

Potency Determination of Essential Drug Samples Manufactured By Small and Medium Pharmaceutical Industries in Bangladesh

Ononna HF¹, Al Hossain ASMM¹, Ganguly A², Faroque ABM¹

¹Department of Pharmaceutical Technology, University of Dhaka, Dhaka, Bangladesh

²Department of Clinical Pharmacy and Pharmacology, University of Dhaka, Dhaka, Bangladesh

e-mail: abmfaroque@yahoo.com

Abstract

Drugs are considered highly essential and sensitive items for saving lives. Pharmaceutical sector in Bangladesh has grown from strength to strength over the last 40 years and evolved from an import dependent to self-reliant, export oriented sector. But counterfeit, adulterated and sub-standard drugs, though small in percentage, still remain to be a threat in the local market. This cross sectional study was conducted during March to September 2016, with the purpose of this study is to determine potency of some essential drugs, which were used vigorously by sub-urban and rural people and manufactured by randomly selected small and medium pharmaceutical industries of Bangladesh. The study revealed that the measured potency of different essential drugs manufactured by randomly selected small pharmaceutical industries was mostly unsatisfactory. Here, it has been found that most of the drug samples did not match with the acceptance level: the potency of Amoxicillin tryhydrate capsule was found 8.25%, 47.9%, 51.1% 19.06%, 57.06% from five different pharmaceutical industries and for Diclofenac Sodium is 44.9%, 26.8%, 27.2%, 29.9%, 19.4%, 62.12%, 15.9% and 60.76% from eight different industries. So, the Drug Administration should have a strict monitoring and controlling mechanism to the distribution of those drugs, otherwise the overall public health of the country will be at stake.

Keywords: Drug potency, Small pharmaceutical industries, Sub-standard drugs

Introduction

Drugs are used to protect, cure and mitigate disease states, but these drugs may cause damage to health, and even death. While Bangladeshi pharmaceutical industries have reached the height of supplying 98% of the country's annual drug market and increased the country's credibility in the international markets; counterfeit, adulterated and sub-standard drugs, though small in percentage, still remain to be a threat in the local market.¹⁻² As reported in the media, in the absence of strict monitoring and effective control by the regulatory authority, some medium and small pharmaceutical companies are being involved repeatedly in manufacturing and marketing of counterfeit, adulterated and sub-standard drugs.

Though many factories have been already closed and license of many companies have been suspended, counterfeit, adulterated and sub-standard drugs are still reported to be extensively available mainly in the small townships and the rural areas. In the absence of

proper control of the countryside, these drugs are on the market to take advantage of unconsciousness of the common people. Users of these drugs do not get the desired therapeutic effects in spite of spending their hard-earned money. Some specified drug business holders with their organized syndicates are responsible for this proliferation of counterfeit, adulterated and sub-standard drugs in the rural countryside areas.

Studies showed that some companies that are engaged in producing sub-standard drugs intentionally mimic products of some big pharmaceutical companies in fixing trade names and designing of packages and labels with a view to selling these products in the market at a cheaper rate. Sometimes these companies just supply these drugs only to the Mitford Market of Dhaka and then, from there those mimicked drugs are distributed throughout the whole country. These companies do not have their own marketing department.³⁻⁴

So, the main objective of this study is to evaluate the potency of the finished drugs that

are being produced and marketed by the small and medium scale pharmaceutical industries in Bangladesh.

Materials and Methods

This cross sectional study was conducted during March to September 2016 for potency determination of some randomly collected essential drug samples, Active Pharmaceutical Ingredients (API) of eight different drugs were collected. Analytical pure standard samples of eight different drugs were received as a kind gift samples from renowned pharmaceutical industries of Bangladesh. These were used without further purification. Name of the APIs are-Amoxicillin Trihydrate, Azithromycin, Cephadrine, Cefixime Trihydrate, Ciprofloxacin Hydrochloride, Diclofenac Sodium, Metronidazole, Ranitidine Hydrochloride. For potency determination of drugs, different chemicals and solvents were used. They were-Hydrochloride acid, Methanol, Sodium Hydroxide, Monobasic Potassium phosphate, Acetonitrile and Distilled water. Except Azithromycin, potency of other generic drug samples were analysed by UV-visible Spectrophotometry method developed by Nayon M et al, Naveed S et al, Omar SARR S et al and others and for Azithromycin, HPLC method was adopted (USP 30-NF 25).

