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Quality of Ampicillin Preparations on the Kenyan Market

F.N. KAMAU, G.N. THOITHI AND I.O. KIBWAGE*

Drug Analysis Research Unit, Department of Pharmaceutical Chemistry, University of Nairobi, P.O. Box 19676 Nairobi
E-mail daru@uonbi.ac.ke.

Ampicillin products, 20 capsules, 2 tablets and 23 dry suspensions were evaluated for quality by liquid chromatography at the Drug Analysis Research Unit University of Nairobi. Four capsule formulations failed limits on content. The Ampicillin content in 5 suspensions dropped below 80% on storage at 25^{0}C for 7 days. The pH of most suspensions dropped on storage, but had no correlation to decrease in chemical content.

Key Words: Ampicillin, formulations, pH and quality.

INTRODUCTION

Ampicillin is a semi-synthetic penicillin used in the management of infections caused by sensitive microorganisms. Microbial resistance against ampicillin is well documented and cross-resistance is a common problem among the penicillins. Development of resistance is always associated with exposure of microorganisms to sub-lethal levels of drugs. The quality of drugs administered and especially low content of ampicillin in a dosage form could therefore contribute to the development of resistance.

Work on the quality of drugs in the period 1982 to 1992 has shown presence of poor quality penicillin products in the market [1-4]. This observation was recently reinforced by the findings on quality of phenoxymethylpenicillin syrups [5]. The extensive use of ampicillin in Kenya as one of the drugs on the essential drugs list of the Ministry of Health [6] led to observed increase in resistance. It was recently replaced by amoxycillin.

This communication presents findings on the quality of ampicillin capsules and tablets and dry syrups found on the Kenyan market using liquid chromatography (LC). The preparations were from private and public sources including those submitted to the Ministry of Health drug regulatory authority. The latter are intended for marketing in Kenya after registration, and for the purpose of this paper are treated as being on the market.

EXPERIMENTAL

Samples and standards

Working standard of ampicillin trihydrate was donated by Cosmos Ltd. Nairobi, Kenya. The sample had a content of 98.84% (anhydrous basis) when assayed against World Health Organization (WHO) reference standard (C. No. 274003) using LC.

The ampicillin preparations evaluated over a period spanning 8 years from 1992 - 2000 were commercial packs purchased in local pharmacies, donated by public hospitals or obtained through the office of Registrar, Pharmacy and Poisons Board, Ministry of Health, Kenya.

Locally Manufactured Products were from Dawa Pharmaceuticals Ltd., Elys Chemical Industries Ltd., Laboratory and Allied Ltd., Cosmos Ltd., and Howse & McGeorge Ltd., all of Nairobi, Kenya.

Imported Products were from Mesco Laboratories Ltd., and Cadila Laboratories Ltd., both of

* Author to whom correspondence should be addressed

Bombay, India; Hoechst Ag., (Germany), Rivopharm Laboratories, (Switzerland), Teva Pharmaceuticals Ltd, (Israel), and Smithkline Beecham, (UK).

Reagents and solvents

HPLC grade Methanol and acetonitrile were purchased from Rathburn chemicals (Walkerburn, Scotland, U.K.). Analytical grade potassium dihydrogen orthophosphate and di-potassium hydrogen orthophosphate (E. Merck, Germany) were used.

1.3 Instrumentation

The liquid chromatographic system consisted of Gilson 305 solvent-delivery system, a Gilson 115 ultraviolet detector (Gilson, Villier le Bel, France) set at 254nm, a Valco model CV-6-UHPa-N60 sampling valve (Valco, Houston, Tx, USA) equipped with a 25 µl loop and a Hewlett Packard model HP 3394 integrating recorder (Hewlett Packard, Avondale, PA, USA). A column of 25 cm x 4.6 mm packed with Rsil C_{18} 10 µm (Bio - Rad RSI , Eke, Belgium) was used and was maintained at 40° using a water bath.

1.4 Methods

1.4.1 Mobile Phase

The mobile phase consisted of methanol-acetonitrile - 0.05M phosphate buffer pH 5.0 - water (15:5:10:70, v/v) and was degassed by ultrasonication for 3 minutes before use. The flow rate was set at 1.0 ml/min.

