



Comparison of Medicine Quality of the Generic Formulation of Amoxicillin Provided by the Government of Karnataka with Marketed Brands - A Public Health Perspective

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ABSTRACT

With the opening up the generic drug store by the government of Karnataka, India, to provide drugs at subsidized prices the study wanted to find the difference in chemical and microbial analysis between the generic drug and other marketed brands. One generic drug and 11 marketed brands were selected for the study. Chemical stability, analytical methods of potency determination, moisture content determination, pH determination, determination of sedimentation volume, stability testing were conducted. Microbial assay was conducted to check for antimicrobial sensitivity and zone of inhibition. One sample 't' test was used to measure statistical significance. The test samples were divided into 4 categories for statistical purpose, i.e., generic amoxicillin, prescribed by specialist, prescribed by dentists and prescribed by general practitioners. Results of potency revealed that all the test samples met the required United States and Indian Pharmacopeia standards on testing for initial potencies except for samples A10, A11, A12. Many samples failed the required potency at the three different temperatures. Results of microbiological assay also support the results of the chemical assay. The statistical analysis of the cost of the generic drug as compared to the other categories showed high significance with p values of 0.013, 0.008 and 0.00. The generic amoxicillin fares better than those prescribed by general practitioners and on par with the prescriptions of specialists in spite of being comparatively inexpensive, making it an affordable, accessible and sustainable drug of choice for general and oral health care.

Keywords: Public Health, Amoxicillin, Karnataka, generic formulation, antibiotics.

INTRODUCTION

Drugs play an important role in improving human health and promoting well-being.¹ Over the past decade, there has been an increase in public awareness of the existence of counterfeit and substandard drugs, which have been increasingly reported in developing countries where drug regulations are ineffective.² In order to produce expected therapeutic effect, the drug needs to be safe, effective and of good quality. But unfortunately, spurious/falsey labelled/counterfeit, medicines which are deliberately and fraudulently mislabelled with respect to identity and source are found everywhere in the world.³ The government institutions making bulk purchases through tender system and settling for the lowest bids are particularly prone to be affected by these drugs.⁴

Over the past decade the Indian economy has developed in complexity with sophisticated service based industries gaining in prominence.⁵ The best examples of this change are the IT-BPO sector and the domestic pharmaceutical industry.⁵ Nominal sales in the pharma sector have increased by 9% per year, outperforming the global average of 7%.⁵ The recent opening up of a generic drug store by a state government in India provides generic formulations of various drugs at subsidized prices for the

public. The overwhelming response to the store has made the government initiate the opening of 19 other such stores in government run district hospitals in the state.

Antibiotics, being the wonder drug, are widely prescribed in the developing countries. In reality, 25-40% prescriptions contain one or more antibiotics.⁶ The lives of individual patients are put at risk by substandard pharmaceutical preparations.⁷ Amoxicillin is an empirical drug of choice by practitioners for a varied number of ailments and hence has an influence on the public at large. Amoxicillin belongs to extended spectrum penicillin of the aminopenicillins group which acts by inhibition of cell wall synthesis.⁸ It is active against organisms sensitive to penicillin's in addition to Gram-negative bacilli. The widespread use of amoxicillin because of its broad spectrum antibacterial activity, low cost and least toxicity prompted us to select amoxicillin for this study, hence comparing the generic versus the retail brands.

MATERIALS AND METHODS

Collection of Samples

The generic sample of amoxicillin trihydrate 500mg were sourced from the government initiated generic drug store. The 11 marketed brands were sourced through five major retail pharmacies in the state and were categorized



as prescribed by specialists (MNC brands), dentists (local pharma) and general practitioners.

Samples were coded (A1 –A12) by a health care personnel and the investigator was kept blinded for the duration of the study.

The samples obtained were stored in the manufacturer's original packaging and kept in appropriate conditions until testing. Tests were completed within 30 days of sample collection.

Guidelines for field surveys of the quality of medicines was followed as recommended by Paul N Newton et al.(2009)⁹

The study was carried out between October and November 2012

Bacterial Strains

Two bacterial strains were used in the study to determine microbial efficacy. Standard strains of *Escherichia coli* (ATCC 25922) and *Staphylococcus aureus* (ATCC 25923) were used in the study according to CLSI guidelines.¹⁰

Chemical stability of the amoxicillin capsules was estimated by:

1. Potency determination

Potency of the amoxicillin samples was measured using alkalimetry analysis of fresh capsules and of capsules stored at varied temperatures; room temperature ($27^{\circ}\text{C} \pm 2^{\circ}\text{C}$), elevated temperature ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}$), and lowered temperature ($5^{\circ}\text{C} \pm 2^{\circ}\text{C}$).

