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A Study of Quality Control of Yemeni Pharmaceutical Industries Products

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Abstract

The present study aimed to evaluate the drugs quality control of available in Yemen . The assessment of the quality of some Yemeni Pharmaceutical Industries products namely Paracetamol tablets 500 mg and Amoxicillin capsules 500 mg was based on United State Pharmacopoeia (USP) and European Pharmacopoeia (Ph. Eur.) The identification , dosage of active pharmaceutical ingredients and galenic tests of Paracetamol tablets and Amoxicillin capsules were performed . The results have shown high dosage of active component in some products which did not met the acceptance criteria in the USP (93%–107%) due to defects in the pharmaceutical production quality, and on the other hand the availability of good-quality another products. This could require setting up quality surveillance systems within drug regulatory authorities in the country, supporting manufacturers to improve Good Manufacturing Practice (GMP) compliance.

Keywords: Amoxicillin , Pharmaceutical Industries , Yemen .

1. Introduction

Drugs must be marketed as safe and therapeutically active formulations whose performance is consistent and predictable [1]. In a FDA and ICH (Food and Drugs Administration and International Conference on Harmonization) document, drug quality is defined as follows: “The suitability of either a drug substance or drug product for its intended use. The main role of nationals laboratories of drugs quality control is to ensure the safety, quality and efficacy of medicinal products and prevent harm to patients [2]. On other hand the increasing globalization of the pharmaceutical industry is a well-recognized phenomenon. In parallel to worldwide development of medicinal products for use, there has been a growing impetus to harmonize the requirements for registering these products with regulatory provisions in different regions [3,4]. Therefore, drug regularity authorities in developing countries must update the instruments for drugs analysis and develop a system of quality assurance namely the tools to audit on pharmaceutical manufacturing process. In Yemen, drug registration is overseen by the Supreme Board of Drugs and Medical Appliances (SBD&MA). There are two national reference laboratories for drug quality control, one in Sana'a and the other in Aden [5]. This study aimed at assessing the quality of the common drugs namely Paracetamol tablets 500 mg and Amoxicillin 500 mg as cases study to evaluate the quality control of Yemeni pharmaceutical Industries (YPIs) products .

2. Materials and Methods

2.1. Chemical

Paracetamol and Amoxicillin were obtained from were obtained from (Laboratoire National de Contrôle des Médicaments "LNCM" – Rabat) as certified internal standards. Methanol and acetonitrile were of HPLC grad from Sigma - Aldrich (Germany) . Potassium hydroxide were supplied by Merck KGaA (Ger\ many). Monobasic potassium was obtained by Riedel – de Haeri (Germany) .

2.2. Apparatus

The chromatographic system based Perkin (USA). Dissolution Test of Hanson SR8-Plus™ (USA) and UV–Vis spectrometer of Perkin - Elmer (USA). Friability Test, Hardness Tester and Disintegration Tests.

2.3. Study Design and Study Area

This pilot study was conducted in 7 selected YPIs available in Sana'a where Paracetamol and Amoxicillin remain commonly used medications and available at all industries .

2.4. Samples Collection

The samples namely Paracetamol tablets 500 mg and Amoxicillin capsules 500 mg (different manufacturers) were collected randomly at various levels of the drug distribution chain, such as pharmacies, manufactures , suppliers at the capitals of the countries involved in this study. The drugs list in Table 1 . The samples were diagnosed and evaluated in accredited laboratory with ISO 17025 namely Drugs Quality Control Laboratory of Rabat. The study adopted according to USP and Ph. Eur .

2.5. Identification and Dosage

The contents of Paracetamol in tablets 500 mg and the content in amoxicillin in capsules 500 mg which are manufactured by YPIs were identified and quantified by High performance liquid chromatography (HPLC) method [6] .

2.5.1. Identification and Dosage of Paracetamol

Prepare a suitable degassed mixture of water and methanol (3:1) which are used as mobile phase . Dissolve an accurately weighed quantity of USP Paracetamol RS in mobile to obtain a solution having a known concentration about 0.01 mg per ml. Weight and finely powder not fewer than 20 tablets. Transfer an accurately weighed portion of powder, equivalent to about 100 mg of Paracetamol , to a 200-ml volumetric flask, add about 100 ml of mobile phase , shake by mechanical means for 10 minutes , sonicate for about 5 minutes , dilute with mobile phase to volume , and mix. Transfer 5.0 ml of this solution to a 250-ml volumetric flask, dilute mobile phase to volume , and mix. Pass a portion of this solution through a filter having a 0.45-µ . The liquid chromatography is equipped with a 243-nm detector and a 3.9-mm ×30-

cm column that contains packing L1. The flow rate is about 1.5 ml per minute. The Procedure-separately inject equal volumes (about 10µl) of the standard preparation and the assay preparation into the chromatography , record the chromatogram , and measure the response for major peaks .

