcium carbonate	0.5	1.20±0.007	1.20	0.1654±0.0006	0.1654	2.6428±0.0035	2.6428

*Maximum recommended daily dose, results are mean±SD, *n*=3, SD: standard deviation, Pb: lead, Cd: cadmium, Ni: nickel

TABLE 8: LEAD, CADMIUM AND NICKEL CONTENTS OF SOME ORAL ANTIDIABETIC AGENTS, ANTILIPEMIC AGENTS AND NRT

Manufacturing country	Active ingredient	Daily dose (g)*	Pb concentration found (µg/tablet)	Maximum daily ingested mass of Pb (µg)	Cd concentration found (µg/tablet)	Maximum daily ingested mass of Cd (µg)	Ni concentration found (µg/tablet)	Maximum daily ingested mass of Ni (µg)
Oral antidiabetic agents								
France	Metformin HCl	2	0.297±0.026	0.594	0.0027±0.0005	0.0054	0.0876±0.0002	0.1752
UAE	Metformin HCl	2.5	0.225±0.011	0.5625	0.0349±0.0011	0.08725	0.0122±0.0002	0.0305
Kuwait	Metformin HCl	2	0.184±0.036	0.368	0.0024±0.0005	0.0048	0.0369±0.0003	0.0738
Antilipemic agents								
USA	Atorvastatin	0.08	0.095±0.001	0.38	0.0199±0.0013	0.0796	0.0331±0.0011	0.1324
Germany	Atorvastatin	0.08	0.059±0.002	0.236	0.0082±0.0005	0.0328	0.0424±0.0002	0.1696
NRT								
UAE	Nicotine	0.03	0.824±0.005	12.36	0.0588±0.0032	0.882	0.1589±0.0051	2.3835

*Maximum recommended daily dose, results are mean±SD, *n*=3. SD: Standard deviation, NRT: nicotine replacement therapy, Pb: lead, Cd: cadmium, Ni: nickel

USA showed comparatively higher levels of Pb and Cd than the product of Germany. The maximum daily ingested masses of Pb, Cd and Ni from the products of USA were 0.38, 0.0796, 0.1324 µg, respectively; from the products of Germany were 0.236 µg Pb, 0.0328 µg Cd, and 0.1696 µg Ni, respectively. The maximum daily ingested masses of these metals were compared with the recommended oral PDE levels set by USP NF 2013[24] and it reveals that all the values were below than the published PDE levels of USP NF 2013.

Nicotine 2 mg (chewing gum) was manufactured in UAE and studied for the presence of Pb, Cd and Ni. It is the only product available under this category in UAE Pharmaceutical markets. This product contained 0.824 µg of Pb, 0.0588 µg of Cd and 0.1589 µg of Ni (Table 8). The recorded level of Pb was higher in the chewing gum as it contained calcium carbonate as excipient, which could be the sources of Pb contaminant. However, the maximum daily ingested mass of Pb, Cd and Ni from this product was 12.36, 0.882 and 2.3835 µg, respectively. In comparison with oral PDE levels of USP NF 2013[24], the level of Pb was higher in the product and the level of Cd and Ni were below than PDE levels of USP NF 2013[24]. Since this product is consumed in large volume for longer period of times, therefore, the patient might develop Pb toxicity on long term consuming this product. Hence this product should not be consumed for longer period of time to avoid lead toxicity.

Thirty-nine pharmaceutical products that include 6 nonsteroidal antiinflammatory drugs, 6 analgesics, 7 antihistamines, 4 oral anti-diabetics, 6 calcium supplements, 2 antilipemic agents and one chewing gum for nicotine replacement therapy were analyzed for quantitation of trace levels of Pb, Cd and Ni by graphite furnace atomic absorption spectrometry. Amongst the samples, 13 products were manufactured in UAE and 26 products were imported from around the world. According to USP NF 2013[24], the maximum daily ingested masses of Pb, Cd and Ni from these pharmaceutical products were lower and safer level than Oral PDE levels of USP NF 2013, except three over the counter products as calcium supplement (Switzerland), acetylsalicylic acid (Germany) and nicotine (UAE)

which showed higher level of Pb than published oral PDE levels. The product of UAE contained calcium carbonate as excipient, whereas the product of Switzerland contained calcium carbonate, calcium lactate gluconate and vitamin C as active drugs which could be responsible for the presence of higher level of Pb in these products. In conclusion, raw materials using in manufacturing processes of medicinal agents are the major contributor for the presence of toxic trace metal contaminants.

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