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Determination and quality evaluation of some imported drugs in Iraqi kurdistan region

Yousif J. Azeez
Chemistry Department , College of Science , Salahaddin University , Erbil , Iraq

Abstract
Some of important drugs in Kurdistan Region are planned to be determined such as analgesics and antibiotics from different available companies. For the first stages Paracetamol, Aspirin, Chloramphenicol, Ibuprofen and Tetracycline drugs were examined and the real quantities determined were compared with that reported on a commercial labels. Mean recoveries 99.2,95.9,99.2,99 and 102.8 respectively, and have percentage errors (%E) -0.80, -4.07,-0.80, 2.80 and -1.00 respectively and the best companies for these drugs.

Key words: Paracetamol, Aspirin, Chloramphenicol, Ibuprophen, Tetracycline, Spectrophotometer.

Introduction

Paracetamol Prior to its' spectrophotometric determination, acetaminophen was separated from combination with other antipyretic-analgesics by column chromatography using purified siliceous earth a cation exchange resine[1-2], or an anion-exchange resine[3]. Recently, high-performance liquid chromatography [4] was utilised in the determination of an acetaminophen-methaqualone(2-methyl-3-o-tolylquinazolin-4-one) mixture. Spectrophotometric methods[5], for the determination of acetaminophen in combination with acetylsaliclic acid (aspirin) have been proposed. In biological fluids,acetaminophen was extracted and determined by spectrophotometry [6], fluorimetry[7], differential spectrophotometry[8] and gas-liquidchromatography[9].

It was concluded that oxidative coupling organic reactions took an important role in the determination of paracetamol[10].Another method is developed in order to improve sensitivity, selectivity and accuracy of the determination of paracetamol.It is based on the oxidative coupling reaction between paracetamol and sodiumperiodate-aniline leading to the formation of a yellow-orange colour[11].

Aspirin The plasma half-life of aspirin is only about 20 minute because it is readily hydrolyzed to salicylic acid(SAL)[12] its' principal metabolite. An anlytical method that measure ASA in biological fluids should, therefore,be capable of measuring SAL also.Such assays are required for many reasons in case of aspirin poisoning, in tolerance reactions, side effects, and for metabolic and pharmacokinetic studies. Low-level determination of thse compounds is usually carried out using HPLC methods, many of which have been described in a review by kwong in 1987.The mobile phase usually contain methanol or acetonitrile and have a low pH (normally 2.5-3.0), with UV. Detection in the range 225-240 nm. Small improvements in validation results (e.g. sensitivity) have been made over the years, but since 1980, HPLC methodology for ASA and SAL has only really charged in terms of applications, at the latter determination of aspirin and salicylic acid in human plasma by column-switching liquid chromatography using on line solid-phase extraction was done[13].

Chloramphenicol has strong UV. Absorption and can be determined directly by LC. It has a maximam absorption at 278 nm.[14]. A comprehensive review of methods for the determination of chloramphenicol residues in food, which included eight GC methods and six LC methods for chloramphenicol in milk, has been reported by Nagata[14]. Since this report provides a detailed review of methods, only additional developments, will be reviewed here.

Pfenning et al.[15] developed a GC method for the determination of chloramphenicol in raw milk. The milk is extracted with acetonitrile, then followed by a C_{18} SpE clean-up, derivatization with sylon BFT and GC determination with electron-capture detection. Average recoveries ranged from 92-104% at levels ranging from 5-80 ng/ml. Kijal[16] presented a GC-Ms method for the confirmation of chloramphenicol residuse in bovine milk. Meta - nitrochloramphenicol was added as a surrogate standard. Chlorampenicol residues were extracted from the milk by mixing the milk with ethyl acetate using a diatomaceous earth SPE column clean-up. This was followed a C_{18} SPE clean-up and derivatization with sylon HTP. Chloramphinicol was determined using GC with a 30 m methylsilicone column and negative ion chemical ionization mass spectrometric determination. The method was validated at levels of .5-2.0 ng/ml.

