QUALITY ASSESSMENT OF SELECTED ANALGESICS CIRCULATING IN LIBERIA

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ABSTRACT

The study was undertaken to determine the level of counterfeit/substandard medicines circulating in Liberia, using selected analgesic as a surrogate. It is widely assumed that there are a lot of fake and counterfeit medicines in circulation in Liberia. The present study aimed at determining quality of Paracetamol, Aspirin, Ibuprofen, and Diclofenac tablets in circulation on the Liberian market. Employing qualitative and quantitative parameters using visual inspection, uniformity of weight test, disintegration test, thin layer chromatography, volumetric and UV-Spectrophotometric methods. Visual inspections showed all the samples were appropriately labeled and packaged. All the samples passed the Uniformity of weight and Disintegration tests. The presence of degraded/related substances was confirmed in one brand of Paracetamol representing 7.14% of total samples. The percent drug content analysis showed that the following percentages of each sample did not comply with their respective pharmacopeia specifications, Paracetamol, 21.43%, Aspirin 36.36%, Ibuprofen 30.00% and Diclofenac 30.00%, since all the samples are used as surrogate, the average non-complying sample or failure to meet specification is 29.50%.

Key words; Paracetamol, Aspirin, Ibuprofen, Diclofenac, Counterfeit drugs.

INTRODUCTION

Counterfeit drugs (fake drugs) are substantial and growing problem, both in the developed and in the developing World. No country is free of this problem, which plagues developing and developed countries. In addition, at the global level, it was estimated that 10% of the Medicines in the World Trade were counterfeit drugs (WHO, 2012).

Analgesics are common over-the-counter drugs that relieve pain. They do not require official prescription, before they can be purchased from the pharmacy, drug store or drug peddler. Pain is not a disease but mostly symptom, to many disease conditions. Analgesics are mainly used for pain relief, fever reduction, and inflammatory conditions (Van et. al. 1995). In Liberia, it is assumed that most of the counterfeit drugs on the market are analgesics. Analgesics are common, cheap, and widely consumed thereby making it attractive for manufacturers of fake drugs. Counterfeit and substandard medicines have been reported to contribute to the high incidences of treatment failure, morbidity, mortality and drug resistance. (Caudron, 2008).

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For example, in Haiti, India, Nigeria, and Bangladesh some 500 children died of acute renal failure after ingesting counterfeit paracetamol (acetaminophen) and cough syrup made using diethylene glycol, a renal toxin (Hanif et al., 1995) Although there are few accurate estimates of the scale of the problem, only a few counterfeit drug incidents are reported to the appropriate enforcement agencies; thus, numbers of those affected by counterfeit drugs are likely to be grossly underestimated. The problem of counterfeit drugs is known to exist in both developed and developing countries however, the true extent of the problem is not really known since no global study has been carried out (Taylor et al. 2001, Kolawole et al. 2002).

The global level of sub-standard/counterfeit/fake drugs was estimated to be about 10% of the medicines in international commerce. It has also been reported that most of the common sources of counterfeit drugs are in India and China (WHO, 2012). Ironically 90% of medicines on the Liberian market were sourced from India and China. It was estimated that up to 60% of the drugs that are on the local market in Liberia are counterfeit, posing a major threat to the population (http://www.havocscope.com/fake-drugs-in-liberia/). The country is bordered by countries with weak legislations on medicines and weak enforcement of such laws. These therefore lend credence to the speculation that there are abundance (between 60-65%) of fake/counterfeit drugs in the Liberian market, however to our knowledge there has been no baseline study conducted for such assertion or assumptions. The aim of this work is to determine the level of counterfeit drugs in circulation in Monrovia/Liberia, using common analgesics as a surrogate through the assessment of the quality of Paracetamol, Aspirin, Ibuprofen and Diclofenac tablets.

MATERIALS AND METHODS

Paracetamol, Aspirin, Ibuprofen, and Diclofenac tablets were purchased from selected Pharmacies, medicine stores and drug peddlers in Monrovia (the commercial City of Liberia). All analyses were performed before the expiry dates of the products.

