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COMPARATIVE *IN-VITRO* QUALITY EVALUATION OF ERYTHROMYCIN STEARATE TABLETS MARKETED IN ADDIS ABABA, ETHIOPIA

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ABSTRACT

In this study, an attempt was made to assess the physicochemical equivalence of four brands of Erythromycin stearate tablets marketed in Addis Ababa. Identity, weight uniformity, disintegration, dissolution and assay for the content of active ingredients were evaluated using the methods described in the British Pharmacopoeia 2007. All the samples passed the identity, disintegration, and dissolution tests but Erythromycin stearate (Produced in Sudan by General Medicines Company) failed to release 80% of the drug content within 45 minutes. It also failed to fulfill the tolerance limits for assay stipulated in the pharmacopoeia. This product therefore does not comply with the BP 2007 dissolution and Assay tolerance limits. This work revealed that the four products included in the study complied with the physicochemical quality parameters except Erythromycin stearate which failed to meet the pharmacopoeial specification for dissolution test and assay.

INTRODUCTION: Erythromycin is a broad-spectrum macrolide antibiotic, which is often used for the treatment of upper and lower respiratory tract infections primarily caused by gram-positive microorganisms. It has some use for certain sexually transmitted diseases such as gonorrhea, which is caused by mixed infections involving cell wall free organisms like *Chalimidia trachomitis*. It is also very widely used in patients sensitive to penicillin's [1, 2].

The quality of some medicinal drugs available in many third-world countries is found to be inadequate. This poor quality of drugs has been linked to counterfeiting of medicines, chemical instability especially in tropical climates, and poor quality control during production [3]. The subject of overall drug quality has been addressed in several World Health Organization (WHO) publications. Several countries have their own definitions as to what constitutes a counterfeit drug and there is no consensus. This poses a problem in that what may be considered a counterfeit product in one country will not necessarily be so in another country. The WHO has defined counterfeit drugs as those that are deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging [4, 5].

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According to the WHO guidelines, factors that influence the prevalence of counterfeit drugs in any particular country include weak or absent of drug regulatory authority, absence of a legal mandate for licensing of manufacture/import of drugs, lack of regulation by exporters and within free trade zones, proliferation of small pharmaceutical industries, complex transactions involving many intermediaries, high demand for curative and preventive drugs and vaccines exceeding supply, high prices and inefficient cooperation among stakeholders. The WHO Essential Drug Program has failed in most countries because of personal financial interests at local, national and foreign levels as well as a black market [4].

Studies indicate that a country's capacity to restrict dangerous drugs depends heavily on its wealth. It is alarming that almost a third of WHO member countries have poor means of controlling counterfeit medications. In these circumstances, the market for counterfeit and substandard drugs becomes a lucrative one. In addition, lack of good manufacturing practices (GMP) is common in local pharmaceutical industries in most developing countries because of many hurdles such as frequent power cuts and shortage of water. In addition to the existence of substandard drugs, assurance of the stability of pharmaceuticals marketed in developing countries (most of which have tropical climates) is a challenging issue as poor storage conditions, high temperature and high humidity conditions generally enhance chemical degradation and may alter the biopharmaceutical properties of the drugs [6-8].

Although practically all types of pharmaceutical products have been shown to be involved, existing data suggests that anti-infective agents, particularly antibiotics and antiparasitic agents used in life-threatening conditions such as malaria, tuberculosis and HIV/AIDS are the most counterfeited products in developing countries [5, 9].

Marketing poor quality and counterfeit drugs has been widely reported in Africa, Asia, and Latin America. WHO has been collecting reports of counterfeit pharmaceuticals since 1982. There were 771 reports from 1982 to 1999 and 46 more reports were received between 1999 and 2000. Of the reports 60% came from developing countries even though there is gross under-reporting. Distribution of the reported cases of counterfeit medicines, from 1999 to 2002, categorized therapeutically was as follows: antibiotics 26%, hormones and steroids 18%, anti-asthmatics and anti-allergy 8%, antimalarials 7%, analgesics and anti-pyretics 6%, others (14 therapeutic categories) 33% [5].

The results of a study done at the Department of Pharmacy of the University of Nairobi showed that 46% of locally manufactured products were substandard when active ingredients were measured by compendial methods. In another study, which assessed the quality of different preparations of antimalarial and antibacterial drugs obtained from retail outlets in Nigeria and Thailand, investigators reported an appreciable proportion of substandard samples [3].