Bayo et al[17] used diphasic dialysis to extract chloramphenicol from milk. Ethyl acetate was added to a piece of hydrated dialysis tubing, The tubing was placed into a flask of milk and mixed with an orbital shaker for 5 hr. The ethyl acetate in the dialysis tubing was dried with sodium sulfate and evaporated. Determination was by LC using a Novapak C_{18} column and UV. Detection. The limit of quantitation was 5 ng/ml. Keeukens et.al[18] presented preliminary studies on the determination of chloramphenicol in milk by modifying a previously reported LC method for chloramphenicol in meat [5]. Extraction and clean-up of the milk was with an extrelut diatomaceous earth SPE column and water-toluene partitioning. The limit of detection was 0.5 ng/ml. Clark et al.[19] presented a GC method for the determination of trace levels of chloramphenicol in milk. Milk was partially defatted by centrifugation.

This was followed by a C_{18} SPE clea-up and derivatization with sylon-HTP. GC was with 2m x 4mm column packed with 3% dimethyl silicon (OV-101) on gas chrom φ and electron-capture detection. The method was validated at levels of 0.5-1.5 ng/ml chloramphenicol in milk.

Ibuprofen: Colorimetric determination of ibuprofen in tablets[20], a simple extraction and colorimetric method for the determination of ibuprofen in its' dosage form based on the conversion of carboxylic acid into an acid chloride and its' coupling with hydroxylamine to get hydroxamic acid which forms a violet coloured complex with vanadium in acidic medium. Ibuprofen and novocaine hydrochloride were determined with the use of water-micellar solutions of surfactants[21]. Simultaneous determination of several antalgic drugs based on their interactions with b-cyclodextrin by capillary zone electrophoresis was done by Wei et al.[22]. The binding constants of b-cyclodextrin (b-CD) with antalgic drugs such as ibuprofen and aspirin are determined by affinity capillary electrophoresis, based on these interactions,a reliable method for separation and simultaneous determinations of these compounds in the presence of 5.0 mM b-CD in phosphate buffer solution is presented by capillary zone electrophoresis with UV. detection at 200 nm for ibuprofen and aspirin. The linear ranges for ibuprofen and aspirin are from 2.5-700 and 2-800 μg/ml. Respectively. Their detection limits are 0.5 and 1.5μg/ml. at a signal to noise ratio of 3 respectively. This method has been successfully applied to the detections of these drugs in the pharmaceutical formulations(tablets or capsules) and urine samples.

Tetracycline : The FDA has set levels of concern for residues of chlortetracycline, oxytetracycline and tetracycline in milk of 30, 30 and 80 ng/ml. Respectively[23]. Oka and Patterson [24], Shaikh and Moats[25], Barker and Walker[26] reviewed chromatographic methods for the determination of tetracyclines in food products. Since these reports provide a detailed review of methods for tetracyclines in milk, additional developments since then will be reviewed here. Nazol et al.[27], reviewed a rapid determination of trace levels tetracycline in surface water using continuous flow manifold coupled to a capillary electrophoresis system. Tetracyclines are widely used as bacterio static and antibiotic drugs. Ttetracycline (TC) and its' derivatives oxytetracycline (OTC), chlortetracycline (CTC), doxycycline (DC) and demeclocycline (DMCC) have been employed extensively in veterinary medicine animal nutrition and feed additives. However, many health authorities do not allow antibiotic residues in foods because of allergic reactions, paricularly hypertensive people[28].