The drug samples were randomly collected from the rural areas of different Upazila of Dhaka, Jamalpur, Faridpur, Magura, Pirojpur, Barisal, Chandpur, Rangpur, Habiganj and Chittagong, which were manufactured by small and medium pharmaceutical industries of Bangladesh. Laboratory analyses were done in Pharmaceutical Lab of the Department of Pharmaceutical Technology of the University of Dhaka and Quality Control Lab of Research and Development, Incepta Pharmaceutical Ltd. These pharmaceutical industries were enlisted in the categories of D, E and F in the 1st report of the Specialist Inspection Team that was constituted by the Parliamentary Standing Committee of Ministry of Health and Family Welfare in 2010.

In this study, for potency determination, different sample brands of each generic drug were collected. However, the number of collected brand sample varied due to availability of sample brand. Table-1 indicates the number of brand sample that were collected for analysis. Each sample was tested three times to ensure correct potency.

Potency determination of drug samples

For the potency determination of Cefixime trihydrate, seven samples of Cefixime trihydrate tablets of different companies were randomly collected from different areas of Bangladesh. The standard stock solution of 100µg/mL of cefixime trihydrate was prepared and was used as standard stock solution

Table I :Number of trade name sample for each generic drug that was analysed

	Name of Generic Drug Molecules							
	Cefixime Trihydrate 200 mg	Cephadrine BP 400 mg	Ciprofloxacin hydrochloride	Diclofenac Sodium 50 mg	Metronidazole BP 400 mg	Ranitidin hydrochloride 150 mg	Amoxicillin Trihydrate	Azithromycin USP
No Collected Drug Samples	7	6	6	8	7	3	6	7

Further dilutions were made with distilled water to obtain different concentrations and the absorbance of the spectra was measured at 287 nm. The calibration curves were then constructed by plotting absorbance versus concentration and the regression equations were calculated. UV-visible spectrophotometry method developed by Nayon M *et al*, was used to determine the potency of these randomly collected samples.⁵

Twenty capsules of samples were dissembled and weight of content of each capsule was taken. The contents were grinded to make fine powder. Appropriate dilution of sample solution was prepared and absorbance was recorded. The concentration of the drug was determined from the regression equation of standard drug. After then, the potency of nine marketed products of cefixime trihydrate was calculated in percentage.

In addition, for rest of the generic drug samples except Azithromycin, the methodology followed

for Cefixime trihydrate was also followed for those generic drug samples. Specifically, Naveed *et al.*, for Cephadrine, Omar S *et al.*, for Ciprofloxacin, Pandey *et al.*, for Diclofenac Sodium, Das *et al.*, for Metronidazole, Salve *et al.*, for Ranitidine and Rele *et al.*, for Amoxicillin were adopted respectively for potency determination of these generic drug samples.⁶⁻¹¹ Azithromycin USP pure drug was obtained as a gift sample from one of the top Pharmaceutical industries of Bangladesh. For the potency determination of Azithromycin, seven samples of Azithromycin tablets of different companies were randomly collected from different areas of Bangladesh.

Preparation of mobile phase

Buffer: 4.6g of monobasic potassium phosphate anhydrous was transferred to a 1000mL volumetric flask and diluted with water to volume. Then it was adjusted with 1N sodium hydroxide to a pH of 7.5 and diluted with water to 1L. Then mobile phase was prepared by filtering and degassing the mixture of acetonitrile and buffer. ((65:35 Preparation of standard Azithromycin solution: First of all, standard azithromycin solution was prepared by taking 10 mg of USP Azithromycin RS in a 10-mL volumetric flask. Then solution of mobile phase was added up to the mark and sonicated to obtain a solution having a concentration of 1mg/mL of Azithromycin.