Methanol, Toluene, Glacial acetic acid, Acetone, Sodium Hydroxide, Hydrochloric acid (BDH Laboratory supplies Poole Bh, 15 l TD, England). TLC aluminum plates pre-coated with silica gel 60 F 254, size 5×10 cm, glass micro capillaries of 2 ul capacity (5ul), hot plate (Phillips travel iron), UV light 254 nm, iodine chamber, Ultraviolet spectrophotometer (Genesis 6, Thermo Scientific, USA), Disintegrating apparatus (USA).

Collection and preservation of samples

Samples were purchased from registered Pharmacies, medicine stores and non-registered medicine stores and drug peddlers premises in Monrovia (commercial city of Liberia). The followings were randomly sampled, Paracetamol fourteen (14) brands, Aspirin eleven (11) brands, Ibuprofen ten (10) brands, and Diclofenac ten (10) brands. Each sample of Paracetamol, Aspirin, Ibuprofen, Diclofenac collected were specially coded as follows; Paracetamol, PCM1, PCM2, PCM3, PCM4, PCM5, PCM6, PCM7, PCM8, PCM9, PCM10, PCM11, PCM12, PCM13, PCM14; Aspirin, ASA1, ASA2, ASA3, ASA4, ASA5, ASA6, ASA7, ASA6, ASA7, ASA8, ASA9, ASA10, ASA11; Ibuprofen, IBU1, IBU2, IBU3, IBU4, IBU5, IBU6, IBU7, IBU8, IBU9, IBU10; Diclofenac DICLO1, DICLO2, DICLO3, DICLO4, DICLO5, DICLO6, DICLO7, DICLO8, DICLO9, DICLO10. The study was carried out between April, 2013 and July, 2013 and all the samples have more than one year before expiration.

METHODS OF ANALYSIS

Visual inspection

Samples were collected and logged using a data collection workbook to record the following information: sample name, sample code, brand name, country of origin, batch number, expiry date, strength, manufacturer address, manufacturing date, packaging, facility types and retail price.
The tablets were examined based on inscription on tablets and packs, colors of tablets, shapes of tablets and presence or absence of scaring/capping/breakage on tablets.

Uniformity of weight

Twenty (20) tablets were taken at random from each sample and weighed individually and their cumulative weights and average weights were determined. The deviation of each of the individual tablets in each sample, from the average masses of the sample was determined. For a sample to pass the uniformity of weight test not more than 2 of the individual masses should deviate from the average mass by more than the percentage deviation shown in the table below and none should deviate by more than twice the percentage.

Table 1: Approved percentage deviation for a sample to pass the uniformity of weight test

Pharmaceutical form	Average mass	Percentage deviation
Tablets (uncoated and film coated)	80mg or less	10
	More than 80 mg and less than 250mg	7.5
	250mg or more	5

Disintegration testing of tablets (BP 2010 method adopted)

Six tablets from each sample were selected at random. One tablet was placed in each of the six tubes of the disintegration basket. The apparatus was operated using distilled water as the medium and immersion fluid and maintained at 37 ± 2 ^{o}C. The dosage units were observed during the process in order to record the time of disintegration. At the end of the specified time (15 minutes for uncoated tablets and 30 minutes for film coated tablets), the basket was lifted from the fluid and the dosage units observed. If 1 or 2 dosage units fail to disintegrate, the test is repeated on 12 additional tablets. The requirements of the test are met if not less than 16 of the 18 dosage units tested have disintegrated.

Thin layer chromatography for identification, degraded or related compounds

For Paracetamol tablet samples:
A 1.25 mg/ml of paracetamol was prepared in methanol as working standard and served as reference. The same concentrations of the samples were prepared for the TLC.

The developing solvents; Toluene (10 ml), Acetone (10 ml) and 10 drops of glacial acetic acid were thoroughly mixed in the developing chamber. The jar was closed for saturation of the chamber with solvent vapor. The loaded TLC plate was placed into the jar. The jar was closed and developed for about three minutes. The plate was removed from the chamber, and the solvent front was marked. Residual solvent was dried off and the chromatoplate was observed with UV light of 254 nm.