Ttetracycline is one of a broad spectrum antibiotics[29] which has the structural formula $C_{22}H_{24}N_2O_8$. HCl(M.Wt.=480.9). Tetracycline was determined by microbiological[30], chromatography [31-32], spectrophotometric[33], fluorimetric[34] titrimetric[35], and chemiluminescence procedure[36-39]. Liquid chromatography in combination with electrochemical detection has been used to evaluate commercial formulations of tetracycline ,demeclocycline, doxycycline ,methacycline, minocycline, oxytetracycline and tetracycline in the presence of common impurities[40]. likewise,two electrochemical methods have appeared for minocycline[41-42],that are useful for measuring the analyte in the microgram per milliliter range and a FIA-chemiluminescence assay has been reported for oxytetracycline, chlortetracycline, and tetracycline [43]. The detection limits for the three analytes are 400, 520 and 600 mg/ml. respectively. In addition, oxytetracycline has been quantified using conventional aqueous-based CE approch[44] and by a non aqueous CE[45] procedure. Capillary electrophoretic methods also have been used to analyze other tetracycline[46-48].

Our preliminary investigations throughout consultants and pharmacies reveal that some of these drugs may be ineffective and the patients already gain little advantages even when they take a high dose of such drugs. Therefore it was decided to analyze such drugs through a long program according to the procedures reported in British Pharmacopoeia Monographs[49], which are alone authoritative and the results will compare with pure compounds which will be analyse in the first stage of the work. For the time being it was possible to obtain five of such pure drugs namely Paracetamol, Aspirin, Chloramphenicol, Ibuprofen and Tetracycline. It was hoped in the next stage more pure drugs would be obtained.

Apparatus:

A PU 8000 UV/VISIBLE double beam scanning spectrophotometry was used to measure the absorbance of both pure and sample of the analysed drugs.

Procedures:

The procedures followed in accordance to British Pharmacopoeia as following [50].

Paracetamol:

0.3 g of the sample was dissolved in a mixture of 10 ml of water and 30 ml of 1M sulphuric acid. Boiled under reflux for one hour, cooled and diluted to 100 ml with water. To 20 ml of the solution 40 ml of water; 4 g of ice, 15 ml of 2M HCl and 0.1 ml of ferroine sulphate solution. The final solution was titrated with 0.1M ammonium cerium (IV) sulphate until a yellow colour is obtained. The procedure was repeated without the substance being examined.

Aspirin:

0.5 g of the drug is dissolved in 10 ml of ethanol (96%), 0.2 ml of dilute phenolaphthaline solution and titrated with 0.1M sodium hydroxide. Each ml of 0.1M sodium hydroxide is equivalent to 0.01802 g of $C_9H_8O_4$.

A 50 ml of 0.1M NaOH is added to the neutral solution so obtained and the mixture was boiled under reflux for 15 minutes. The mixture was allowed to cool in a fume cupboard to preclude CO_2 absorption and then titrated with 0.1M HCl. The difference between the volumes of 0.1M NaOH used in the first and second titration was not more than 0.4 ml. Calculated with reference to 0.5 g of the substance.

Chloramphenicol:

1 g of the substance was dissolved in sufficient water to produce 500 ml. 10 ml was diluted to 100 ml with water and the absorbance of the resulting solution was measured at the a maximum at 278 nm. The content of chloraphenicol $C_{11}H_{12}Cl_2N_2O_5$ was calculated. Taking 297 on the value of A (1%, 1 cm) at the maximum at 278 nm.

Ibuprofen:

Dissolve 0.18g. in 100ml. Of ethanol(98%) and titrate with 0.1M sodium hydroxide using 0.2 ml. Of phenolaphthaline solution RI (retention index) as indicator until a red colour is produced. Repeat the procedure without the substance being examined. The difference between the titrations represents the amounts of sodium hydroxide required. Each ml. Of 0.1M sodium hydroxide is equivalent to 20.63 mg. Of $C_{13}H_{18}O_2$.

Tetracycline:

10 mg of the substance was dissolved in 0.01M Hydrochloric acid solution to produce 100 ml solution. To 10 ml of the resulting solution add 75 ml of water, 5 ml of 5M sodium hydroxide and sufficient water to produce 100 ml, and mix immediately. The absorbance was taken at 380 nm six minutes after the addition of the NaOH solution.