Preparation of sample solution: Seven market products of Azithromycin were collected. Twenty tablets from each formulation were weighed and finely powdered. An accurately weighed portion of the powder, equivalent to about 50mg of Azithromycin was transferred to a 50mL volumetric flask. The solution of mobile phase 25mL was added up to the mark and sonicated for not less than 15 minutes. The solution was allowed to equilibrate to room temperature, diluted with mobile phase to volume and mixed to obtain a solution having a nominal concentration of 1mg of Azithromycin per mL. Sample solutions of seven market products were prepared following this method.

Analysis: Samples: Standard solution and sample solution

The percentage of the labeled amount of Azithromycin ($C_{38}H_{72}N_2O$) in the portion of tablets taken: $\text{Result} = (r_u/r_s) \times (C_s/C_u) \times P \times F \times 100$

r_u = peak response of Azithromycin from the sample solution, r_s = peak response of Azithromycin from the standard solution, C_s = concentration of USP Azithromycin RS in the standard solution (mg/ml), C_u = nominal concentration of Azithromycin in the sample solution (mg/ml), P = Potency of USP Azithromycin RS ($\mu\text{g}/\text{mg}$), F = conversion factor, 0.001mg/ml; Acceptance criteria: -%90 .%110

The potency of collected drug samples was determined using standard curve of respective drugs (Except Azithromycin drug samples). The potency of Azithromycin drug samples was measured using HPLC method according to USP monograph¹².

The standard curves of drugs were constructed by plotting different concentration of standard solution of drug in X axis and measured absorbance at definite wavelength of respective concentration in Y axis. The regression equation was also determined from the standard curve. The standard curve with regression equation has been given in figure-1.7-1.1