Assay of individual samples

Assay of Paracetamol Tablet

The BP 2010 method was adopted. The Paracetamol tablet samples used were labeled as: PCM1, PCM2, PCM3, PCM4, PCM5, PCM6, PCM7, PCM8, PCM9, PCM10, PCM11, PCM12, PCM13, PCM14 and reference standard. Twenty tablets were individually weighed and then powdered in a mortar. For each sample, an amount of powder equivalent to 0.15 g paracetamol content was accurately weighed and transferred into different 200 ml volumetric flasks. To each volumetric flask, was added 50 ml of 0.1 M sodium hydroxide and 100 ml of distilled water and shaken for 15 minutes and placed in the ultrasonicator for 5 minutes. The volume was made to 200 ml with distilled water shaken and filtered. A 10 ml volume of the filtrate was transferred into a 100 ml volumetric flask and made up to volume with distilled water. A 10 ml volume of the resultant solution was transferred into a 100 ml volumetric flask and 10 ml of 0.1 M sodium hydroxide was added, then made up to volume with distilled water. The absorbances of the solutions were determined using 0.1 M NaOH solution as blank at 257 nm using the UV-Vis Spectrophotometer. Concentrations for each sample was determined using the calibration curve equation $y = 0.070 x$ on a curve with R^2 of 0.999.

Assay of Aspirin tablets

The Aspirin tablet samples used were labeled as: ASA1, ASA2, ASA3, ASA4, ASA5, ASA6, ASA7, ASA6, ASA7, ASA8, ASA9, ASA10, ASA11 and the reference sample.

The International Pharmacopoeia (2006), method was adopted. Twenty tablets (20) of Aspirin samples were individually weighed and the average weight of tablets was determined. The tablets were powered. For each sample, a quantity of powder equivalent to 0.5 gram of Aspirin was accurately weighed and 30 ml of 0.5 M sodium hydroxide (VS), was added and boiled gently within 10 minutes. The resultant solution was titrated with 0.5 M hydrochloric acid (VS) using Phenol red solution as indicator. A blank titration was carried out for each assay. The difference between the titrations represents the amount of sodium hydroxide required. The amount of Aspirin in each sample was calculated from the equivalency; each ml of 0.5 M sodium hydroxide VS is equivalent to 45.04 mg of $C_9H_8O_4$.

Assay of Ibuprofen tablets

The Ibuprofen tablet samples used were labeled as: IBU1, IBU 2, IBU 3, IBU 4, IBU 5, IBU 6, IBU 7, IBU 8, IBU 9, IBU 10, and Ibuprofen reference sample. The Indian Pharmacopoeia (1999), method was adopted. Twenty tablets (20) of Ibuprofen samples were individually weighed and the average weight of tablets was determined. The tablets were powdered. For each sample, a quantity of powder equivalent to 0.5 g of Ibuprofen was extracted with 60 ml of chloroform for 15 minutes and filter. The residue was washed with three quantities of 10 ml each of chloroform and the combined filtrates gently evaporated to dryness. The residue was dissolve in 100 ml of ethanol (95%), previously neutralized to phenolphthalein solution and then titrated with 0.1 M sodium hydroxide using phenolphthalein solution as indicator. The amount of Ibuprofen in each sample was calculated from the equivalency; 'each ml of 0.1 M sodium hydroxide is equivalent to 0.02063 g of $C_{13}H_{18}O_2$'.

Assay of Diclofenac tablets

The Diclofenac tablet samples used were labeled as: DICLO1, DICLO2, DICLO3, DICLO4, DICLO5, DICLO6DICLO7, DICLO8, DICLO9, DICLO10 and reference sample. The Indian Pharmacopoeia (1999) was adopted. Twenty tablets were individually weighed

and the average weight per tablet determined.

The tablets were powdered and a quantity of the powder equivalent to 50 mg of Diclofenac sodium was accurately weighed out and transferred into a 200 ml volumetric flask. Methanol was gradually added and shaken and finally made to volume. A 1.0 ml of the solution was added to 9.0 ml of methanol and the absorbance was measure at 285 nm using the UV-Vis Spectrophotometer. Concentrations for each sample was determined using the calibration curve equation y = 0.040 x on a curve with R^2 of 0.992.

RESULTS AND DISCUSSION

Visual inspection of samples

The results of visual inspection of the samples showed that all of the samples have on their packaging, brand name, full address/country of origin, batch number, expiry/manufacturing dates, strength and dose/advice to see the physician.

All the samples are well labeled with name of product, manufacturers address, expiry/manufacturing date and lot/batch numbers. Physical inspection of individual tablets showed no visible physical deterioration, capping or breakage.