In Ethiopia and elsewhere, high rate of prevalence of antibiotic resistance including erythromycin have been reported [10-13]. Other studies also document less rate of resistance prevalence to erythromycin and recommend it to be reserved for serious cases [14, 15]. Besides other possible causes of resistance the quality of Erythromycin is obviously a significant contributor for such resistance development. Hence, the aim of this study is to evaluate the chemical and physical equivalence of imported and locally manufactured erythromycin stearate tablets available in drug retail outlets of Addis Ababa, Ethiopia.

MATERIALS AND METHODS:

Materials and Reagents: Erythromycin stearate tablets produced by different manufacturers were collected from various drug retail outlets in Addis Ababa (**Table 1**). Chemicals and reagents used were of analytical grade. Methanol [99.8%], acetone [99.5%], hydro-chloric acid [35.4%], chloroform [99-99.4%], distilled water, 0.1 M sodium hydroxide, 10% w/v solution of calcium chloride, buffer solution pH 8, sodium acetate, glacial acetic acid [99.8%], erythromycin stearate working standard, erythromycin stearate reference standard, 0.5 % w/v solution of 4-dimethylamino benzaldehyde in glacial acetic acid, *Micrococcus lutus* (ATCC 9341), antibiotic assay medium number 11 and (seed and base agar), mixture of 35 volumes of glacial acetic acid [99.8%] and 70 volumes of hydrochloric acid [35.4%] were employed to perform the required experiments.

Equipments used in the study: It includes UV- visible spectrophotometer (PERKINELMER, Model-Lamda 25), dissolution tester USP (ELECTROLAB, Model- ED- 2L), tablet hardness tester (KARNAVAT ENGINEERING LTD, Model-K-DHT100), disintegration tester USP (ELECTRO-LAB, Model-EFD-2L), incubators (THERMOLAB SCIENTIFIC EQUIPMENTS PVT LTD, Ser no 752 and 748/ 02/0506), laminar air flow bench (DYNA FILITERS PVT LTD), autoclave (EQUTRON: Model-7451FASP3P), inhibition zone reader (CINTEX: Model-CIC 89), sonicator (BRANSONIC: Model-3510E-MT), top loading balance (Sartorious: Model-225D), analytical balance (Sartorious: Model-TE212), Infrared Spectrophoto-meter, 100 ml volumetric flasks, sterile pippets, petridishes, sterile borer or assay cylinder, sterile test tubes, sterile tips, micropipets.

Methods: The quality of tablets was assessed according to BP 2007 and USP 2007 [16, 17]. The quality of the samples was examined with respect to six aspects. All the samples analyzed were within their shelf life at the time of investigation**.**

Identification test: Three identification tests for erythromycin stearate used in this study are indicated in BP 2007 as:

1. To a quantity of the powdered tablets containing the equivalent of 0.1g Erythromycin stearate, 10 ml of water was added and the solution was shaked well. The supernatant liquid was discarded and the residue was extracted by shaking with 10 ml of methanol, then after filtering the extract, it was evaporated to dryness. The infrared absorption of the residue after drying at a pressure not exceeding 0.7 KPa was compared with the reference spectrum of erythromycin stearate.
2. A quantity of the powdered tablets containing the equivalent of 3 mg of erythromycin stearate was dissolved in 2 ml of acetone and 2ml of hydrochloric acid was added into it and the color produced was noted. Then 2 ml of chloroform was added into it and shaked. Then the colour produced was noted.
3. A quantity of the powdered tablets containing the equivalent of 50 mg of erythromycin was extracted with 10ml 0f chloroform. The solution was filtered and evaporated to dryness. Then 0.01gm of the residue was heated gently with 5ml of 2M hydrochloric acid and 10 ml of water until the solution boils. Then the observation was noted. The solution was cooled and the fatty layer was removed. The solution was heated with 3 ml of 0.1 M sodium hydroxide and allowed to cool. Into the gel formed, 10 ml of hot water was added and shaked. Then to 1ml of the solution a 10 % w/v solution of calcium chloride was added and the observation was noted

Physical tests: Hardness or crushing strength, disintegration, weight variation, and dissolution tests of Erythromycin stearate tablets were determined according to the procedures specified [16]. The British Pharmacopoeia states that Erythromycin stearate tablets should release 80% of the labeled claim within 45 minutes using BP type II dissolution apparatus. Concentration of the sample diluted with the dissolution media was determined spectrophoto-metrically at 485 nm [16].