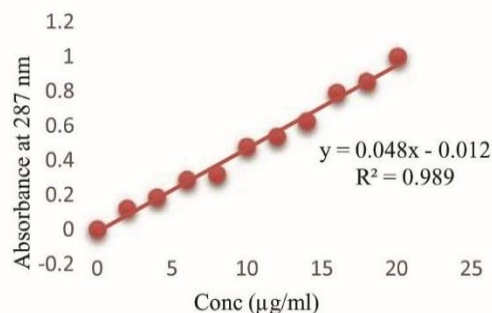


Fig 1.1 Standard Curve for Cefexime Trihydrate

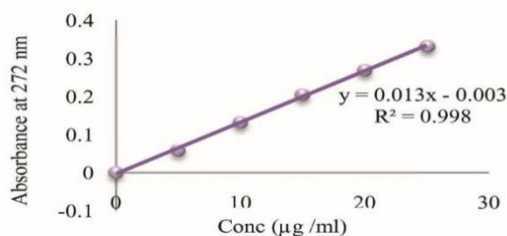


Fig 1.2 Standard Curve of Cephadrine

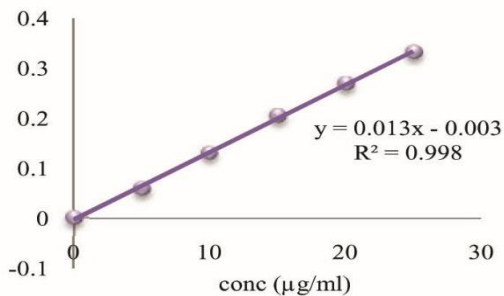


Fig 1.3 Standard Curve for Ciprofloxacin HCl

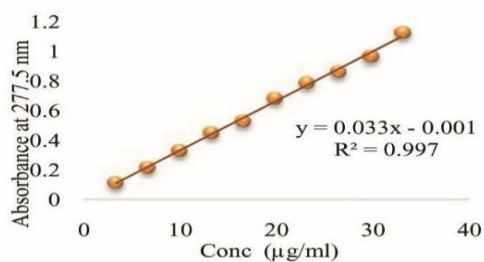


Fig 1.4 Standard Curve for Diclofenac Sodium

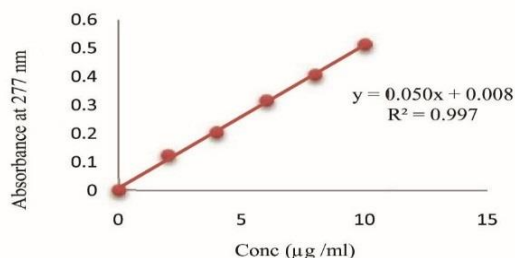


Fig 1.5 Standard Curve of Metronidazole

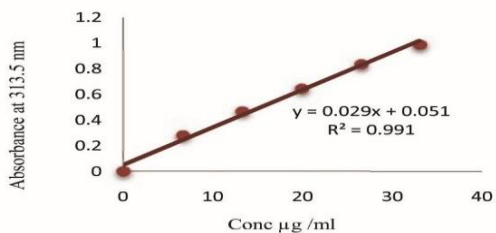


Fig 1.6 Standard Curve of Ranitidine Hydrochloride

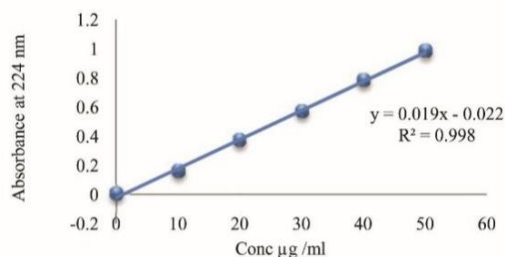


Fig 1.7 Standard Curve for Amoxicillin Trihydrate

After preparing sample solution of drug samples, the absorbance value (y) of respective samples were measured at same wavelength as standard curve. Then absorbance found with unknown concentration were placed in the equation and the concentration (x) of the drug samples were measured. The determined concentration were multiplied with the proper dilution factor and the actual amount of drug in the sample were calculated.

Results

Amount (mg) of drug actually found in commercial samples after analysis is shown in table I and the potency of different drug samples manufactured by different small and medium pharmaceutical companies in Bangladesh shown in (Table- II).

Table II: Amount (mg) of drug actually found in commercial samples after analysis

	Cefexime Trihydrate Capsule	Cephadrin BP Capsule	Cipro-floxacin HCl Tablet	Diclofenac Sodium Tablet	Metronidazole BP Tablet	Ranitidin HCl Tablet	Amoxicillin Trihydrate Capsule	Azithromycin USP Tablet
Amount declared by the Companies	200 mg	400 mg	500 mg	50 mg	400 mg	150 mg	500 mg	500 mg
Company A							96.3	
Company B	129			22.5				
Company C				13.4				
Company D		235.6	352	13.6			287.5	
Company E	100.2	194.4	267	14.95	224.8	86.7		
Company F							255.5	
Company G					179.6			
Company H				9.7	59.2			
Company I							95.3	
Company J	138.28	303.6	332	31.06	274.4		376.5	520.7
Company K		226.4	255.2		183.6			439
Company L								343
Company M				7.95			74.6	
Company N	142.4							
Company O	44.4	4.16	7.65		19.6		41.25	12.45
Company P								474
Company Q	107							463.5
Company R							239.5	342.5
Company S	148.5	242.2	410	30.4	255			

From the above results, it has been found that most of randomly collected drugs samples of different pharmaceutical industries did not

match with the acceptance level. These industries were enlisted in the categories D, E and F in the 1st Report of the Specialist Inspection Team that was constituted by the Parliamentary Standing Committee in 2010

For the determination of potency of the drug samples, mainly simple UV Spectrophotometric methods were applied. According to USP monograph, each of tablet or capsule should

contain not less than 90 percent and not more than 110 percent of drugs to their label claim. In this study, drug samples from eighteen pharmaceutical industries were randomly collected. Amongst these industries, a few have comparatively better potency than others. Some have moderate drug potency but still they are far from fulfilling the acceptance level. All other samples have very unsatisfactory results. (figure 2-9)