2.5.2. Identification and Dosage of Amoxicillin

Prepare a suitable filtered mixture of diluent (Dissolve 13.6 g of monobasic potassium phosphate in 2000 ml water , and adjust with a 45 % (w/w) solution of potassium hydroxide to a pH of 5.0 ± 0.1.) and acetonitrile (94:4) which is used as mobile phase .Remove , as completely as possible , the contents of not fewer than 20 capsules , and weighed quantity , equivalent to about 200 mg of anhydrous Amoxicillin , to a 200-ml volumetric flask , and diluent to volume , and mix . Sonicate if necessary to ensure complete dissolution .Pass a portion of this solution through a suitable filter having a 0.45 -µm. The liquid chromatography is equipped with a 230-nm and a 4-mm × 25-cm column that contains packing L1. The flow rate is about 1.5 ml per minute. The Procedure-separately inject equal volumes (about 10µl) of the standard preparation and the assay preparation into the chromatography , record the chromatogram , and measure the response for major peaks .

2.6. Dissolution Tests

2.6.1. Dissolution Test of Paracetamol Tablets 500 mg

The dissolution rate studies on conventional Paracetamol tablets 500 mg were carried out according to USP paddle method (Apparatus 2), at a stirring rate of 50 rotation per minutes (rpm) for 30 minutes. The dissolution medium was 900 ml of buffer 5.8 at 37 ± 0.5 C ° . Determine the amount of dissolved from UV absorbance at wavelength of maximum absorbance at about 243 nm of filtered portions of the solution under test . If necessary, suitable dilution with Dissolution Medium was used in comparison with a Standard solution having a known concentration of Paracetamol RS in the same standard [6].

2.6.2. Dissolution Test of Amoxicillin Capsules 500 mg

The dissolution rate studies on conventional Amoxicillin capsules 500 mg were carried out according to USP paddle method (Apparatus 2), at a stirring rate of 100 rpm for 45 minutes. The dissolution medium was 900 ml of distilled water at 37 ± 0.5 C ° . Determine the amount of dissolved from UV absorbance at wavelength of maximum absorbance at about 343 nm of filtered portions of the solution under test . If necessary, suitable dilution with Dissolution Medium was used in comparison with a Standard solution having a known concentration of Amoxicillin RS in the same standard [6] .

2.7. Disintegration Tests

The disintegration test is a method to determine the resistance or disintegration of solid preparations for internal use in the test fluids . The disintegration studies on conventional Paracetamol tablets and Amoxicillin capsules were carried out according to (Eur.Ph) basket method. The disintegration medium was 800 ml of distilled water at 37 ± 0.5 C ° for 15 minutes [7] .

2.8. Hardness and Friability Tests

This is to determine the physical strength of tablets upon exposure to mechanical shock, attrition and weight loss. The test was performed using a hardness tester on 10 tablets from each brand. Ten tablets from each brand were also weighted and put into the friabilitor. Tablets were rotated at 25 rpm, and then the friability percentage was calculated for each batch [7].

2.9. Data analysis

These analytical methods need verification of system suitability (revalidation or partial validation) , the method's pharmacopeia (reference method) for quality control of drug substance isn't formal partial validation required based on EP concept, while these methods for quality control of drug product need revalidation based on EP and USP requirement. The descriptive statistic (mea, standard deviation (SD) , relative stanadard deviation (RSD) were carried out to analysis the data obtained [6-8].

3. Results

The results of dosage of Paracetamol content in tablets and Amoxicillin content in capsules produced by YPIs were reported in Tables 1 and 2. The content of Paracetamol tablets was found to be within normal range of USP (93 % - 107 %) in YPIs A, D and E namely 101.5 % , 103.7 % and 97.2 % respectively and the overdose in B and C namely 121.6 % and 109.4 % respectively. While the results of Amoxicillin content in capsules were found, the overdose in products of YPIs B and G namely 110.9 % and 111.0 % respectively and the results of products of YPIs A , C and F (99.5 %, 97.7% and 104.1 % respectively) showed according to USP norm (93 % - 107 %) . On the other hand, the dissolution percentage of Paracetamol within 30 minutes and Amoxicillin within 45 were confirmed for all YPIs products according to USP (Not less than 80 % (Q) of the labelled amount of Paracetamol). The disintegration time for all Paracetamol tablets and Amoxicillin were within the pharmacopoeial range (≤15 min) (See Table 4). The results of friability showed the conformity of products according to pharmacopeial norm except the friability of Paracetamol of Pharmaceutical Industry A more than 1 % due to low quality packaging system. (See Table 5) .The hardness of the tablets were assessed and the results are shown in Table 5. Differences in tablets hardness of some batch are due to the differences in the process of tablets manufacturing mainly the compression force. In general, the tablets hardness was neither low to become friable nor high to affect the disintegration and dissolution of products. The highest and lowest values of hardness were found in Paracetamol of YPI E (168.1) and Paracetamol of YPI B (86.2), respectively.

