The Quality of Drugs Manufactured in Tanzania

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Evaluation of five quality parameters, namely friability, content, identity, disintegration and dissolution of four locally manufactured drugs in comparison with innovator brands was done. The locally manufactured drugs and the brands performed similarly in disintegration and identity of the active drug. The local samples had higher friability compared to the innovator brands. Whereas all the innovator brands passed the requirements for content of the active ingredient, only four out of eight of the analyzed local drugs met the British and United States pharmacopoeia requirements. Only one of the tested samples failed the dissolution test. In general, the innovator brands had superior dissolution profiles compared to the local drugs.

Key Words: Quality, assay, friability, disintegration, dissolution

INTRODUCTION

Tanzania, like other developing countries, is a net importer of pharmaceuticals. Approximately 90% of the drugs on the Tanzanian market are imported from different countries. It is in recognition of this fact that the local manufacture of drugs has been encouraged in the National Drug Policy [1]. The World Health Organization (WHO) supports local manufacture of drugs, especially the essential drugs. During its first meeting on the local production of essential drugs, in the African region held in Cape Verde, WHO encouraged the participating countries to develop national drug policies that promote viable local pharmaceutical industry capable of producing good quality drugs at an affordable cost [2].

The local manufacture of pharmaceuticals has several advantages. In addition to a possible price reduction due to lower transportation costs, it is easier for the Drug Regulatory Authorities to inspect the factories and hence assure the quality of the drugs. The undertaking also creates employment opportunity and provides the potential for the production of priority medicinal preparations to meet local needs.

In order to ensure a sustained growth of the local industry, it is necessary for the proprietors to ensure that they product drugs that can compete with imports, both in quality and price. The importance of the quality of the locally produced drugs cannot be over-emphasized especially when complaints by consumers are being aired in the media concerning the perceived quality of some drugs on the market [3]. To win consumer confidence, it is necessary for these drugs to meet all quality parameters prescribed by the regulatory authorities and, in addition, be comparable in quality with those manufactured by reputable international pharmaceutical companies.

Development of the pharmaceutical industry in Tanzania is at the infancy stage. Currently there are eleven registered pharmaceutical manufacturing firms in the country. Of these, more than fifty percent are small scale, dealing mainly with compounding. Four of them can be ranked as large scale manufacturers. However, no single manufacturing firm has satisfied the minimum conditions prescribed in the Tanzanian Good Manufacturing Practices [4]. This paints a gloomy picture and raises concern on the quality of the locally manufactured drugs. It is against this background that the quality and the in vitro bioavailability of some locally produced drugs were examined and compared to innovator brands.

MATERIALS AND METHODS

Samples, Reference materials and Reagents

Samples of four drugs, two antiparasitic, one analgesic/antipyretic and one antibacterial manufactured by three different local pharmaceutical industries, in their original containers were obtained from Medical Stores Department (MSD), which is the major stockist and distributor of drugs in the country. Corresponding innovator brands were purchased from pharmacies in Dar es Salaam. The samples were kept under conditions prescribed by the manufacturer prior to testing. All samples had minimum two years of the specified shelf life remaining. Details of the samples are shown in Table 1.

Table 1: Products Analyzed and Their Respective Manufacturer

Manufacturer	Product
Tanzania Pharmaceutical Industries	Chloroquine Phosphate 250mg tablets
	Metronidazole 200mg tablets
	Co-trimoxazole 400/80mg tablets
Shelys Pharmaceutical Industries Limited (SPL), Dar es Salaam	Shellyquine (chloroquine phosphate 250mg) tablets
	Metronidazole 200mg tablets
Interchem Pharma Limited (IPL), Moshi	Paracetamol 500mg tablets
	Co-trimoxazole 400/80mg tablets
Rhone Poulenc Rorer	Nivaquine® (Chloroquine sulphate 100mg) tablets
	Flagyl (metronidazole 400mg) tablets
Sterling Health	Panadol®, (paracetamol 500mg) tablets
Roche	Bactrim® (Cotrimoxazole 400/80mg) tablets

Key: ® = Innovator brand

Reference Standards and Reagents

Chemical reference standards of chloroquine diphosphate, acetamidophenol (paracetamol), metronidazole, trimethoprim (TMP) and sulfamethoxazole (SMZ) were obtained from Sigma Chemical Company (Steinheim, Germany). Analytical grade reagents used in the assay and identification tests were from BDH Chemicals Ltd., Poole, England.