Table III: Potency of different commercial samples analyzed

Drug samples	Potency (%)							
	Cefixime Trihydrate 200 mg Capsule	Cephadrin BP 400 mg Capsule	Ciprofloxacin HCl 500 mg Tablet	Diclofenac Sodium 50 mg Tablet	Metronidazole BP 400 mg Tablet	Ranitidin HCl 150 mg Tablet	Amoxicillin Trihydrate 500 mg Capsule	Azithromycin USP 500 mg Tablet
Company A						64.2		
Company B	64.5			44.9				
Company C				26.8				
Company D		58.9	70.4	27.2			57.5	
Company E	51.2	48.9	53.4	29.9	56.2	57.8		
Company F							51.1	
Company G					44.9			
Company H				19.4	14.8			
Company I							19.06	
Company J	69.14	75.9	66.4	62.12	68.6		75.3	104.14
Company K		56.6	51.04		45.9			87.8
Company L								68.6
Company M				15.9		49.7		
Company N	71.2							
Company O	2.22	1.04	1.53		4.9		8.25	2.49
Company P								94.8
Company Q	53.5							92.7
Company R							47.9	68.5
Company S	74.26	60.54	82.02	60.76	63.8			

In addition, those collected drugs have low physical as well as packaging qualities. The finishing and coating of tablets of those drug samples were mostly questionable. The hardness of the tablets was also very low. Again, some have other physical problems like capping, lamination and sticking. Packaging design of some big companies were also copied by some of these companies.

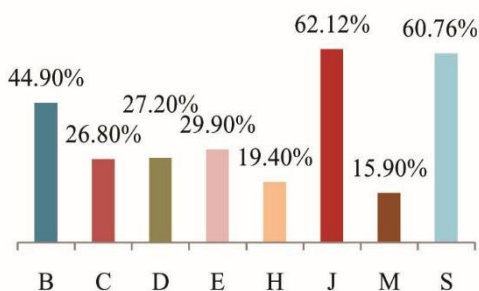


Fig-2: Potency of seven randomly collected marketed products of Cefixime Trihydrate Capsule

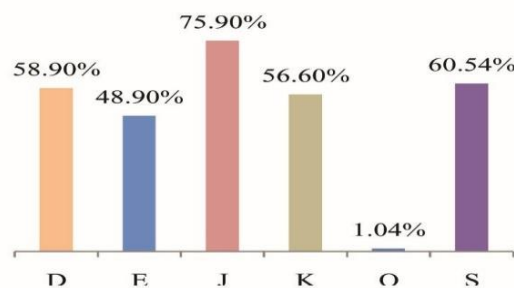


Fig-3: Potency of six randomly collected marketed products of Cephadrine Capsule

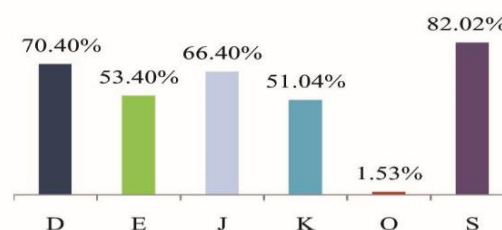


Fig-4: Potency of six randomly collected marketed products of Ciprofloxacin HCl Tablet

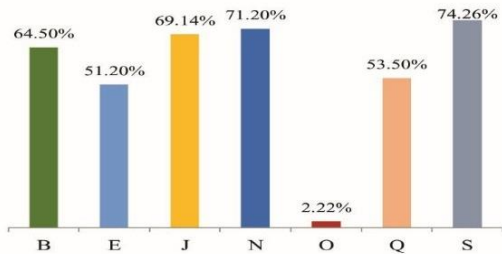


Fig-5: Potency of eight randomly collected marketed products of Diclofenac Sodium Tablet

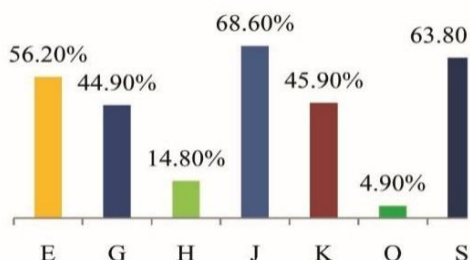


Fig-6: Potency of seven randomly collected samples of Metronidazole Tablet

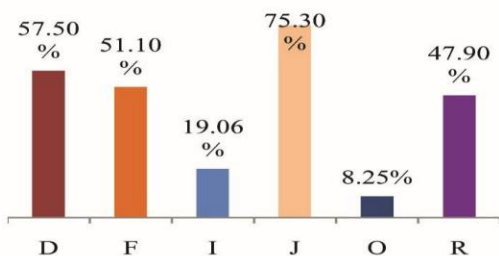


Fig-7: Potency of three randomly collected marketed products of Ranitidine Hydrochloride Tablet