Reagents:

Pure reagents of the drug examined obtained from sammara drugs institute/ Iraq (SDI).Commercial drugs are purchased from local farmacies in Erbil city, Table(1) illustrate the details.

Results and Discussions:

Table (2) illustrates the results obtained for the drugs studied. From this table seems that paracetamol manufacture NECIP AKAR Gripinilas A.S. Turkey, Aspirin ZMG ZHEJIANG Medicine & Health products China, Chloramphenicol DRISM international India, Ibuproten ELCEE Lab. England and Tetracycline SIGMA / Germany which have mean recoveries 99.2, 95.9, 99.2, 99.0, and 102.8 respectively, and have percentage errors (%E) -0.80, -4.07, -0.80, 2.80, and -1.00 respectively, are the best companies for producing these drugs.

Table (1): General Commercial Characteristic of the Drugs Analyzed

No.	Species to be determined	Commerical Name	Manufacturer	Drug Content	Drug State	Expiry Date
1.	Paracetamol	Piral	Kahira Pharm. & Chem. IND. CO. Cairo Egypt	125 mg	Syrup	7/2004
2.	Paracetamol	Gripin Babe Pediatric Syrup	NECIP AKAR Gripinilas A.S. Turkey	120 mg	Syrup	2/2006
3.	Paracetamol	PrIsMOL-500	PRISM PRISM-International India	500 mg	Tablet	3/2004
4.	Paracetamol	Paracetol	SDI/IRAQ	500 mg	Tablet	10/2006
5.	Paracetamol	Paracil	China	500 mg	Tablet	9/2005
6.	Paracetamol	Paracetamol BP 500	TROGE Germany	500 mg	Tablet	2/2005
7.	Paracetamol	CADOL-100	HOLDEN Medical Holland	100 mg	Tablet	2/2005
8.	Acetyl Salsysilic acid (Aspirin)	Asiapirine	Asia Pharmaceutical Industries Aleppo/Syria	81 mg	Tablet	2/2005
9.	Aspirin	A.S.A for Children	Pars Medical IRAN	100 mg	Tablet	2/2004
10.	Aspirin	Aspirin	ZMG ZHEJIANG Medicine & Health Products. China	300 mg	Tablet	11/2002
11.	Chloramphenicol	Chloramphenicol	TROGE/Hamburg Germany	250 mg	Capsules	11/2002
12.	Chloramphenicol	Prichlor-250	PRISM International India	250 mg	Capsules	3/2003
13.	Chloramphenicol	Chloramphenical Capsules BP	Holden Holland	250 mg	Capsules	7/2002
14.	Chloramphenicol	Samaphenical	SDI /IRAQ	250 mg	Capsules	8/2004
15.	Ibuprofen	Apifen-400	India/afanta pharma.LTD.	400 mg.	Tablet	8/2004
16.	Ibuprofen	Ibuprofen/BP 400mg	Troge/Germany	400 mg	Tablet	9/2005
17.	Ibuprofen	Actifen	Tenderwell LTD/England	200 mg	Tablet	9/2005
18.	Ibuprofen	Richfen-200	Richy Gold-international Hamberg.Germany	200 mg	Tablet	5/2004
19	Ibuprofen	Promafen	ELCEE/London-England	200 mg	Capsul	6/2006
20	Tetracycline	APCYCLINE-250	Ajanta Pharmacy Limited India	250 mg	Capsules	8/2004
21	Tetracycline	Tetracycline 250 mg	IRAN/DARU	250 mg	Capsules	5/2003
22	Tetracycline	Tetracycline RP	SIGMA / Germany	250 mg	Capsules	8/2006
23	Tetracycline	Samacycline	SDI/IRAQ	250 mg	Capsules	6/2004

Table (2): Determination of some pharmaceutical drugs.

