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Evaluation of Quality Control Parameters and In-Vitro Comparative assessment of formulation of Nitazoxanide Tablets Available in Bangladesh

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ABSTRACT: ***Nitazoxanide is a broad-spectrum anti-parasitic drug. It has been used to treat a variety of protozoan parasitic diseases, such as giardiasis and cryptosporidiosis. It is marketed for the treatment of equine myeloencephalitis caused by S. neurona. In Bangladesh, it is the first and only US FDA-approved drug for treatment of Cryptosporidium infection. In our study, we evaluated and compared equivalence of five different brands products of Nitazoxanide 500 mg tablets manufactured by different pharmaceutical industries in Bangladesh. We observed different parameter including, diameter, thickness, hardness, friability, disintegration time and dissolution time. The results of this study suggest that the quality control parameters of the five different brand products are satisfactory.***

Keywords: Giardiasis, cryptosporidiosis, S. neurona, Cryptosporidium infection.

1. INTRODUCTION

Nitazoxanide is a broad-spectrum anti-parasitic drug and anti-protozoal drugs. Anti-protozoal drugs are any agent that kills or inhibits the growth of organisms known as protozoans [1].

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Nitazoxanide has been used to treat a variety of protozoan parasitic diseases, such as giardiasis and cryptosporidiosis. Recently this drug has been studied as a broad spectrum anti-viral agent due to its ability to inhibit the replication of viruses [2]. *Giardia lambila* is the most commonly diagnosed intestinal parasite in the world. It has only two life-cycle stages: the binucleate trophozoite with four flagella, and the drug-resistant, four-nucleate cyst [4]. Furthermore, nitazoxanide has demonstrated efficacy against a number of viruses, including hepatitis B, hepatitis C, and influenza. It was first described in 1975 by Jean Francois Rossignol and was initially developed as a veterinary anti-helminthic with activity against intestinal nematodes, cestodes, and liver trematodes [5].

Since 1996, nitazoxanide has been marketed in most of Latin America and has been studied worldwide. The US Food and Drug Administration (FDA) approved oral suspension nitazoxanide in December of 2002 for the treatment of diarrhoea caused by Cryptosporidium species and Giardia intestinalis in pediatric patients 1–11 years of age, and in July 2004, nitazoxanide was approved for treatment of diarrhoea caused by G. intestinalis in adults [3]. In June 2005 the drug was approved for treatment of diarrhoea caused by Cryptosporidium in children ≥ 12 years of age and adults. In addition, the drug is marketed for the treatment of equine myeloencephalitis caused by S. neurona. Application for approval in the EU was filed, but not granted [5].

It is the first and only US FDA-approved drug for treatment of Cryptosporidium infection and is the first new drug approved for treatment of *Giardia lambila* infection in 140 years [3]. It is also effective in treating diarrhoea caused by C. parvum in patients with AIDS; its activity varies, depending on the degree of immunosuppression and the duration of treatment [6]. In vitro studies have also shown antimicrobial activity against numerous gram-positive and gram-negative anaerobic bacteria, specifically Bacteroides species, Clostridium species, and *Helicobacter pylori*, and against aerobic gram-positive bacteria [7, 8]. Over 50% of the global population suffers from parasitic illnesses, which constitute a significant health risk, especially in developing nations where they are most common.

The present study deals with performing a comparative evaluation of the quality control parameters are including; hardness, weight variation, friability, disintegration, and dissolution time of five tablet containing Nitazoxanide 500mg.

2. METHODS AND MATERIALS

2.1. Materials

Nitazoxanide 500 mg tablets were collected from local markets, manufactured by different pharmaceutical industries in Bangladesh and Potassium hydrogen Phosphate ($KHPO_4$), distilled water and Hydrochloric acid (HCl) were collected from Merck Germany. Nitazoxanide 500 mg tablets of five different manufacturers were purchased from a model pharmacy in Dhaka and designated as A, B, C, D and E. Instruments used were analytical balance, tablet hardness tester, UV- vis spectrophotometer, disintegration tester, dissolution test apparatus and pH meter.

2.2. Diameter and Thickness

The thickness and diameter of individual tablet was measured using ERWEKA TBH 425 TD (Erweka, Germany). 20 tablets from each brand were used and the average value of diameter and thickens were calculated.