Methods of Analysis

Disintegration test

Disintegration time for each sample was determined using methods outlined in the British Pharmacopoeia (BP) 1993 [5]. Erweka tablet disintegration tester (Erweka Aparatebau GmbH) was used.

Friability test

Erweka TA3 tablet friabilator was used to determine the friability of the samples. Ten tablets were accurately weighed and then placed in the apparatus. This was rotated one hundred times at 25rpm. The tablets were then examined for presence of broken parts and then re-weighed.

Assay

Chloroquine phosphate tablets were spectrophotometrically analyzed as described in the United States Pharmacopoeia (USP XX) [6]. Paracetamol and metronidazole tablets were respectively assayed spectrophotometrically and titrimetrically using methods outlined in BP 1993 [5]. In the assay of co-trimoxazole tablets, the procedure for ultraviolet spectroscopy determination of TMP and SMZ after extraction, as described in the British Pharmaceutical Codex 1973, was used [7]. A precaution was taken to use standard samples for both TMP and SMZ alongside the test samples in order to bring about reliability of the results. A Perkin Elmer 551 spectrophotometer was used in the respective spectrophotometric analysis.

Identity tests

The identification of the active constituents, i.e., chloroquine phosphate, paracetamol, metronidazole and SMZ was done by Thin Layer Chromatography (TLC) as outlined by Clarke [8]. The identification of TMP was done spectrophotometrically by comparing the UV spectrum of sample with that of the standard reference TMP in the wavelenght range 320 - 240nm.

Dissolution test

Dissolution profiles of each drug sample were obtained by performing dissolution test using Erweka DT6 dissolution tester (Erweka, Damstard, Germany). The dissolution media, rotation speed and type of stirrer were as outlined in the USP 23 [9]. Samples of all drugs were analyzed spectrophotometrically, except those of co-trimoxazole which were analyzed by HPLC.

RESULTS

The results on weight uniformity, friability, disintegration time, identity and assay of the active substance for each sample are summarized in Table 2. All the drugs passed the identification tests and the BP 1993 disintegration test. The disintegration of the locally manufactured drugs compared favorably with the innovator brands. The disintegration time for all the samples ranged between 1 and 8 minutes, well below the specified time limit of 15 minutes.

Table 2: Quality Evaluation of the Samples

PRODUCT	MAN.	FRIABILITY %	DIT (min.)	IDENTITY TEST	ASSAY (%)	PHARMACOPOEIAL SPECIFICATIONS ON ASSAY
Metronidazole	B	0.8	1	+	94.0	
	A	0.4	3	+	93.0	95.0 - 105.0%*
Flagyl	RPR	0.007	8	+	103.4	
Chloroquine	B	0.1	6	+	92.0	
	A	0.5	8	+	101.6	93.0 - 107.0%**
Nivaquine	RPR	0.04	9	+	102.6	
Paracetamol	A	0.5	3	+	96.2	
	C	0.1	3	+	93.0	95.0 105.0*
Panadol	SH	0.002	8	+	103.0	
Co-trimoxazole	A	0.2	2	+	SMZ 100.0 TMP 98.8	
	C	0.5	5	+	SMZ 98.0 TMP 108.0	TMP 92.5 - 107.5* SMZ 92.5 - 107.5*
Bactrim	R	0.006	1	+	SMZ 100.2 TMP 99.4	

Key:

* = BP 1993 specifications ** = USP XX specifications

SH = Sterling Health, R = Roche, RPR = Rhone Poulenc Rorer, MAN = Manufacturer, DIT = Disintegration time

The friability of all tablet samples passed the recommended values in that all were below 1%. However, it was observed that all the local drugs were more friable than the innovator brands. The friability of the locally manufactured drugs was ten to hundred times higher than that of the corresponding innovator brands.