The result of the visual inspection showed three supposedly different products of paracetamol tablets (PCM6, PCM9, PCM10) bear the same manufacturer address. The three samples do not bear any other similarity or semblance. The results of other parameters showed they are not identical though similar. The only reason that can be adduced for these is to increase the total volume of sales.

Uniformity of weight

The result of the uniformity of weight tests (see Table 2) indicated that all the samples (paracetamol aspirin, ibuprofen and diclofenac tablets) passed by their respective pharmacopoeia (BP 2010, IP 2006 and Indian Pharmacopoeia 1999) specification.

Table 2. Uniformity of weight of Paracetamol, Aspirin, Ibruprofen and Diclofenac tablets

	Paracetamol	**Aspirin**	**Ibuprofen**	**Diclofenac**
Number of batches	**Average/G (X/20)**	**Average/G (X/20)**	**Average/G (X/20)**	**Average/G (X/20)**
	PCM	ASA	**IBU**	**DICLO**
1	0.5978g	0.4505g	0.6124	0.3334
2	0.5818g	0.3138g	0.5165	0.4426
3	0.5595g	0.3776g	0.7156	0.2639
4	0.5853g	0.5398g	0.7274	0.3846
5	0.5540g	0.3115g	0.6158	0.3615
6	0.5808g	0.3637g	0.3108	0.1733
7	0.5977g	0.3501g	0.6056	0.3024
8	0.5447g	0.3669g	0.6909	0.2116
9	0.5673g	0.3432g	0.5003	0.1899
10	0.5780g	0.3539g	0.4850	0.2070
11	0.5788g	0.3427g	-	-
12	0.6225g	-	-	-
13	0.5465g	-	-	-
14	0.5730g	-	-	-

PASS- not more than 2 of the individual masses deviates from the average mass by more than 5% and none deviate by more than 10% (British Pharmacopoeia, 2010).

Disintegration test

Disintegration testing of paracetamol aspirin, ibuprofen and diclofenac tablets
The tablets of paracetamol and aspirin which were uncoated tablets passed the test (Table 3). Also the few uncoated tablets of Ibuprofen and diclofenac passed the test within the approved limits. However the disintegration time of about 10 minutes and 14 minutes for PCM 13 and PCM14 respectively are not desirable for analgesics that needed to act fast. For example, Paracetamol with a time to reach maximum concentration (Tmax) of 15 to 45 minutes will in this case be adding extra 14 minutes as 'lag time' in the absorption phase and consequently the bioavailability. Disintegration testing was not carried out for the coated tablets.

Table 3. Showing the Disintegration time (minutes) of the tablets of Paracetamol and Aspirin.

Number of batches	PCM	ASA
1	3:15	58sec
2	3:34	47sec
3	3:35	3:42
4	3:49	47sec
5	2:34	1:26
6	4:16	6.00
7	1:36	15sec
8	4:41	18sec
9	53sec	37sec
10	4:26	1:31
11	51sec	2:35
12	5:09	-
13	9:55	-
14	14:05	-

PASS-for uncoated tablets, disintegration should be within 15 minutes, (British Pharmacopoeia, 2010).

Degraded and Related substances
Detection of degraded and related substances by the TLC technique using iodine and the ultraviolet light, showed one sample of paracetamol –PCM12 to contain other spots other than the paracetamol spot. Also the paracetamol spot on the TLC is very small, indicating little or no paracetamol in sample.

Assay (% drug content determination) of Paracetamol samples
Eleven (11) of the fourteen (14) Paracetamol samples passed the percent drug content analysis with a range of 97 to 105%. All these samples passed the other test such as the Uniformity of weight and disintegration time; therefore they are most likely to release their drug content satisfactorily when used by patients. Three (3) samples of paracetamol PCM12, PCM13, PCM14, (representing 21.43% of total sample size) did not comply with the BP 2010 specification (Table 4). Two of the samples (PCM 12, PCM 13) contained less amount of paracetamol and deviated from the lower limit with 81% and 9.58% respectively, this however confirm the TLC result for sample PCM13 where there was virtually no spot shown. One sample (PCM10) contained quantities higher than the specification with a deviation of 10% from the upper limit.

Table 4. Table Showing the Percent drug content, the actual content per tablet, and deviation from pharmacopeia specification (DfPS) for Paracetamol, Aspirin, Ibuprofen, and Diclofenac.