1.4.2 Ampicillin Standard solutions

About 115-175 mg ampicillin trihydrate standard was accurately weighed into a 10 ml volumetric flask, dissolved in, and made to volume with distilled water. An aliquot (4.0 ml) of this solution was transferred into a 25 ml volumetric flask and made to volume with distilled water to make a Yug/ml solution.

1.4.2 Ampicillin Sample solution

Capsules and Tablets

Powder equivalent to 125-mg ampicillin was accurately weighed into a 100-ml volumetric flask. This was dissolved in and made to volume with water and filtered through a 0.45 µm membrane filter. 4.0 ml of the filtrate was transferred into a 25-ml volumetric flask and made to volume (Z µg/ml).

Dry suspensions

Powder for ampicillin suspensions was reconstituted with distilled water, following the manufacturer's label instructions. The reconstituted volume and pH of the suspension were determined after sonication to remove air bubbles. A volume of suspension equivalent to 125 mg ampicillin was pipetted into a 100 ml volumetric flask rinsing the pipette with water.

The volume was made to the mark with water and filtered through a 0.45 µm membrane filter. An aliquot (4.0 ml) of the filtrate was used to prepare sample solution as described for the standard solution.

RESULTS

Data analysis

Direct comparison of peak areas with those of the standard were used for quantitation.

The chemical content of 20 ampicillin capsules and 2 tablet products were evaluated and are shown in Table 1. The pharmacopoeal limits (7) of ampicillin content expressed as a percentage of label claim are 92.5-107.5. Products IIa, IIIa, IIIb1 and VIIIa were above the limit and thus failed.

Table 2 shows the pH and ampicillin content as determined on day 0 and day 7 for the different ampicillin suspensions examined. Two products, Ia and XIIa, were above the upper limit of 120.0% specified by the pharmacopoeia, while XIIb was below the lower limit of 80%. On storage for 7 days at 25°C, the ampicillin content of IVb, Va and VIc fell below from acceptable limits of 80%. The content of XIIa fell drastically from 127.2% to 78.1% of the label claim. The content of sample XIIb did not change within 7 days. Ampicillin suspensions are normally buffered to maintain stability once reconstituted.

TABLE 1: Ampicillin content of some ampicillin Capsule and tablet products

Product	Ampicillin content as % label claim
Ia	105.4
Ib	105..5
IIa	109.9
IIb	95.6
IIIa	107.6
IIIb1	110.0
IIIb2	96.0
IV b	106.7
Va	
Va	95.2
Vb	98.6
VIb	100.1
$VIIa_1$	100.6
$VIIa_2$	102.1
VIIb	99.6
VIIIa	107.8
IXa	104.6
Xa	96.2
Xb	98.9
XIa	99.1
XIIa	106.5
XIIIa	106.9

a: 250 mg strength, b: 500 mg strength

a_1, a_2: different batches from the same manufacturer. Ditto b_1, b_2

I - XIII = Different manufacturers

I - XI: capsule formulations. XII and XIII are tablet formulations.

The recommend pH range of 4.0-7.0 was achieved in all cases. For most of the suspensions examined there was a drop in pH on storage except for XIIa. The pH drops had no correlation to the decrease in chemical content.

The effects of storage temperature on the pH of the suspensions, during a 7-day period, was investigated and the results are shown in Table 3. There was observed a general drop in pH at all storage temperatures. The drop in pH increased with increase in temperatures except for IVa and IVb. The changes in pH were recorded as percentage drop in relation to the initial pH. Table 3 shows the percentage drop in pH after storage for 7d at different temperatures.

