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# Sulphadoxine/Pyrimethamine Tablet Products on the Kenyan Market: Quality Concerns

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**Sulfadoxine/Pyrimethamine tablets preparations were recently made the first line antimalarial drug. In response to reports on falciparum malaria resistance to such products, sulfadoxine/pyrimethamine tablets in Kenya were evaluated for their *in–vitro* performance using the parameters of content and dissolution test for the Active Pharmaceutical Ingredient. One brand product had a content of both sulfadoxine and pyrimethamine well below allowed limits. Amongst the brands analysed only 44% had batches that released more than Q = 60% of labelled dose in 30 minutes. Batches of some brands had wide variations in content with some failing the dissolution test. Other brands released less than 60% in 60 minutes. Most brands failed the dissolution test for pyrimethamine and 33% for both sulfadoxine and pyrimethamine. The quality of sulfadoxine/pyrimethamine products on the Kenyan market should be a cause for concern to the drug regulatory authority and the Malaria Control Program.**

**Key Words:** Sulfadoxine/Pyrimethamine, Content, Dissolution.

## INTRODUCTION

Malaria has been identified as a major killer disease in the world with an estimated 500 million cases occuring annually (1). Mortality due to *Plasmodium falciparum* is between one and two million deaths annually (2,3).

The combination of sulphadoxine/ pyrimethamine (500 mg/25 mg) is currently the first line antimalarial drug in Kenya and appear in the WHO list of drugs used in parasitic diseases (4). The combination has blood schizontocidal activity against *P. falciparum* the causative organism for falciparum malaria, which is also sensitive to halofanthrine, mefloquine, chloroquine, amodiaquine, quinine and pyrimethamine in combination with other sulphonamides. In the past few years, there have been reports of emerging strains of *P. falciparum* that are resistant to a number of antimalarial agents (2,5-7). Sulphadoxine/ Pyrimethamine (SP) is one of such agents. Exposure of *P. falciparum* to sub-lethal levels of drugs is one of the contributing factors to the emergence of resistant strains. Drug levels in the body are consequent to proper dose that is well absorbed. Dissolution of drugs from a solid dosage form is pre-requisite for absorption.

The availability of SP in solution after administration is therefore important. In a bioavailability study it has been shown that both sulfadoxine (SDX) and pyrimethamine (PMT) are readily absorbed after oral administration but the quality aspects of the tablets used were not given (8). It is therefore not possible to comment on the pharmaceutical equivalence of the two except assume that they were consonant.

Combination drugs such as SP present formulation problems because excepients could have different interactive properties for the two active ingredients, especially PMT which has poor solubility. It is in recognition of such problems that pharmacopoeias like the United States Pharmacopoeia (USP) prescribe a dissolution test for investigating the amount of drugs that dissolve from an SP tablet within 30 minutes (9). However, the dissolution test does not exactly mimic the *in-vivo* conditions. The drug SP is commonly administered to adults, as a single dose of three

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tablets for curative purposes. It is therefore expected to avail adequate blood levels to effect clearance of parasitecemia. In this paper we report investigation of the content and dissolution of SP products in the Kenyan market as an indicator to their *in-vivo* performance.

## EXPERIMENTAL

### Reference Samples

Working standards of Sulphadoxine (SDX) (100.4 %) and Pyrimethamine (PTM) (100.2 %) were obtained courtesy of Laboratory and Allied Ltd., Nairobi and analyzed against the respective USP standards. Pharmaceutical grade caffeine was used as an internal standard (IS).

### Sampling

Samples of SP preparations were obtained from pharmacies and distributors in Nairobi. They are:

**Local:** Orodar (Elys Chemical Industries Ltd.), Intadoxin (Regal Pharmaceutical Ltd.,) Malodar (Laboratory and Allied Ltd.), Falcidin (Cosmos Ltd.), Unidar (Pharmaceutical Manufacturing Company) and Fanlar (Dawa Pharmaceuticals, Kenya).

**Imported:** Fansidar (Roche, Switzerland), Methomine S (Nairobi Enterprises Ltd., Nairobi – India), Viparum (Bulk Medicals, Nairobi – India) and Malocide (Torrent Pharmaceuticals Ltd. – India), Amalar (Brown and Burk Pharm, India), Laridox (IPCA, India), Falcitat (Remedica, Cyprus), Malidar (Caplin Point Laboratories, India), SP (IDA, Netherlands) and SP (Panacea, India).