2.3. Weight Variation Test

Twenty tablets were randomly selected from each brand and weighed individually using an analytical balance RADWAG (AS 220.R2 Plus). The mean and standard deviation were calculated. Then the percentage of weight variation was calculated by using the following formula:

$$\%\ \text{of weight Variation} = \frac{\text{Average weight} - \text{individual weight}}{\text{Average weight}}\ 100\%$$

$$\text{Highest weight Variation} = \frac{\text{Highest weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

$$\text{Lowest weight Variation} = \frac{\text{Lowest weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

2.4. Hardness

To conduct the hardness test, 10 tablets of each brand were randomly selected and the crushing strength of the tablets was measured by Monsanto hardness tester. The average hardness of the tablet was calculated and the standard deviation was determined.

2.5. Friability

For each of the brands, 10 tablets were selected and carefully dusted before testing, and weighed. Then the tablets were placed in the drum of friability tester (VEEGO, India) and rotated at the speed of 25rpm for 4 minutes. After 100 revolutions and de-dusting, tablets were re-weighed and the friability percentage was calculated by the following equation:

$$\%\text{Friability} = \frac{\text{Weight before test} - \text{Weight after test}}{\text{Weight before test}} 100\%$$

2.6. Disintegration Time

Six tablets were randomly selected from each brand and placed in the disintegration apparatus (Electronics India Model-912), which is filled by 900 mL of distilled water (disintegration medium) maintained at 37±1°C. The time taken to disintegrate the tablet and pass through the mesh was recorded and the mean of time taken was calculated.

2.7. In vitro release studies

The dissolution test was carried out using USP apparatus 2 (paddle method). A buffer was prepared from potassium phosphate (pH 5.8) with a temperature maintained at 37±1°C throughout the experiment. The samples were withdrawn after 5, 10, 20, 30, 45, and 60 minutes and the equivalent amount of fresh buffer solution was immediately introduced as a replacement. The samples were filtered and assayed for drug content by measuring the absorbance at 243nm using a UV spectrophotometer. Phosphate buffer was used as a blank.

2.8. Statistical analysis

The information of the collected prescription data was input into Microsoft excel sheet and analyzed following descriptive statistics. Results were expressed graphically in frequency and percentage. The prescription data was double checked for accuracy.

3. RESULTS AND DISCUSSIONS

The study was conducted using five different trades products of Nitazoxanide 500 mg tablets. All five trades are manufactured and marketed by different pharmaceutical industries in Bangladesh. Here, all trade products contain Nitazoxanide 500 mg active ingredient. Several tests were performed to evaluate the quality control parameters of five different brands of Nitazoxanide 500 mg tablets.

Table 01: Disintegration variation among five brands of Nitazoxanide 500 mg tablets.

Trades	Disintegration time in second													
	Sample										Mean	Maximum	Minimum	SD
	1	2	3	4	5	6	7	8	9	10				
A	300	375	318	335	315	355	396	308	343	302	334.7	396	300	32.52
B	80	74	102	95	107	85	77	113	92	123	94.8	123	74	16.33
C	152	111	135	142	129	117	99	175	131	109	130	175	99	22.63
D	383	435	487	391	424	398	413	462	406	431	423	487	383	32.43
E	552	602	597	580	633	649	564	586	619	568	595	649	552	31.33

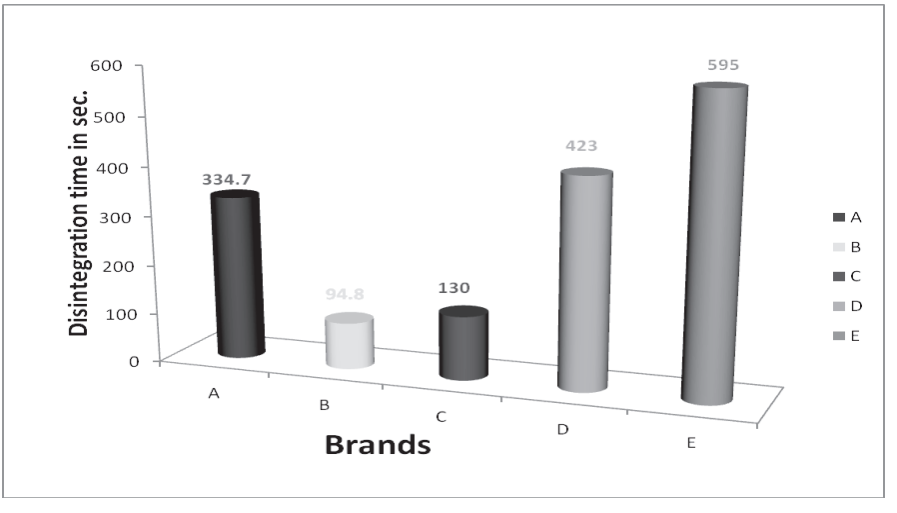

Figure 01: Comparative disintegration variation among five trades of Nitazoxanide 500 mg tablet.