Chemical Assay: Amount of active ingredient in each of the study sample was determined following the bioassay method given in BP 2007. Results are expressed as the percentage of the labeled claim.

TABLE 1: DETAILS OF ERYTHROMYCIN STEARATE TABLETS EVALUATED IN THE STUDY

Product name	Package	Batch no.	Mfg. Date	Exp. Date	Manufacturer	Country of Origin
Erycin (500mg)	Blister	B239	09/08	08 /11	Flamingo pharmaceuticals limited co.	India
Etocin (250mg)	Blister	D9008BXY62	04/09	03/ 12	Cadila , Ethiopia	Ethiopia
Rythro (250mg)	Blister	RD5012	10/07	09 /10	SB Smithkline Beecham	India
Erythromycin stearate (250mg)	Blister	116	02/08	09 / 12	General medicines company	Sudan

RESULTS AND DISCUSSION:

Identification Test: All tablets showed positive results of identification test as per the specification of BP 2007. The infrared absorption of spectrum of all the samples was concordant with the reference spectrum of Erythromycin stearate reference standard. All the four tablets comply with the remaining two identification tests specified for Erythromycin stearate.

Physical Tests:

Hardness and Disintegration: Results of hardness and disintegration tests are summarized in **table 2**. All the samples of erythromycin stearate included in the study passed the hardness test but there is large difference in crushing strength of the products. The great variation in the crushing strength between the tablets could be due to the fact that the manufacturers utilized different types of excipients or compression techniques. Generally conventional compressed tablets that have crushing strength or hardness greater than 50 N are considered to be acceptable [18]. The disintegration test data showed that out of the four tablets investigated Erythromycin stearate (Sudan) did not comply with the USP and BP specification. There are different factors that affect disintegration time of a tablet like type of binder; lubricants used, compression force applied during manufacturing. When disintegration is slow the dissolution process will be slow as disintegration is a rate limiting step for dissolution.

TABLE 2: SUMMARIES OF THE PHYSICAL PARAMETERS OF THE STUDIED ERYTHROMYCIN STEARATE TABLETS

Product name	Hardness (N) ± SD	Disintegration time (min) ± SD	Average weight ± RSD (g)
Limits for the tests	>50 N	< 15 minute	
Ethocin	146.0 ± 4.8	1.56 ± 0.6	580 ± 0.39
Erycin	121.1 ± 7.0	1.09 ± 0.2	891 ± 0.63
Rythro	86.5 ± 17.5	2.10 ± 0.9	454 ± 1.3
Erythromycin stearate	145.7 ± 12.9	15.21 ± 2.2	621 ± 1.2

Weight Variation Test: BP specifies that no more than two of the individual tablet weights deviate from the average weight by more than 5 % and none should deviate by more than 10%. As can be seen from the results in table 2, none of the tablets used in the study deviate from the average weight by more than 5% and hence passed the pharmacopeia specification (BP 2007 and USP 2007). Thus, all products fulfill the dosage unit uniformity requirement.

Dissolution Profile Studies:

Calibration curve: A stock solution was prepared from a reference standard and different concentrations were prepared from the stock solution by serial dilution. Absorbance was measured at 485 nm against a blank for each diluted solution and values obtained were used to prepare the calibration curve (**table 3**).

TABLE 3: SERIALLY DILUTED SOLUTION PREPARATIONS AND THEIR ABSORBANCE

Conc.(µg/ml) of Erythromycin Stearate working standard	Absorbance
1.39	0.03
2.78	0.062
5.56	0.118
11.11	0.228
13.89	0.277
16.67	0.331

The standard calibration curve was plotted as shown in the following **figure 2**.