The results of the determination of the content of active ingredient showed that all the innovator brands passed the pharmacopoeial specifications. However, half of the locally manufactured sampled did not pass because they contained the active ingredient in amounts that were slightly below the specified range. The failure in all these samples was marginal. On the other hand, with the exception of the co-trimoxazole tablets, all the local drugs that passed the assay tests did so marginally.

The dissolution profiles as depicted in figures 1-4 show that all but one of the samples passed the USP 23 requirements on dissolution. The failed sample was paracetamol tablets from manufacturer C, which released 76.6% of the drug within 30 minutes instead of the required 80%. Again this may be considered as a marginal failure. Compared to the locally manufactured drugs, the innovator brands had superior dissolution profiles in that they released more then 98% of the drug.

FIG. 1: Dissolution Profiles for Paracetamol Tablets

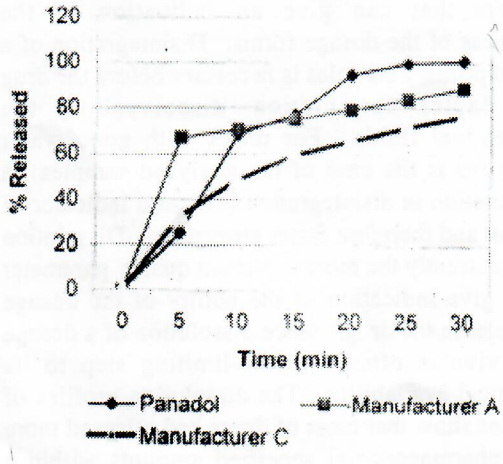


FIG. 2: Dissolution Profiles for Chloroquine Tablets

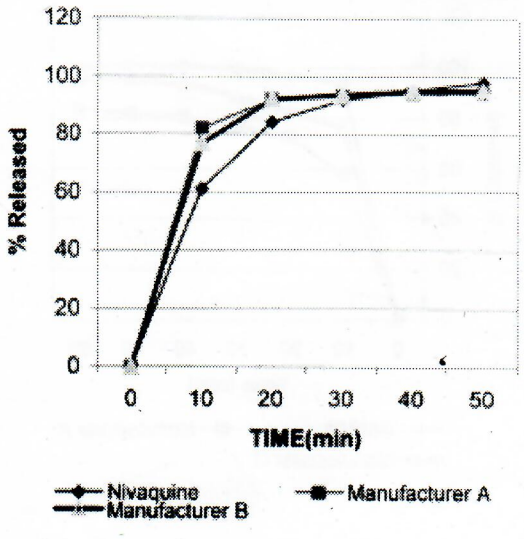


FIG. 3: Dissolution Profiles for Metronidazole Tablets

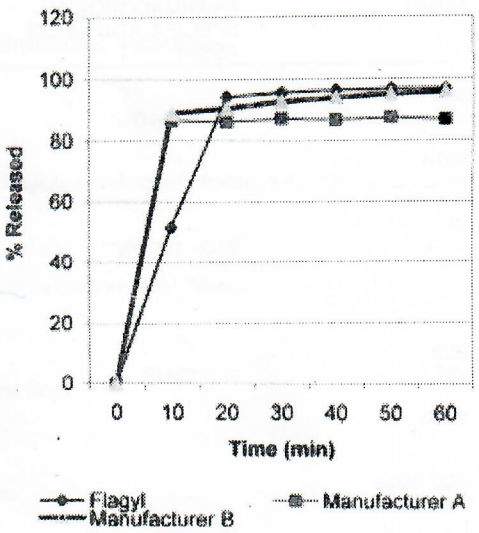


FIG. 4A: Dissolution Profiles for Co-Trimoxazole Tabs: Trimethoprim

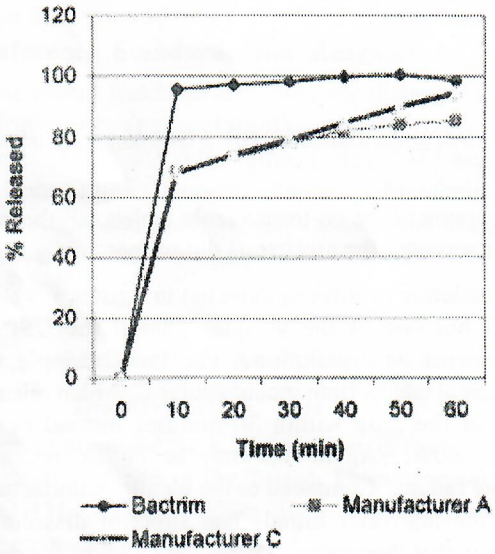
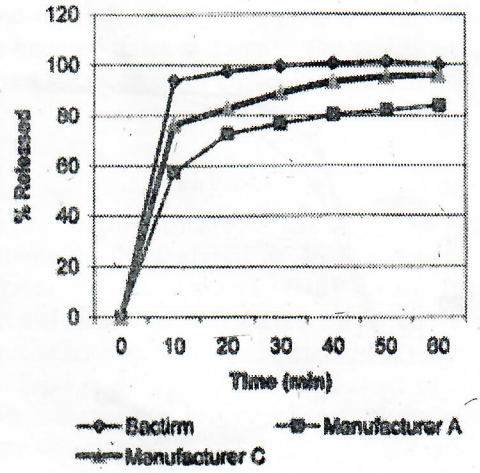


TABLE 4B: Dissolution Profiles for Co-Trimoxazole Tabs: Sulfamethoxazole



DISCUSSION

The higher friability of the local samples, as compared to the innovator brands, may explain the aired complaints form the public on the quality of some drugs. Friability tests measure the ability of tablets to resist abrasion due to small impacts. Abrasion may occur during packing, handling and transportation. Tablets with high friability have a higher probability of reaching the final consumer in a highly abraded state and with broken surfaces. Such tablets will have lost their elegance, an important quality attribute to consumers, who have neither facilities nor knowledge for testing the products. On the contrary, the lower friability shown by the innovator brands implies that these can withstand impacts and remain as whole tablets. They would thus be perceived by the consumer as being of higher quality despite the fact that they might have a similar clinical profile to that of the local products.