Table 02: Percent of Drug release rate of different trades of Nitazoxanide.

Brand	0 min	5 min	10 min	20 min	30 min	45 min	60 min
A	0	35.1	52.39	69.78	90.87	95.87	97.29
B	0	30.6	48.77	60.74	86.25	92.15	96.26
C	0	27	44.25	54.78	80	91.14	94.34
D	0	33.3	54.18	67.08	87.25	94.03	96.35
E	0	26.1	45.24	62.49	83.54	88.5	92.58

The 5 different trades of Nitazoxanide 500 mg tablets were evaluated in terms of diameter, thickness, weight variation, hardness, friability, disintegration time and dissolution time. In case of diameter, the minimum value was 16.62mm and maximum value was 19.11mm. The range of thickness varies in between 5.64mm and 6.70mm but there was a significant difference in terms of average weight different brands of Nitazoxanide 500mg tablets. The maximum average weight found as 1037.51mg for brand B followed by 833.83mg, 816.29mg and 782.72mg for brand C, brand D and brand A respectively. On the other-hand, the minimum weight was found on brand E which was 714.82 mg. Highest Weight Variation for the brand A is 0.866% and the limitation is ±5%. So, it is passing in highest weight variation test. Lowest Weight Variation for the brand A is 1.165% and the limitation is ±5%. So, it was passing in lowest weight variation test. Hardness of the brand A is 276.80N. Hardness test was also an unofficial test. According to Lachman, Oral tablets should have hardness minimum 4 kg or 39.24 N. The tablet size is big and its average weight was 782.72 mg. So, it is passing the hardness test. The calculated friability of the brand is 0.0396% & limitation is less than 0.5% to 1%. So, it is passing the friability test.

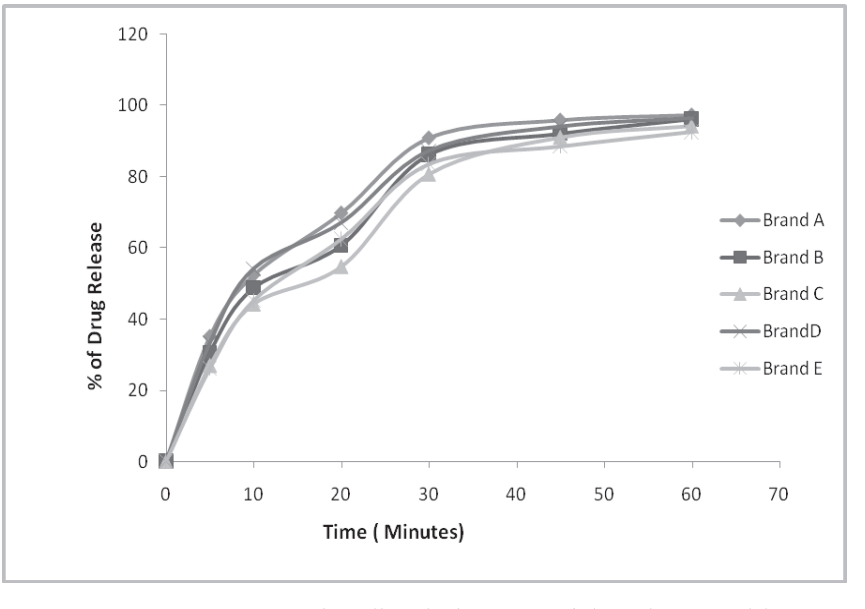

Figure 02: Comparative dissolution rate of the Nitazoxanide 500mg tablets of different brands in Bangladesh.

Table 03: Quality controls parameters of the five trades of Nitazoxanide 500 mg tablets.