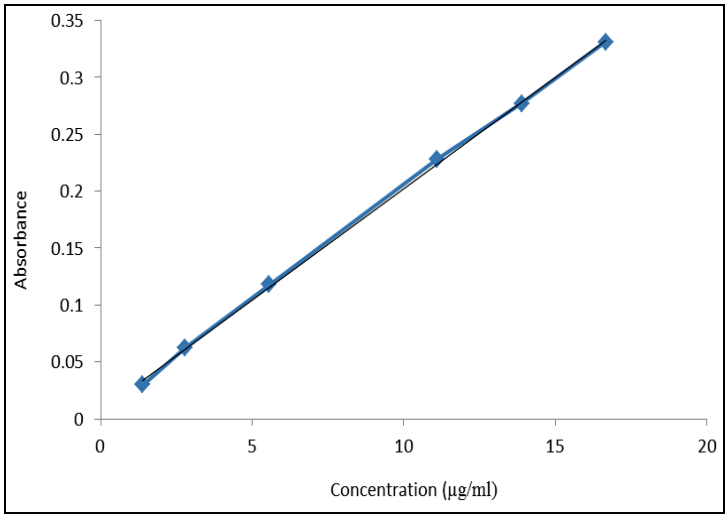

FIGURE 2: BEER-LAMBERT CALIBRATION CURVE OF ERYTHROMYCIN STEARATE WITH THE REFERENCE STANDARD

The regression equation is Y= 0.019x +0.006

Where y is the absorbance and x is the concentration in mcg/ml; $r^2 = 0.9994$

The calibration curve is constructed to cover all the concentrations expected during the analysis of the specimen.

The lowest concentration selected (1.39 µg/ml) represents a 10 % release and the highest concentration (16.67 µg/ml) represents 120 % release. The r^2 value of the regression (0.999) is satisfactory to allow use of the regression equation for dissolution testing.

Dissolution Rate Test: As can be seen **from table 4 and figure 3**, all the three products of Erythromycin stearate released greater than 80 % of their contents within 45 minutes. But Erythromycin stearate (Sudan) released less than 80 % of its content even after one hour. From the combined time dependent drug release profile (table 4 and figure 3), Rythro is the fastest in releasing its contents within a very short period of time followed by Erycin and Ethocin. The very slow drug release profile from Eryhromycin stearate is in line with the disintegration time profile observed. That is higher disintegration time leads to slower dissolution rate.

TABLE 4: DISSOLUTION PROFILE RESULT OF ERYTHROMYCIN STEARATE TABLETS USED IN THE STUDY

Time of sampling (min)	Percent drug released			
	Erycin	Ethocin	Rythro	Erythromycin stearate
0	0	0	0	0
5	54.93	27.29	68.18	11.38
10	73.15	61.77	76.53	48.09
15	94.38	73.15	83.12	64.00
20	95.10	81.86	84.09	69.33
30	98.92	87.54	84.88	73.87
45	104.18	91.29	86.75	78.83
60	103.82	92.44	96.80	79.91