Table 1: Yemeni Pharmaceutical Products

Manufactures	Paracetamol	Manufactures
A	500 mg	500 mg
B	500 mg	500 mg
C	500 mg	500 mg
D	500 mg	500 mg
E	500 mg	500 mg

Table 2 : Dosage and Dissolution of Paracetamol Tablets

Manufactures	Dosage of Active Ingredient				Dissolution Rate		
	Assay mg	Assay %	SD	RSD%	Q – Value %	SD	RSD %
A	507.52	101.5	1.79	1.76	99.10	5.054	5.09
B	608.36	121.6	5.92	4.86	88.85	5.57	2.95
C	547.39	109.4	0.33	0.30	90.74	2.68	2.90
D	518.60	103.7	0.19	0.18	90.40	7.83	8.26
E	486.94	97.2	1.99	2.04	101.55	2.88	2.83

SD : Standard Deviation RSD : Relative Standard Deviation

Table 3 : Dosage and Dissolution of Amoxicillin

Manufactures	Dosage of Active Ingredient				Dissolution Rate		
	Assay mg	Assay %	SD	RSD %	Q – Value %	SD	RSD %
A	497.50	99.5	0.47	0.48	85.49	3.06	3.57
B	554.93	110.9	0.37	0.33	88.89	2.93	3.29
C	488.58	97.7	1.93	1.98	83.80	2.29	2.73
D	520.63	104.1	1.12	1.07	85.28	1.83	2.14
E	555.33	111.0	0.17	0.15	83.13	2.31	2.77

RSD of Dosage : ≤ 2.5 . RSD of Dissolution : ≤ 10.

Table 4 : Disintegration of Paracetamol Tablets and Amoxicillin Capsules

Manufactures	Disintegration			Amoxicillin	Disintegration		
	Mean	SD	RSD %		Mean	SD	RSD %
A	1.18	0.12	10	A	9.49	1.23	12.9
B	1.30	0.28	21	B	7.81	2.97	38.0
C	0.55	0.29	52.7	C	5.47	0.81	14.8
D	1.41	0.00	0.00	F	7.56	1.24	16.4
E	1.18	0.10	8.0	G	9.36	2.84	30.3

Table 5: Hardness and Friability Tests of Paracetamol Tables

Manufactures	Hardness			Friability
	Mean	SD	RSD %	< 1 %
A	152.1	31.76	20.8	**1.53**
B	86.2	6.62	7.67	**0.14**
C	145.3	13.32	9.16	**0.29**
D	127.7	7.66	5.99	**0.45**
E	168.1	12.93	7.69	**0.10**

(n) : Newton

4. Discussion

The results proved that some YPIs have good quality because these are staffed by qualified persons who are fully equipped for performing all the quality control tests required. The tests are performed in accordance with validated procedures delivered from British Pharmacopoeia (BP) , USP and Ph. Eur or developed by quality control staff [9,10]. The production in these industries depends on GMP guideline. On the other hand, the results showed high dosage of active component in some products and these figures suggest a significant problem of overdose in some Yemeni Pharmaceutical Industries. In the samples below, the main problem seemed to be the upper limit of specification. These high dosage in Paracetamol namely B 121.6 % (608.36 mg) and product C 109.4% (547.39 mg) and Amoxicillin namely product B 110.9 % (554.93 mg) and E 111.0 % (555.33 mg) do not represent a risk for the patient but overdose in other pharmaceutical products by YPIs constitute a risk for the patient. This problem may be due to non-compliance with Good Manufacturing Practice (GMP) guidelines by manufacturers in the production of the Paracetamol and Amoxicillin such as poor homogeneity mixing before tablets compression, and capsules filling or inferior qualification of instruments [11]. In general, the quality of products is achieved in some YPIs and is not in others. The problem of quality failure often occurs in poor- resource countries lacking effective drug regulatory agencies and proper drug quality testing laboratories. A drug quality assurance system relies on the ability to identify counterfeit or poor quality pharmaceuticals. Also, National Drugs Quality Control Laboratory is required to keep a check on pharmaceutical industries machineries and equipments. The main responsibilities and priorities of the laboratory are to ensure an updated check of the equipments . The laboratory has the authority to approve or reject all closures, in-process materials, components, labelling, drug product containers, packaging material and drugs. Moreover, the laboratory can control the review production records to assure that no errors have occurred. If errors have occurred, they are completely investigated and sorted out. Apart from certain authorities, drugs quality control laboratory has also certain responsibilities to handle, reject or approve drug products manufactured [12,13]**.** In comparison with previous studies were carried out for products marketed in Yemen , there are substandard antimalarial , calcium products circulating within the drug distribution chains in Yemen, which will have serious implications on the reduced therapeutic effectiveness and on the development of drug efficacy [5,14,15,16] **.** The Supreme Board of Drugs and Medical Appliances of Yemen (SBD&MA) must play an important role in post–marketing control and assessment of the pharmaceutical products as a permanent control.

4. Conclusion

Overdose has been observed in some Paracetamol tablets and Amoxicillin capsules manufactured by some YPIs. This appears to be due to non-compliance in production with GMP guidelines by manufacturers. This could require setting up quality surveillance systems within drug regulatory authorities in the country, supporting manufacturers to improve the GMP compliance. Pharmaceutical products in the market in the post–production stage as (Pharmacy, Wholesaler and Pharmaceutical Industries) need a permanent quality control. National authority must ensure quality, safety and efficacy of human medicines and other health care products through the regulation and control of their production, importation, distribution and use .

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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