### Liquid Chromatographic Analysis of Pyrimethamine and Sulphadoxine

The liquid chromatographic method used for simultaneous analysis of PTM and SDX was modified from that described in the USP with the incorporation of phosphate buffer. The method afforded good separation of active ingredients and caffeine which was used as the internal standard. The LC system consisted of a model 305 solvent delivery system and a model 115 ultra violet spectrophotometer detector set at 254 nm (Gilson, Paris, France), coupled to a model HP 3936B integrating recorder (Hewlett Packard), and a model CV-6-UHPa-N60 sample injection valve (Valco, Houston, TX, USA) equipped with a 25 µl. The column 250 x 4.6 mm ID was laboratory packed with RSil $C_{18}$HL, 10 µm ( BioRad, Eke, Belgium) and was maintained at 40°C by immersion in a water-bath.

### Reagents, solvents and mobile phase

Potassium dihydrogen phosphate and potassium hydrogen phosphate (Acros Organics, New Jersey, USA), acetonitrile and glacial acetic acid (Fisher Scientific, UK) were all analytical grade. Acetonitrile and water were glass distilled before use.

The mobile phase consisted of water/acetonitrile/ acetic acid/0.1M potassium dihydrogen phosphate buffer (69:20:1:10) volume parts.

### Preparation of Sample for Analysis

*Internal standard solution:* This was prepared to a concentration of caffeine 1 mg/ml in *methanol.*

*Standard solution:* Pyrimethamine, 31.25 mg, was transfered to a 25 ml volumetric flask, dissolved in and put to the mark with methanol. Sulfadoxine, 25mg, was weighed into a 50 ml volumetric flask and dissolved in 20 ml acetronitrile. To this solution was added 1.0 ml of the pyrimethamine solution and made to volume with the mobile phase nine. The solution (0.9 ml) was mixed with 1 ml of internal standard and injected onto the column.

*Sample solution:* Tablet powder equivalent to 125 mg sulfadoxine was transferred into a 25 ml volumetric flask. To the powder was added 5 ml methanol and 10 ml acetonitrile, sonicated for 5 minutes, filled to the mark with mobile phase and filtered through a 0.45 µm membrane filter. 1.0 ml of the filtrate was diluted to 10.0 ml with mobile phase. 9.0 ml of the solution was mixed with 1 ml of internal standard and injected onto the column.

### Dissolution study

Dissolution was performed using a one station equipment following the USP paddle method (9)

with 0.05M potassium phosphate buffer, pH 6.8 as the dissolution medium. Samples of 10 ml aliquots were withdrawn from the dissolution medium and replaced with a similar volume of fresh medium. Sampling times were 10, 30, and 60 minutes. The withdrawn sample was filtered through a 0.45 μm membrane filter. 9.0 ml of the filtrate was mixed with 1 ml of internal standard and injected onto the column.

## RESULTS AND DISSCUSSIONS

The study involved the evaluation of parameters of the tablets that are likely to affect their bioavailability. These were contents of the active pharmaceutical ingredients (APIs) and dissolution.

Linearity of the assay method was examined by replicate analysis (n=3) of a series of concentrations corresponding to 3% -150% of label claim for both SDX and PTM. The following correlation coefficients were obtained. SDX (150 – 7500 μg/ mL), $r^2 = 0.9986$ and PTM (7.5 – 375 μg/ ml), $r^2 = 0.9998$. The response was found to be linear and directly proportional to concentration. The method was therefore suitable for determination of dissolution covering the expected concentration ranges.

In table 1 are shown results of the APIs content and the dissolution test of the tablets. 26 batches out of 33 were analyzed for content. The content of APIs for all the examined batches were within the USP limits of 90 –110 % of label amount, except for product IX which was below the limits for both.

The content of APIs in some batches of III and XIII were marginally above the lower limits. The results for the dissolution test (30 min) are interpreted on the average values from 6 tablets only whereby the amount of both pyrimethamine and sulfadoxine should be more than 60% (Q=60%) of the label. Only 10 samples of 6 products had an average of above Q = 60% the label amount of pyrimethamine and sulfadoxine. This represents 30% of the samples analyzed. Amongst the locally manufactured products, only some batches of III, IV and VI had this level of performance whilst for foreign manufactured samples it was only I, XIII and XVII. It was further noted that only batches of I were consistent in passing the dissolution test.