2. Moisture content determination

0.5g sample was put into a test tube and weighed, and dried in an oven for 4 hours at 105°C . The test tube was taken out and dried again. The difference of the two values gave the amount of water in the sample. Thus the percentage of loss in weight on drying (LOD) was calculated by taking the ratio of weight of water in the sample to the initial weight of the sample and multiplying with 100.

3. pH determination

The pH values of the freshly reconstituted amoxicillin with distilled water in the ratio of 1:1 was measured using a pH meter.

4. Determination of sedimentation volume

Sedimentation volume was determined by taking a definite volume of the reconstituted sample into a graduated cylinder and then keeping it undisturbed for 7 days. After 7 days, sedimentation volume (F) was calculated from the ratio of the final volume (V_f) of the sediment to the original volume or initial volume (V_i) of the suspension before settling.

5. Microbiological Assay

Standard strains of *Escherichia coli* (ATCC 25922) and *Staphylococcus aureus* (ATCC 25923) was tested for amoxicillin sensitivity by disc diffusion and minimum inhibitory concentration (MIC) was calculated.

a. Sensitivity was screened by Kirby Bauer disc diffusion method using Mueller Hinton Agar. The media was prepared according to the standard CLSI guideline that is, 20ml of the medium was poured into a 9cm diameter petri dish. Three to four colonies of pure culture was inoculated into peptone water broth and incubated at 37°C for 3 hours and adjusted to 0.5 McFarland standards.

This broth culture was then spread evenly on the MHA plates to get a lawn of growth. Sterile filter paper disc with 30 mL (must be L and not mL) of test antibiotics A1 – A12 were tested.

b. Minimum Inhibitory Concentration (MIC) of amoxicillin for the above isolates was tested by agar dilution method in accordance to CLSI guidelines. Three to four colonies of pure culture were inoculated in peptone water broth and incubated at 37°C for 3 hours. Turbidity of the broth culture was adjusted to 0.5 McFarland standards. Stock solutions of the antibiotics were prepared according to the recommended guidelines. Dilutions of amoxicillin from 2-512 mg/L were tested.

Statistical analysis (one tailed-t test) was used to find the significance between the generic drug and the different groups.

RESULTS

% Potency of amoxicillin capsule

Determination of potency was divided into two segments: i) Determination of initial potencies of the fresh samples immediately after reconstitution and ii) Determination of potencies of the samples kept at three controlled temperature conditions for 7 days. The temperatures were refrigerated ($5^{\circ}\text{C} \pm 2^{\circ}\text{C}$), room ($29.5^{\circ}\text{C} \pm 2^{\circ}\text{C}$) and elevated ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}$) temperatures. All the samples were assayed chemically by alkalimetry test.

The result of the percentage potency of the twelve samples shows that there is a striking difference in the initial concentrations of the amoxicillin among the various samples. A2 being the generic drug supplied by the government was in compliance with the lower limit of the USP¹⁰ and ISP¹¹ specification both at potencies of fresh capsule and at room temperature, so were most of the drugs excepting A10, A11, A12. Only A3 was in compliance at refrigerated temperature, while none of the drugs complied at the elevated temperature.

Determination of sedimentation volume

The highest sedimentation volumes were found to be in A2., while, A4 and A5 had the lowest sedimentation volume respectively.



The sedimentation volumes of the reconstituted suspensions also varied accordingly, the highest being 160.00 in A2 the lowest 100.00.