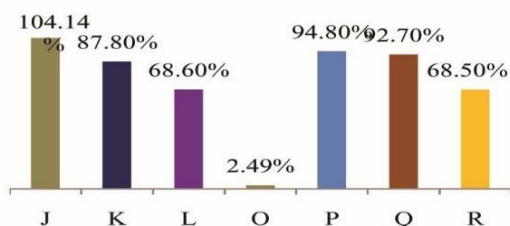


Fig-8: Potency of six randomly collected marketed products of Amoxicillin Trihydrate Capsule

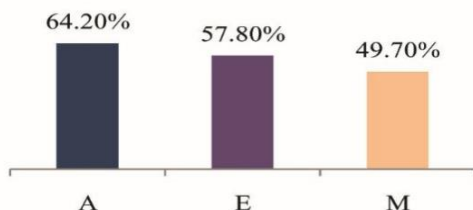


Fig-9: Potency of seven randomly collected marketed products of Azithromycin Tablet

Discussion

Drugs of these industries are extensively available in the rural and countryside areas of Bangladesh. They were not found in Dhaka city or other city areas. The study opens a hard reality that though drugs are a commodity where quality and potency cannot be compromised, some middle and small pharmaceutical industries are engaged in producing sub-standard drugs. This is an important public health threat. It is especially true in case of antibiotics. Azithromycin, Amoxicillin, Ciprofloxacin, Cephadrine, Cefixime etc. are widely used antibiotics in the country because these are very effective weapons against microbial diseases prevailing in the country. But as these antibiotics are not being manufactured by maintaining proper protocol, they cannot cure these deadly diseases. Moreover, these sub-standard antibiotics are causing development of drug-resistant microorganisms that are again an additional threat both for the present and coming generations.¹³

To prevent this public health menace, immediate measures should be taken by the government to save our population. The industries that have been engaged in manufacturing these sub-standard drugs should be awarded strong exemplary punishment like cancellation of their manufacturing license, rigorous imprisonment, huge fine and confiscation of their properties.

Moreover, the study also focus that these industries are marketing their sub-standard drugs in the remote rural areas where monitoring by the Drug Administration is feeble or absent. Taking this opportunity, these companies in collaboration with the retail drug stores are selling their sub-standard products. Thus, it is urged that as a regulatory body, the Drug Administration should improve their monitoring activities effectively so that no sub-standard drug can infiltrate the market and cause damage to public health. One of the reasons as to why some middle and small pharmaceutical industries have been engaging themselves to produce sub-standard drugs can be that they do not have the necessary manufacturing facilities to produce standard quality drugs. In this case, before issuing a new or renewing an existing manufacturing license authority must ensure that

all required facilities are being present in the premise of the industry.

Conclusion

In this study, potency of some randomly selected essential drug samples of some medium and small pharmaceutical industries of Bangladesh were analyzed and found unsatisfactory. As drugs are for the well being of health and health can't be risked, thus proper regulatory control and monitoring should be applied for the distribution of these sub-standard drugs manufactured by the medium and small pharmaceutical industries of Bangladesh. Based on the findings of the study, it is recommended that the Drug Administration should come out of its monitoring limitations, and introduce a strengthened and transparent monitoring mechanism covering the whole chain across the country; manufacturing licenses should not be renewed or issued to drug companies which are non compliant with the WHO's GMP Guidelines of 1975 and standards set out under the laws and regulations of the country; and licenses of such companies may be cancelled or suspended until the satisfactory correction. Furthermore, for small and medium pharmaceutical companies, the Drug Administration should stop issuing product registration of high technology drugs or drugs that need dedicated areas and machines to manufacture such as antibiotics. These types of product registrations already issued to these companies may be withdrawn or suspended immediately.

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