The dissolution test is a more valid indicator of differences between batches and reflects the potential for good bio-availability of a product. The USP attaches greater importance to dissolution tests and it is especially important for drugs that have poor solubility. It is clear that the majority of the products present with a problem in the dissolution of pyrimethamine. Since this component has poor solubility, manufacturers should focus their research in alleviating the problem. Generally, 23 samples failed the dissolution test and only 10 passed. Dissolution test range for SDX was 8.3 – 102% with 66% samples releasing less than 60% of label dose. For PMT it was 6.0 – 98.4 with 36% failing. Nine samples from 7 products failed ($Q \leq 60\%$) in both SDX and PMT.

### Dissolution of batches of the same product

In the study we also investigated different batches for a number of products. The dissolution of four batches of I had range of label claim 86.2 – 89.2 % for SDX and 82.8 – 98.4 % for PMT. All four batches passed this dissolution test. The range for XIII (n = 4) was SDX 39.2 – 62.2 % and PMT, 25 – 87.34 %, IV (n = 3), SDX was 87 – 95.46 % and PMT, 59.75 – 69.5 % and VII (n = 3) SDX, 50.1 – 74.0 % and for PMT, 36.5 – 50.7 %.

The big differences in the dissolution test for batches of the same brand suggest lack of stringent current good manufacturing practices.

### Cummulative dissolution Profile

A dissolution profile for products is shown in table 2. Eighteen samples from 13 brands released less than Q = 60 % of APIs even after 60 minutes, which is twice the allowable time. Since dissolution of a drug is necessary before absorption, it would be interesting to investigate the bioavailability of these products against the innovator product (I)

That malaria is a serious health threat is a recognized fact. That is why the government has a malaria policy on how to contain its spread and treatment. The SP product was recently designated as the first line product in the

**Table 1**
**Content of active pharmaceutical ingredients and dissolution Test (RSD) for Sulfadoxine Pyrimethamine Tablet Products**

| Product (Batch) | Chemical content % Label claim | | Dissolution test (30 min) Dose released as % label claim | |
|---|---|---|---|---|
| | SDX | PMT | SDX | PMT |
| I. (a) | 101.0 ( 0.56) | 101.8 (2.23) | 87.4 (4.23) | 82.8 (4.71) |
| (b) | 99.3 (1.56) | 98.6 (1.11) | 89.2 (1.48) | 98.4 (2.79) |
| (c) | 98.6 (1.10) | 98.6 (0.54) | 87.4 (3.02) | 85.5 (1.60) |
| (d) | 98.5 (0.47) | 99.3 (0.41) | 86.2 (3.15) | 85.2 (2.02) |
| II. | 101.1 | 100.6 | 20.8 | nq |
| III. (a) | 93.0 (0.05) | 95.3 (0.01) | 59.5 (5.35) | 90.7 (6.33) |
| (b) | 99.6 (0.77) | 100.9 (1.57) | 82.5 (3.40) | 49.0 (0.80) |
| (c) | 98.5 (1.4) | 98.7 (0.81) | 93.2 (3.7) | 68.3 (5.72) |
| IV. (a) | nd | nd | 95.5 (2.27) | 59.8 (14.43) |
| (b) | 102.6 | 99.9 | 89.7 (3.59) | 69.5 (4.13) |
| (c) | 96.2 (0.55) | 97.0 (0.32) | 94.7 (1.36) | 63.8 (1.51) |
| V. (a) | nd | nd | 32.6 (18.83) | 41.3 (20.25) |
| (b) | 107.1 (2.11) | 95.7 (1.94) | 102.0 (1.72) | 97.3 (3.43) |
| VI. (a) | nd | nd | 88.8 (7.25) | 29.0 (7.61) |
| (b) | nd | nd | 92.1 (3.06) | 88.8 (4.89) |
| VII. (a) | 98.7 (0.05) | 98.7 (0.02) | 50.2 (8.41) | 50.7 (2.96) |
| (b) | 104.4 (0.74) | 109.6 (1.05) | 73.3 (2.88) | 36.7 (3.00) |
| (c) | 99.6 (3.76) | 99.7 (1.82) | 74.0 (0.81) | 36.5 (0.61) |
| VIII. (a) | 101.3 (0.70) | 101.0 (1.62) | 55.3 (7.20) | 23.6 (7.20) |
| (b) | 99.3 (2.71) | 103.7 (4.28) | 56.3 (2.49) | 32.8 (6.65) |
| XI | 84.3 (0.86) | 83.3 (0.29) | 87.4 (3.24) | 19.9 (9.17) |
| X. | 94.9 (0.72) | 99.7 (0.51) | 83.4 (4.92) | 58.5 (3.23) |
| XI. | 101.2 (1.06) | 95.1 (0.47) | 8.3 (6.61) | 6.0 (6.64) |
| XII. (a) | nd | nd | 77.5 (10.19) | 23.0 (8.35) |
| (b) | 102.9 ( 0.73) | 98.1 (1.45) | 34.6 (6.10) | 26.3 (9.19) |
| XIII. (a) | 91.5 (1.21) | 96.6 (1.25) | 39.2 (3.32) | 87.4 (4.88) |
| (b) | 106.8 (0.97) | 100.1 (1.33) | 62.2 (2.43) | 26.2 (3.98) |
| (c) | 91.7 (2.61) | 92.0 (0.78) | 59.6 (6.01) | 27.3 (4.15) |
| (d) | 105.7 (1.00) | 100.4 (0.73) | 52.3 (3.42) | 25.0 (6.12) |
| XIV. | 97.7 (1.63) | 96.0 (1.42) | 90.6 (2.04) | 20.2 (2.24) |
| XV. | nd | nd | 73.9 (2.00) | 48.5 (6.82) |
| XVI. | 98.5 (0.92) | 99.5 (1.02) | 87.0 (2.58) | 89.4 (3.14) |
| XVII. | nd | nd | 70.7 (3.11) | 38.3 (1.41) |