Table 1: Potency (%) of the various brands of amoxicillin at various temperatures

Sample code	Initial potency (%)	Final Potency (%)		
		Condition of temperature		
		Room Temperature	Refrigerated Temperature	Elevated temperature
A1	89.65	87.65	88.31	81.01
A2	90.97	92.3	79.02	87.65
A3	99.6	95.62	96.95	86.32
A4	97.61	98.27	81.01	78.35
A5	99.6	90.97	90.97	89.64
A6	93.63	89.64	94.29	77.69
A7	96.95	85.66	86.99	72.38
A8	104.91	104.91	77.02	79.02
A9	92.96	88.98	88.98	83.1
A10	84.99	83.67	85.06	81.01
A11	60.42	55.11	59.76	49.8
A12	86.99	86.99	83.67	81.01

USP specification: (90-120%); IP specification: (90-110%)

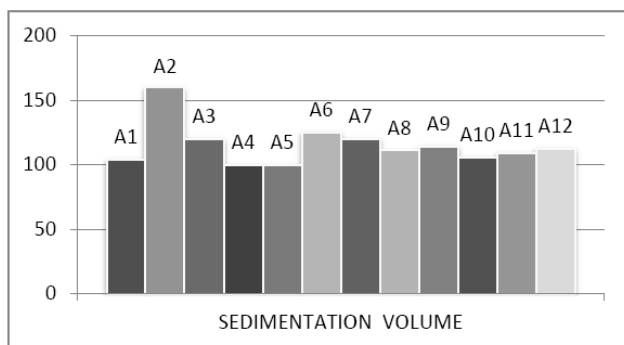


Figure 1: Sedimentation volume

Moisture content and pH

The moisture content of the samples (Figure 2) complied the USP specification of not more than 3% (USP, XXIII, NF

XVIII, 1995a), the highest being in A11 and the lowest being in A3. The pH of the tested samples also complied with the USP (USP, XXIII, NF XVIII 1995a) and ISP specifications, with all samples coming in the range of 5.0-7.5. A11 showed a slight higher pH (7.43) compared to the rest (6.3 – 6.71) but within the complied range limits.

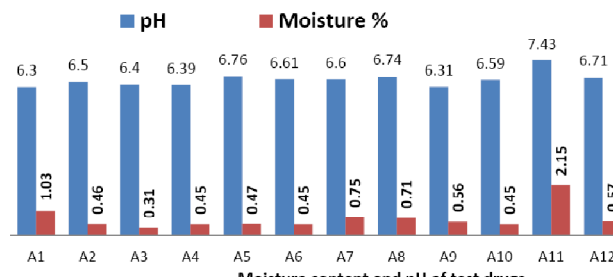


Figure 2: Moisture content and pH of various brands of Amoxicillin.

Cost of the drug

A2 being the generic drug given at a subsidized rate was the cheapest as compared to the rest of the retail brands (table 5).

Microbiological Assay

Disc diffusion test (Table 3) revealed that A2 showed the least Zone of inhibition for *Escherichia coli* culture, while A12 showed the greatest Zone of inhibition. For the standard strain of *Staphylococcus aureus* culture A10, A11 and A12 showed the least zone diameter. While the greatest diameter being for A4 and A9.

The brands A2, A3, A4, A5, A7, A9, A10, showed a MIC of 2 µg/mL when tested with *Staphylococcus aureus*, while A8 inhibited growth at a higher concentration of 18 µg/mL. A3 inhibited the growth of standard strain of *Escherichia coli* at concentrations of less than 1 µg/mL and A11 inhibited growth at 16 µg/mL.

Table 2: Sedimentation volumes % after freshly reconstituted and when kept for 7 days

Sample code	Sedimentation volumes			F
	When freshly reconstituted in ml (Vi)	After 24 hrs at room temperature in ml	After 7 days at room temperature in ml (Vf)	
A1	1.2	1.2	1.2	104.16
A2	0.5	0.7	0.8	160.00
A3	0.5	0.5	0.6	120.00
A4	0.8	0.7	0.8	100.00
A5	1.0	1.0	1.0	100.00
A6	1.0	0.8	0.8	125.00
A7	1.2	1.0	1.2	120.00
A8	0.9	0.8	0.9	111.11
A9	0.7	0.6	0.8	114.29
A10	1.0	0.9	0.95	105.56
A11	1.2	1.1	1.1	109.09
A12	0.8	0.8	0.9	112.50

Initial volume after few minutes = Vi, Final volume sediment = Vf, F = sedimentation volume = 100Vf/Vi



Table 3: Zone of inhibition

Sample Code	Strength of disc	Zone of inhibition in mm	
		<i>Streptococcus aureus</i> 25923	<i>Escherichia coli</i> 25922
A1	30µg	18	21
A2	30µg	18	16
A3	30µg	18	22
A4	30µg	20	21
A5	30µg	18	18
A6	30µg	17	18
A7	30µg	18	21
A8	30µg	19	21
A9	30µg	20	21
A10	30µg	16	18
A11	30µg	16	18
A12	30µg	16	22