Sample code /SN	% drug content	Actual content/tablet (**mg**)	% drug content	Actual Content/tablet (**mg**)	% drug content	Actual Content/tablet (**mg**)	% drug content	Actual Content/tablet (**mg**)
	PCM	PCM	ASA	**ASA**	IBU	IBU	DICLO	DICLO
1	101.0	504	96.0	288	98.7	394	97.4	97
2	97.2	485	99.6	299	87.9#	351	100.2	100
3	98.7	490	67.0#	201	95.8	383	88.0#	88
4	100.1	500	97.7	293	98.5	394	91.4	91
5	100.4	502	99.0	297	99.0	396	86.6#	86
6	103.9	519	98.1	294	56.1#	224	81.0#	81
7	105.5	527	104.2	312	101.5	406	94.2	94
8	99.2	496	68.0#	204	98.0	392	94.2	94
9	98.9	495	94.0#	282	99.3	397	93.6	94
10	115.5#	578	94.5#	284	87.5#	350	95.6	96
11	98.5	493	102.0	306	-	-	-	-
12	18.3#	491	-	-	-	-	-	-
13	85.9#	429	-	-	-	-	-	-
14	105.0	525mg	-	-	-	-	-	-
# Failed samples in %	21.43%		36.36%		30.00%		30.00%	

Specifications as required for each sample as per its pharmacopeia: Paracetamol ($C_8H_9NO_2$; 95 -105% BP), Aspirin ($C_9H_8O_4$; 95 -105% IP 2006), Ibruprofen ($C_{13}H_{18}O_2$; 90 -110% IP); Diclofenac ($C_{14}H_{10}Cl_2NNaO_2$; 90 – 110% IP).

Failed samples' (#) magnitude of deviation from the Pharmacopeia specifications (DfPS):
Lower limit '-' and Upper limit '+':
Paracetamol PCM10, +10%, PCM12, -81%, PCM13, -9.58%
Aspirin ASA3, -29.5%, ASA8, -28.4%, ASA9, -1.05%, ASA10 -0.5%
Ibruprofen IBU2, -2.3%, IBU6, -37.7%, IBU10, -2.8%
Diclofenac DICLO3, -2.2%, DICLO5, -3.8, DICLO6, -10%

Assay of aspirin tablets

All the aspirin samples complied with the IP 2006 specification except for four samples (ASA3, ASA8, ASA9 and ASA10) representing 36.36%, failure rate. However samples ASA9 and ASA10 marginal deviation (0.5% and 1.05% respectively) from the lower limit of specification might be due to degradation of the dosage form and not necessarily produced as counterfeit.

Assay of ibuprofen tablets

Out of the ten samples of Ibuprofen analyzed, seven samples complied with the IP 1999 specified limit of 90 -110%. Three of the samples, IBU2, IBU6, IBU10, representing 30% of total sample size did not comply with the pharmacopoeia specification. These samples deviated from the lower limit of the specification with, 2.3%, 37.7% and 2.8% respectively.

Assay of diclofenac tablets

Out of the ten samples of Ibuprofen analyzed, seven samples complied with the IP 1999 specified limit of 90 -110%. Three of the samples, DICLO3, DICLO5, DICLO6, representing 30% of sample size, did not comply with specification. These samples deviated from the lower limit of the specification with, 2.2%, 3.8% and 10% respectively.

CONCLUSION

The selected analgesics (Paracetamol, Aspirin, Ibuprofen, and Diclofenac) are available in pharmacies, medicine stores and with drugs peddlers in Monrovia, Liberia.

Visual inspections showed all the samples were appropriately labeled and fairly packaged. All the samples passed the Uniformity of weight and Disintegration tests. The presence of degraded/related substances was confirmed in one sample of paracetamol tablet (representing 7.14% of sample size). The following percentages of the samples did not comply with the respective pharmacopeias specifications for percent drug content, these are, Paracetamol 21.43%, Aspirin 36.36%, Ibruprofen 30.00% and Diclofenac 30.00%. Since all the samples are used as surrogate, the average failure is therefore 29.5%. Consequent upon this finding it can be said that the proportion of drugs below specification and in circulation in the market is about 30% as against the speculated 60%.

Finally, it was proven that most of the analgesics circulating in Liberia contained most of the recommended active pharmaceuticals ingredients.

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