Limits; Assay 92.5% to 107.5% , Dissolution test Q = 60% in 30 min.
Figures in parenthesis are RSD, nd – not determined, nq – not quantified

treatment of malaria. The SP product has good compliance since it is taken as a single dose. That a majority of the SP products on the market are of poor quality with respect to dissolution is a worrisome observation. Reported therapeutic failure (8) of such products could be due to quality problems. Dissolution of a dosage form *in-vitro* is often the rate-limiting step to its physiological availability, the products failing in the official specification for dissolution test suggests that they would fail to elicit the desired clinical performance and thus contribute to emergence of *P. falciparum* resistance.

The importance of malaria in both economic cost and human suffering demands that it be effectively treated and controlled. Drugs such as SP that are available in combating this scourge must be of good quality. Substandard drugs must be weeded out through thorough market surveillance. It is also recommended that the quality of SP products be ascertained by both the

**Table 2: MEAN (RSD) DISSOLUTION PROFILE OF SULFADOXINE AND PYRIMETHANINE TABLETS**

| BRAND (BATCH) | TIME IN MINUTES | | | | | |
|---|---|---|---|---|---|---|
| | **10 MIN** | | **30 MIN** | | **60 MIN** | |
| | **SDX** | **PMT** | **SDX** | **PMT** | **SDX** | **PMT** |
| I. (a) | - | - | 87.4 (4.23) | 82.8 (4.71) | 93.9 (2.98) | 96.5 (4.35) |
| (b) | 65.9 (6.05) | 54.3 (16.92) | 89.2 (1.48) | 98.4 (2.79) | 103.5 (2.44) | 104.3 (3.02) |
| (c) | 67.7 (4.36) | 52.7 (6.03) | 87.4 (3.02) | 85.5 (1.60) | 91.9 (2.21) | 93.3 (2.09) |
| (d) | 69.1 (5.00) | 53.2 (5.56) | 86.2 (3.15) | 85.2 (2.02) | 89.1 (3.72) | 95.1 (5.38) |
| II. | 12.0 (9.48) | nq | 20.8 | nq | 33.4 (5.32) | 12.8 (10.04) |
| III (a) | 31.9 (7.97) | 38.0 (15.99) | 59.5 (5.35) | 90.7 (6.33) | 69.6 (6.44) | 101.8 (2.34) |
| (b) | 37.4 (2.34) | 21.2 (2.69) | 82.5 (3.40) | 49.0 (0.80) | 93.7 (1.24) | 78.8 (2.20) |
| (c) | 89.6 (2.87) | 48.4 (4.65) | 93.2 (3.7) | 68.3 (5.72) | 94.7 (1.82) | 76.9 (9.93) |
| IV. (a) | 80.5 (2.55) | 42.9 (4.08) | 95.5 (2.27) | 59.6 (14.43) | 98.9 (3.05) | 75.6 (6.83) |
| (b) | 75.2 (2.04) | 47.1 (2.06) | 89.7 (3.59) | 69.5 (4.13) | 95.7 (4.52) | 79.7 (4.02) |
| (c) | 90.6 (1.96) | 35.8 (5.10) | 94.7 (1.36) | 63.8 (1.51) | 95.7 (1.22) | 74.6 (4.74) |