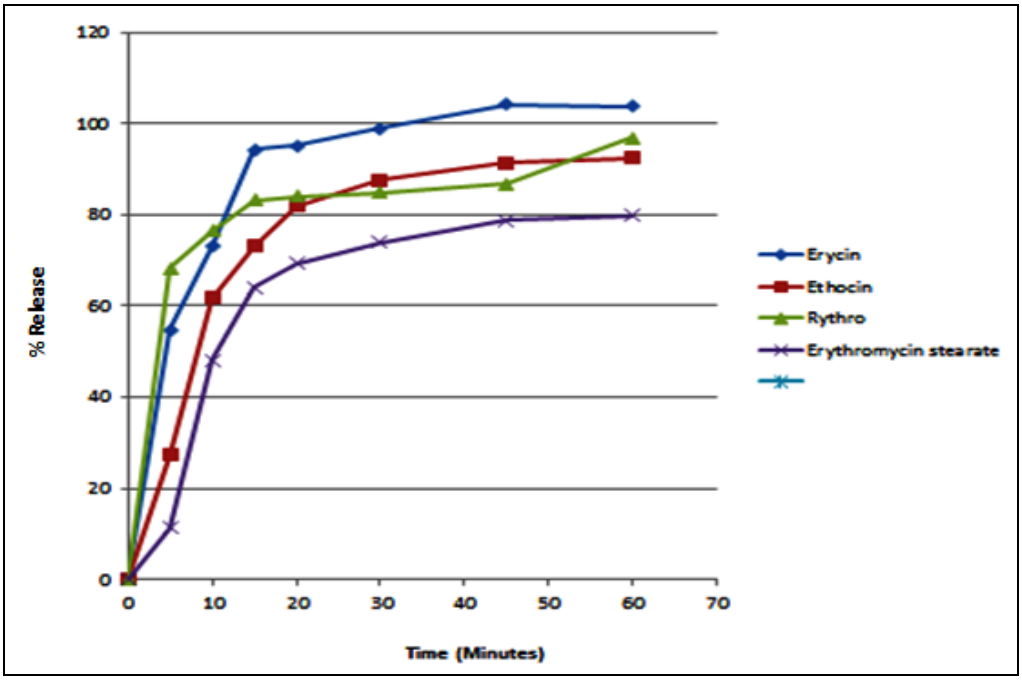

FIGURE 3: TIME DEPENDENT DISSOLUTION PROFILE OF ERYTHROMYCIN STEARATE TABLETS USED IN THE STUDY; Y-AXIS: RELEASE (%) AND X-AXIS: TIME IN MINUTES

In general; the four products of erythromycin stearate showed differences in their drug release *in vitro* which could also result in differences in their bioavailablity *in vivo*. However, *in vitro* testing predicts only the *in vivo* bioavailablity and bioequivalence of oral solid dosage forms but does not exclusively indicate the *in vivo* performance of a drug. The value of dissolution as a quality control tool for predicting *in vivo* performance of a drug product is significantly enhanced if an *in vitro* - *in vivo* relationship (correlation or association) is established.

Assay determination using Agar Diffusion Method: Inhibition zones are formed through the interaction between the growth inhibiting substances diffusing through the agar gel and increasing population of the sensitive organisms with which the gel had been inoculated.

To understand zone formation, it is necessary to visualize what is happening in physical, chemical and biological terms.

The main constituent of agar is the calcium salt of a sulphuric esters of the polysaccharide, agaracae. This consists of long chains of galactose units with α and β linkages. The agar forms a continuous lattice imparting rigidity to the gel. The lattice and the dilute aqueous solution are inter woven so the solution is a continuous phase through which solutes may diffuse almost as freely as through water, provided that the molecules are not large compared with the pore size of the lattice.

The scenario of zone formation is a solution of the growth inhibiting substance, the test solution; being placed in a reservoir in contact with the agar medium, which is inoculated uniformly with a test organism that is sensitive to the growth inhibiting substance. During incubation, the active substance (growth- inhibiting substance) diffuses in to the agar medium; at the same time, in areas of the plate that the growth inhibiting substance has not reached, the test organism population increases until it attains a level at which the growth inhibiting substance is absorbed and so can not advance further. At this time, known as the critical time, the position of the zone boundary is fixed. Further growth of the test organism leads to opacity of the medium around clear zones, where growth has been inhibited.

In fact, zone boundaries are often quite sharp. One possible explanation for sharp boundaries is that when the zone boundary has been established and vigorous growth takes place in the inhibited areas, nutrients and oxygen will begin to be depleted. However, nutrients and oxygen will diffuse out wards from the inhibition zones, leading to increased growth at the boundary and thus, to sharper zone boundaries.

Linearity determination: The linearity of the method is its ability to elicit results that are directly or by a well defined mathematical transformation, proportional to the concentration of the analyte in sample within a specified range. Series of dilutions of erythromycin stearate drug solutions were prepared and their inhibition zones were measured using an inhibition zone reader. The following is the graph of the data.

TABLE 5: INHIBITION ZONE READINGS FOR DIFFERENT CONCENTRATIONS OF ERYTHROMYCIN STEARATE

Concentration (µg/ml)	0.25	0.5	0.75	1.00	1.25	1.5
Inhibition zone diameter (mm)	15.1	16.68	18.24	19.72	21.15	22.96