No.	Species to be determined	Commerical Name	Manufacturer	mg/Tablet labeled commerciall y	mg/Tablet * determine d	Mean Recover y %	%E**
1.	Paracetamol	Piral	Kahira Pharm. & Chem. IND. CO. Cairo Egypt	125 mg	123.5	98.8	-1.20
2.	Paracetamol	Gripin Babe Pediatric Syrup	NECIP AKAR Gripinilas A.S. Turkey	120 mg	119	98.2	-0.80
3.	Paracetamol	PrIsMOL-500	PRISM PRISM-International India	500 mg	480.7	96.1	-3.86
4.	Paracetamol	Paracetol	SDI/IRAQ	500 mg	430	86.0	-14.00
5.	Paracetamol	Paracil	China	500 mg	485	97.0	-3.00
6.	Paracetamol	Paracetamol BP 500	TROGE Germany	500 mg	465	93.0	-7.00
7.	Paracetamol	CADOL-100	HOLDEN Medical Holland	100 mg	98.8	98.8	-1.20
8.	Acetyl Salsysilic acid (Aspirin)	Asiapirine	Asia Pharmaceutical Industries Aleppo/Syria	81 mg	77.1	95.2	-4.81
9.	Aspirin	A.S.A for Children	Pars Medical IRAN	100 mg	119.9	119.9	19.90
10.	Aspirin	Aspirin	ZMG ZHEJIANG Medicine & Health Products. China	300 mg	287.8	95.9	-4.07
11.	Chloramphenicol	Chloramphenicol	TROGE/Hamburg Germany	250 mg	259	103.6	-3.60
12.	Chloramphenicol	Prichlor-250	PRISM International India	250 mg	248	99.2	-0.80
13.	Chloramphenicol	Chloramphenical Capsules BP	Holden Holland	250 mg	254	101.6	1.60
14.	Chloramphenicol	Samaphenical	SDI /IRAQ	250 mg	258	103.2	3.20
15.	Ibuprofen	Apifen-400	Afantapharma/LTDIndia Geo2Eo	400 mg	392	98.0	-2.00
16.	Ibuprofen	Troge	Troge/Hamburg/Germany	400 mg	390	97.5	-2.50
17.	Ibuprofen	Actifen	Tenderwell/LTD London /England	200 mg	197	98.5	-1.50
18.	Ibuprofen	Richfeen-200	Ricy Gold Int.Germany	200 mg	194	97.0	-3.0
19	Ibuprofen	Promafen	ELCEELab.England	200 mg	198	99.0	-1.00
20	Tetracycline	APCYCLINE-250	Ajanta Pharmacy Limited India	250 mg	297	118.8	18.80
21	Tetracycline	Tetracycline 250 mg	IRAN/DARU	250 mg	209	83.6	-16.40
22	Tetracycline	Tetracycline RP	SIGMA / Germany	250 mg	257	102.8	2.80
23	Tetracycline	Samacycline	SDI/IRAQ	250 mg	242	96.8	-3.20

*Mean of three determinations.

**%E=[(Observed value – Theoritical value) / Theoritical value] X 100

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تقدير و تخمين نوعية بعض الأدوية المستوردة في كردستان – العراق

يوسف جلال عزيز

قسم الكيمياء ، كلية العلوم ، جامعة صلاح الدين ، اربيل ، العراق

الملخص

تم تقدير بعض ادوية مهمة في منطقة كردستان و بطريقة قياسية وكمياتهم ومقارنتهم مع المكتوب على غلاف الورقة والأدوية المهمة عبارة عن: باراسيتامول، أسبرين، الكلورمفينكول، ابوالبرفين، و تيتراسايكلين و استرجاعية 99.2, 99,99.2,95.9 و 102.8 على التوالي ونسبة الخطأ(%E) −0.80,−4.07, 0.80 ,2.80و −1.00 على التوالي وأفضل شركة لأنتاج هذه الأدوية.