| V. | 25.1 (24.0) | 31.4 (21.02) | 32.5 (18.83) | 41.3 (20.25) | 41.1 (2.65) | 63.6 (5.22) |
| VI. (a) | 58.3 (7.40) | 21.3 (12.63) | 88.8 (7.25) | 29.0 (7.61) | 104.0 (2.75) | 37.0 (7.89) |
| (b) | 83.8 (4.67) | 571 (5.25) | 92.1 (3.06) | 88.8 (4.89) | 93.8 (3.32) | 95.6 (3.53) |
| (c) | 84.0 (3.34) | 57.1 (2.53) | 92.1 (2.48) | 88.7 (3.62) | 93.8 (2.09) | 95.6 (2.89) |
| VII. (a) | 20.4 (10.02) | 20.2 (3.87) | 50.1 (8.41) | 50.7 (2.96) | 72.4 (5.39) | 84.9 (2.22) |
| (b) | 43.2 (4.10) | 18.3 (3.11) | 73.3 (2.88) | 36.7 (3.00) | 86.6 (2.12) | 53.9 (2.80) |
| (c) | 45.6 (1.86) | 18.7 (1.12) | 74.0 (0.81) | 36.5 (0.61) | 86.0 (1.71) | 53.6 (1.18) |
| VIII. (a) | 23.22 (7.31) | 13.7 (5.17) | 55.3 (7.20) | 23.6 (7.20) | 81.2 (1.96) | 42.6 (4.53) |
| (b) | 46.2 (6.93) | 21.4 (7.48) | 56.3 (2.49) | 32.7 (6.65) | 82.5 (2.38) | 54.8 (7.30) |
| IX | 82.3 (3.78) | 9.9 (14.76) | 87.4 (3.24) | 19.8 (9.17) | 87.2 (4.56) | 29.6 (7.62) |
| X. | 80.2 (1.33) | 39.8 (5.26) | 83.4 (4.92) | 58.5 (3.23) | 88.2 (3.90) | 68.7 (1.57) |
| XI. | 1.9 (6.38) | 2.8 (19.78) | 8.3 (6.61) | 6.0 (6.64) | 16.21 (6.17) | 10.4 (8.55) |
| XII. (a) | 55.9 (2.4) | 13.5 (4.87) | 77.5 (10.19) | 23.0 (8.35) | 93.8 (1.71) | 31.3 (4.66) |
| (b) | 14.4 (4.24) | 12.4 (6.13) | 34.6 (6.10) | 26.2 (9.19) | 64.8 (4.18) | 56.4 (6.21) |
| XIII (a) | 33.5 (4.18) | 55.0 (4.51) | 39.2 (3.32) | 87.3 (4.88) | 42.3 (3.54) | 99.1 (3.41) |
| (b) | 28.3 (9.36) | 15.5 (12.38) | 62.2 (2.43) | 26.2 (3.98) | 69.5 (3.55) | 31.2 (3.37) |
| XV. Rivopharm SP | 62.3 (9.36) | 40.0 (9.95) | 73.9 (2.00) | 48.5 (6.82) | 79.7 (1.87) | 59.0 (2.22) |
| XVI. | 76.8 (2.7) | 61.0 (3.0) | 87.0 (2.58) | 89.4 (3.14) | 91.9 (1.9) | 94.0 (2.13) |
| XVII. | 50.4 (2.01) | 23.0 (1.28) | 70.7 (3.11) | 38.3 (1.41) | 77.7 (1.07) | 45.3 (1.24) |

nd = not determined, nq = not quantified.

manufacturer and the Pharmacy and Poisons Board before they are released to the market. Local manufacturers need to put in more effort to improve on quality and GMP. It should be mandatory that foreign source products undergo routine quality evaluation at the National Quality Control Laboratory or a third party laboratory before they are released onto the domestic market. Constant market surveillance of SP products to ensure continued pharmaceutical equivalence to the innovator product is crucial in the effective use of this medicine in the management of malaria.

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