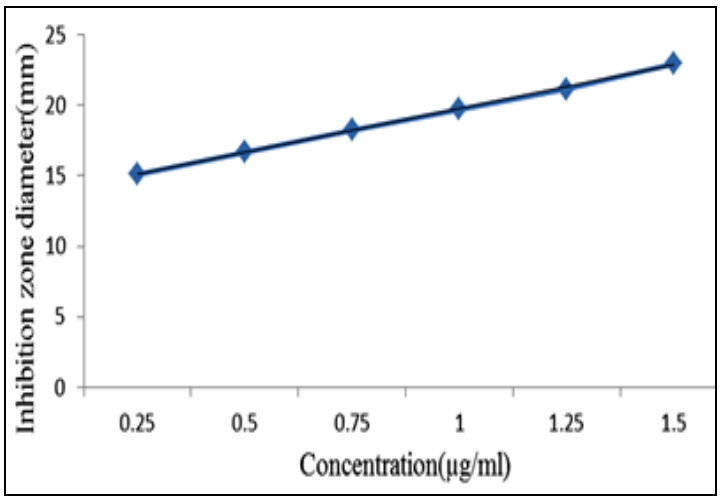

FIGURE 4: CALIBRATION CURVE FOR ZONE INHIBITION ASSAY

The Regression equation is Y= 6.193X + 13.55, r^2= .999

Where Y is the inhibition zone diameter and x is the concentration of the drug.

Inoculum: For agar diffusion assay, the inoculum for one large plate typically consists of a suspension containing 10^8 or 10^9 /ml of cells. These may be vegetative cells from an overnight culture from a stock suspension. The exact size of the inoculums in terms of viable cell is not highly critical. In this experiment an overnight grown culture of about 10^{10} organisms/ml were washed from the slants prepared using 10 ml of sterile distilled water and added in to a 90 ml of prepared seed agar, 5 ml of this mixture of organisms and seed agar were poured in to each of 4 plates.

The plates were then allowed to stand on a leveled position to make the inoculum distributed uniformly. Then, 4 cavities were made on each of the plats and then the prepared solutions were added into each of the cavities parallely and by alternating the higher and the lower concentrations of both the standard and the sample solutions.

TABLE 6: ASSAY RESULTS OF ERYTHROMYCIN STEARATE TABLETS USED IN THE STUDY

Name of Tablet	Inhibition zone readings (mm) ±RSD				Assay results (mg/tab.)	Assay results (%)
	Standard high	Standard low	Test high	Test low		
Rythro	19.00±2.7	14.94 ±3.2	18.93±4.0	14.91±1.4	245.8	98.3
Ethocin	19.38±1.0	15.14±2.7	19.26±2.7	15.05±1.2	241.5	96.6
Erycin	19.49±3.1	15.61±2.8	19.56±2.5	15.68±1.8	510.0	102.0
Erythromycin stearate	19.00±2.1	14.45±2.3	18 .01±3.6	10.37±2.4	190.4	76.2

Assay results showed that three of the four products studied were within the limits specified in the pharmacopoeia which is (95-105) % of the labeled claim. But Erythromycin stearate failed to fulfill the specified tolerance limits. Ethiopia tries to exert vigorous procedures to control the quality of drugs produced inside the country as well as those imported from abroad by the regulatory agency of the then Drug Adminstration and Quality Control Authority (DACA) and now renamed and expanded Food Medicines Health care administration and control Authority (FMHACA). But studies in post marketing surveillance documented presence of unregistered drugs [19]; one or more defects in the pharmacopoeial requirements to be fulfilled as minimum standard [20] and also non equivalence of some antibiotics making the decision to substitute generic choices difficult [21].

Ethiopia being located in tropical climate zone stability studies of some drugs simulating this condition up to six months shows positive and negative results [22, 23].

In a similar pattern to the above studies, our study of erythromycin tablets we detected an erythromycin stearate tablet manufactured by the General Medicines Company of Sudan failed to fulfill the requirements stipulated by Pharmacopoeias. This indicates for the FMHACA and other stakeholders in drug regulation and quality should work hard to fill any loopholes in the drug registration system and exert and strength strict post marketing surveillance mechanism in order to safe guard the public from such poor quality drugs.

CONCLUSION: In this study four products of Erythromycin stearate tablets were evaluated. All the four products comply with the tests for identification and physical properties of tablets such as hardness, disintegration time and weight variation. Assay results showed that three products of erythromycin stearate were within pharmacopoeial specifications except the generic product Erythromycin stearate from Sudan that was out of the given limits.

All the tablets included in this study released 80% of labeled amount of drug within the specified time except Erythromycin stearate (General medicines Company, Sudan). This suggests that the product which failed to fulfill Pharmacopoeial specifications in assay and dissolution test results could show a problem of bioequivalence and therapeutic efficacy. But this has to be supported by *in vivo* study.

In general the study revealed that there is an incidence of sub-standard drug product circulating in the market. Hence, the safety, quality and efficacy of essential drugs in the market should be continuously monitored through post marketing surveillance practices.

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