Table 4: Minimum Inhibitory Concentration

Sample code	Minimum Inhibitory Concentration (MIC) in µg/mL	
	<i>Streptococcus aureus</i> 25923	<i>Escherichia Coli</i> 25922
A1	4	2
A2	2	2
A3	2	1
A4	2	4
A5	2	4
A6	4	8
A7	2	2
A8	16	8
A9	2	2
A10	2	2
A11	8	16
A12	8	4

Table 5: Cost of the drug

Sample code	Cost in Rupees per 10 Capsules
A1	76.00
A2	18.00
A3	96.66
A4	75.00
A5	103.33
A6	62.00
A7	72.00
A8	68.00
A9	84.00
A10	69.00
A11	75.00
A12	75.00

Table 6: Statistical analysis

Categories	Generic Amox	Specialist Prescribed amox (A1, A3, A4, A5)	Dentist prescribed amox (A6, A7, A8)	General Practitioner prescribed amox (A9, A10, A11, A12)
Initial Potency of fresh amox	90.97	M = 98.93 ± 1.15 p=0.007**	M = 98.77 ± 4.77 p=0.047*	M = 81.34 ± 14.35 p=0.272
MIC of E. coli	2.0	M = 2.33 ± 1.52 p=0.742	M = 6.0 ± 3.46 p=0.184	M = 6.0 ± 6.73 p=0.320
MIC of Staph. Aureus	2	M = 2 ± 0.00	M = 7.3 ± 7.57 p=0.346	M = 5 ± 3.46 p=0.182
Cost of the drug in Indian Rupees	18	M = 91.55 ± 14.68 p=0.013*	M = 76.25 ± 18.30 p=0.008**	M = 75.75 ± 6.18 p=0.000***

Statistical significance : Significant (*) = p 0.05 ; Highly significant (**) = p 0.01; Very Highly significant (***) = p 0.001.

DISCUSSION

The study conducted was to find the efficacy of the drug supplied by the Government of Karnataka to its people comparing with those brands marketed by Multinational and Indian pharmaceutical companies. In developing countries with limited pharmaceutical production capabilities of their own, Indian generics are of real importance. Given the nature of substandard drugs it is

difficult to estimate exact sums, but the scale of both counterfeiting and substandard drugs is alarming. In 2008, the OECD estimated that 75% of the world's total supply of counterfeit and/or substandard drugs came from India.⁵

The potency of most of the drugs complied with the lower limits of USP and ISP range, but few complied with the range on exposure to room temperature after 7 days. The

same could be seen in studies done by Nasim et al., (1998)⁷ where brand labelled K, L, N and to a lesser extent brands P and Q were comparatively better than the rest. Similar results were seen in the study conducted by Haider et al., (2011).¹³ The low potencies of the samples might be attributed to the inadequate amount of amoxicillin initially, degradation of the drug due to improper handling, storing under improper conditions, etc. Mangalore being a hot and humid city could cause problems in maintenance of the potencies. Drug A8 showed higher potency that could be due to awareness of the manufacture regarding declining potencies. The international Pharmaceutical Federation has recommended that overages be limited to a maximum of 30% over the labelled potency of an ingredient Gennaro AR, (1985).¹⁴ At 40°C, there was considerable loss of potencies in all samples. Potency of the samples was carried out using alkalimetry analysis according to Sethi PD, (2008)¹⁵ since the iodometric assay as specified by USP was cumbersome and needed expert skill. Alkalimetry was found to be simple and reproducible, cost effective and could be done by a novice. New technologies are making it easier to test the authenticity of drugs in field settings.¹⁶ Study conducted by Huda et al., (2009)¹⁷ found that all brands under investigation met the official standard, although few of them were at a lower region within the specified standards of USP and BP. According to a review done by Kelesidis et al., (2007)² India, China, Nepal, Thailand, Sierra Leone, Nigeria, Cameroon, Guinea were the countries from which substandard amoxicillin was reported.

The moisture content of the samples was within the USP specifications of not more than 3%. The maximum stability of aqueous preparations of penicillin is within pH range 6-6.8 Martin, (1998)¹⁸ the low pH could be due to high amount of moisture. Haider et al., (2011)¹³ found moisture and pH in the samples of amoxicillin were within the USP specifications, suggesting proper drying of preparations which limits temperature and humidity variations. Storing in containers lined with silica desiccant bags would limit moisture as well. The addition of phosphate and citrate buffer could exert a favourable effect on penicillin stability independent of pH effect.