Half of the analyzed local samples did not meet the pharmacopoeial requirements. In contrast, all the innovator brands met this requirement. The failure by the local drugs, however, was marginal. The results of the assays in this study were similar to those observed by Shakoor et al [10]. On quality analysis of drugs from developing countries, the authors reported that about 33% of all the analyzed samples did not pass the pharmacopoeial standards for active ingredient. However, the content in the failed samples was not too far outside the acceptable standards. Again, similar failure rate has been reported by Kibwage et al [11]. In a study on the quality of co-trimoxazole products available on the Kenyan market, the authors observed that only 78% of the locally manufactured and 69% of the imported tablets passed the compendial assay requirement.

In general, the locally manufactured drugs compared favorably with the innovator brands in the following quality parameters; identity, disintegration and dissolution rate. One of the most important criteria for quality of tablet dosage forms, as drug delivery systems, is the measure of their ability to release the active ingredient upon administration. In this context, disintegration time and dissolution rates are two parameters that can give an indication of the effectiveness of the dosage forms. Disintegration of a tablet into primary particles is necessary before the drug in the tablet formulation dissolves in the gastrointestinal fluids. For drugs with good water solubility (as is the case of the analyzed samples), a shorter duration in disintegration is a good indicator of dissolution and therefore faster absorption. Dissolution testing is currently the most important quality parameter that may give indication of the ability of the dosage form to release the drug. Since dissolution of a dosage form in vivo is often the rate-limiting step to its physiological availability. The dissolution profiles of the samples show that most of drugs had released more than the pharmacopoeial specified amounts within a

shorter interval. This may be attributed to their faster disintegration rate. For the locally manufactured drugs that passed the official specification for dissolution, their profiles suggest that they would bring about the desired clinical performance, despite failing marginally in the assay.

CONCLUSION

The findings of this study show that the locally manufactured drugs failed in some important quality parameters. Improvement of the manufacturing methods and adherence to the Good Manufacturing Practices could remedy the situation. Therefore, the local manufacturers and the Drug Regulatory Authority in Tanzania have to put in more efforts in their endeavor to improve the quality of the locally manufactured drugs.

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