TABLE 2: Ampicillin content of some ampicillin oral suspensions

Product	Unit (ml)	pH at 25°C (storage days)		Ampicillin content % label claim (storage days)	
		Day O	Day 7	Day O	Day 7
Ia	100	6.06	5.63	188.0	n.d
Iia	100	n.d	n.d	115.0	n.d
IIIa	100	5.90	5.40	99.3	82.1
Iva	100	5.16	4.86	94.5	90.5
IVb	100*	4.82	4.52	90.7	77.9
Va	60	6.38	5.94	95.7	67.6
Vb	100*	6.16	5.72	?	?
Via	100	6.59	5.99	100.8	82.3
Vib	100	?	?	98.7	90.1
Vic	100	6.73	6.01	85.7	68.8
VIIa	100	6.33	5.91	99.9	91.7
VIIIa	100	6.44	5.96	104.9	97.3
Ixa	100	n.d	n.d	85.6	n.d
Ixb	100	n.d	n.d	126.8	n.d
Xa	100	n.d	n.d	104.3	n.d
Xb	100	n.d	n.d	96.5	n.d
Xia	100	5.57	n.d	114.8	106.8
XIb	100	5.64		113.1	104.8
Xic	100	5.56	n.d	n.d	n.d
Xid	100	5.57	n.d	106.3	106.3
Xie	100	5.58	n.d	107.8	102.4
XIIa	100	5.78	5.96	127.2	78.1
XIIb	100*	5.05	4.95	66.4	66.4

All suspension had a label strength of 125 mg/5ml except those with an asterisk* which had strength of 250 mg/5ml.

a - e represent different batches from the same manufacturer.

I - XII = Different manufacturers

n.d = not determined[1]

A comparison of pH for products IIIa and XIIb shows that the strength of the suspension has no effect on the extent of pH change on storage.

The drop in pH varies between 10.2% for product Va and 4.1% for IVb when the samples are stored at 25°C for 7 days.

Increase in storage temperature showed a rough correlation to drop in pH.

Products Iva and IVb Have the least pH drop of 4.3 and 8.1 respectively for 125mg/5ml and 250mg/5ml suspensions over the whole range of temperatures.
product IIIa.

TABLE 3: Percentage drop in pH reconstituted suspensions after storage for 7 days at different temperatures

Product	Initial pH	% drop in pH at different storage temperature			
		25°C	30°C	35°C	45°C
IIIa	5.90	8.0	9.7	13.6	21.4
IVa	5.16	5.8	10.6	7.8	8.1
IVb	4.63	4.1	4.3	3.5	4.3
Va	6.38	6.9	8.9	13.3	20.7
VIa	6.59	9.1	11.4	23.1	17.3
VIb	6.64	10.2	11.4	15.8	18.7
VIIa	6.33	6.6	8.2	12.5	16.9
VIIIa	6.44	7.5	9.5	14.0	19.6
XIIa	5.78	6.2	8.1	11.9	19.4

Suspensions had a labeled strength of 125 mg/5ml, except those indicated by b, which had strength of 250 mg/5ml.

Storage at 45°C for 7 days gave pH drop of between 4.3% for product IVb, and 21.4% for products. These two extremes represent preparations of 125mg/5ml and 250 mg/5ml from different manufacturers.

DISCUSSION

The results show that out of 20 capsules and 2 tablet Ampicillin products, four capsule products IIa IIIa IIIb1 and VIIIa had a chemical content exceeding the upper limit of 107.5% set by BP.

Product XIa was submitted to Ministry of Health for registration. The capsule, colour and size were the same as for Xib (500-mg strength). However they were presented in a container labeled 250mg ampicillin capsules.

Products Ia and Ib exhibited wide variation in fill weight, but still passed the stipulated requirements of the B.P. These products are manufactured by the same manufacturer. The capsule filling machine and equipment of this manufacturer would require re-calibration and closer scrutiny during a production run.

The content of ampicillin in oral suspensions is specified not to exceed 120% label claim on reconstitution. However on storage for 7 days, the drop in content should not be lower than 80% of the label claim. In this regard products IVb, Va, VIa, XIIa and XIIb failed the requirements. All these products are also presented in 100ml bottles.

Ampicillin suspensions are normally buffered to maintain stability once reconstituted. The observed drop in pH of suspensions on storage at different temperatures indicate the effect of this buffering to be variable. The pH drop of investigated suspension products was found to be between 4.1 and 10.2% when stored at 25°C. The quality of water used could also have an effect on chemical stability of the suspensions. This aspect is under investigation.

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