ATCC 25922 *Escherichia coli* was taken as a standard microorganism to test the effectiveness of amoxicillin as mentioned in the Clinical and Laboratory Standards Institute performance standards guidelines for antimicrobial susceptibility testing (CLSI document M100-19).¹⁰ *Staphylococcus aureus* was taken as an organism causing dental infections. Haider et al., (2011)¹³ revealed that *Streptococcus pyogenes*, *Streptococcus viridans* and *Escherichia coli* were sensitive to the test samples, while *Klebsiella*, *Shigella*, *Bacillus cereus* were resistant.

After the chemical and microbial analysis the code were revealed and were then grouped, ie. A2 being the generic drug, A1, A3, A4, A5 being MNC brands prescribed mostly by specialists, A6, A7, A8 local pharma companies prescribed mostly by dentists and A9, A10, A11, A12

prescribed mostly by the local physicians. There was statistically significant difference in relation to potency of the generic brand when compared with the MNC brands ($p=0.007$) and when compared with those prescribed by dentists ($p=0.047$). Nasim et al., (1998)⁷ concluded that there was no difference in the efficacy of the brands produced by multinational and local companies. The cost of the generic drug compared with the groups showed high significance with p values of 0.013 (specialists), 0.008 (dentists) and 0.00 (general physician).

CONCLUSION

Substandard medicines are a real and growing threat to public health. The spread of resistant bacteria in India, Pakistan, United Kingdom of Great Britain and Northern Ireland was described in a paper published in the Lancet Infectious Diseases in August 2010.¹⁹ Appropriate and correct use of an antibiotic is essential to ensure that effective and safe treatment is available. The main problem in India is that we lack quality infrastructure where the prices are controlled but quality remains unmonitored. With simple test one should be able to find out the effectiveness of drugs in the market where many brands are available for one drug. In India, several initiatives are underway to address the problem. A national antibiotic policy is being prepared, though not yet in the public domain.¹⁹ The Karnataka government intervention in helping its people to get better treatment and drugs seems to be going in the right direction with the opening up of the generic drug stores with quality drugs and subsidized pricing, making it an accessible, affordable and sustainable venture. Ineffective legal and regulatory frameworks, on-going gaps between legislation and practices on the ground and lack of transparency have led to the creeping of substandard drug into the Indian market.

Another main public health concern is the antimicrobial resistance, "super bug", on use of substandard drugs. According to WHO, relative inexpensive drugs will become ineffective, leading to increase in R&D, which could lead to expensive drug, and selection of drugs resistant to pathogens will lead to increased morbidity, mortality and significant economic burden on developing countries. It is often said that the workman is as good as his skill and his tools. Hence doctors and pharmacists should be aware of the effectiveness of standard drugs in the market.

The outcome of the present study will help raise awareness among both the government and public regarding the use of quality products and aid in forming stringent legislation to counter illicit drugs in the public domain.

Limitations of the study

Not all amoxicillin brands available in Mangalore city were analysed. Only most popularly prescribed ones were looked into. The main aim of the study was to compare the medicine quality of the amoxicillin supplied by the



Government of Karnataka (which was found to be good) to the marketed brands. Hence the names of the brands need not have to be revealed, also citing legal issues which could crop up.

This study has been a self-funded study with no authors having conflict of interest.

Summary Box

What is already known about this subject	What does this study add
According to the World Health Organization there are a number of spurious and fake drugs available around the world and especially in developing countries such as India. Amoxicillin an antibiotic is one such drug that has many false brands and fake composition in India too. At the moment in India there is a regulatory agency to monitor fake and spurious drugs but the laws governing are not stringent to act at present. Bulk purchases and tender system in government agencies can result in the procurement of substandard drugs, thus leading to poor health of the public at large.	The generic amoxicillin dispersed by the Government of Karnataka (Southern State in India) at a subsidized rate is as equally good as those marketed by the multinational brands. Thus allaying the fear of substandard, subsidized drugs given to the public. Hence government regulation and supply of subsidized drugs would be a boon in the public health perspective, giving an opportunity for the poor to avail their fundamental right to HEALTH. Thus initiatives by the government will usher in a new era of cheap and quality drugs to the socioeconomically challenged.

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