Parameter	Trades				
	A	B	C	D	E
Diameter(mm)	17.17	19.11	18.21	18.09	16.62
Thickness(mm)	6.25	5.67	5.93	5.64	6.70
Weight (mg)	782.72	1037.51	833.83	816.29	714.82
Highest Weight variation (%)	0.866	1.782	1.850	1.385	2.221
Lowest Weight variation (%)	1.165	3.306	1.202	.709	2.395
Hardness (N)	276.80	280.40	238.20	218.40	276.60
Friability (%)	0.0396	0.0134	0.0288	0.0342	0.0293
Disintegration Time (Sec)	334.7	94.8	130.0	423.0	595.0
DissolutionTime (60min)	97.29	96.26	94.34	96.35	92.58

Disintegration time for this brand is 334.7 sec & limitation is 900 sec. So, it is passing the disintegration test. The Dissolution time for this brand is released 96.26% in 60 minutes & more than 80% is released within 30 minutes. It is an immediate release tablet. So, it is passing the dissolution test. In case of Brand B, Highest Weight Variation for this brand is 1.782%& the limitation is ±5%. So, it is passing in highest weight variation test. The Lowest Weight Variation for this brand is 3.306%& the limitation is ±5%. So it is passing in lowest weight variation test. The Hardness of this brand is 280.40 N. Hardness test is also an unofficial test. According to Lachman, Oral tablets should have hardness minimum 4 kg or 39.24 N. The tablet size is big & its average weight is 1037.5 mg. So, it is passing the hardness test. The calculated friability of this brand is 0.0134% & limitation is less than 0.5% to 1%. So, it is passing the friability test. Disintegration time for this brand is 94.8 sec & limitation is 900 sec. So, it is passing the disintegration test. Dissolution time for this brand is released 97.29% in 60 minutes & more than 80% is released within 30 minutes. It is an immediate release tablet. So, it is passing the dissolution test.

In case of generic product C, Highest Weight Variation for this brand is 1.850% & the limitation is ±5%. So, it is passing in highest weight variation test. Lowest Weight Variation for this brand is 1.202% & the limitation is ±5%. So, it is passing in lowest weight variation test. Hardness of this brand is 238.20 N. Hardness test is also an unofficial test.

According to Lachman, Oral tablets should have hardness minimum 4 kg or 39.24 N. The tablet size is big & its average weight is 833.83 mg. So, it is passing the hardness test. The calculated friability of this brand is 0.0288% & limitation is less than 0.5% to 1%. So, it is passing the friability test. Disintegration time for this brand is 130 sec & limitation is 900 sec. So, it is passing the disintegration test. Dissolution time for this brand is released 94.34% in 60 minutes & more than 80% is released within 30 minutes. It is an immediate release tablet. So, it is passing the dissolution test.

In case of generic product D, Highest Weight Variation for this brand is 1.385% & the limitation is ±5%. So, it is passing in highest weight variation test. Lowest Weight Variation for this brand is .709% & the limitation is ±5%. So, it is passing in lowest weight variation test. Hardness of this brand is 218.40 N. Hardness test is also an unofficial test. According to Lachman, Oral tablets should have hardness minimum 4 kg or 39.24 N. The tablet size is big & its average weight is 816.29 mg. So, it is passing the hardness test. The calculated friability of this brand is 0.0342% & limitation is less than 0.5% to 1%. So, it is passing the friability test. Disintegration time for this brand is 423 sec & limitation is 900 sec. So, it is passing the disintegration test. Dissolution time for this brand is released 96.35% in 60 minutes & more than 80% is released within 30 minutes. It is an immediate release tablet. So, it is passing the dissolution test.

In case of generic product E, Highest Weight Variation for this brand is 2.221% & the limitation is ±5%. So, it is passing in highest weight variation test. Lowest Weight Variation for this brand is 2.395%& the limitation is ±5%. So it is passing in lowest weight variation test. Hardness of this brand is 276.60N. Hardness test is also an unofficial test. According to Lachman, Oral tablets should have hardness minimum 4 kg or 39.24 N. The tablet size is big & its average weight is 714.82mg. So, it is passing the hardness test. The calculated friability of this brand is 0.0293% & limitation is less than 0.5% to 1%. So, it is passing the friability test. Disintegration time for this brand is 595sec & limitation is 900 sec. So, it is passing the disintegration test. Dissolution time for this brand is released 92.58% in 60 minutes & more than 80% is released within 30 minutes. It is an immediate release tablet. So, it is passing the dissolution test.

4. CONCLUSIONS

Nitazoxanide is an antiprotozoal medicine that treats infections caused by protozoa (single-cell parasites that live in moist places such as lakes, streams, and soil). Nitazoxanide is used to treat diarrhoea caused by Giardia or Cryptosporidium.

These conditions are sometimes called "Traveler's diarrhoea." Nitazoxanide is used in adults and children who are at least 1 year old. In our study, we evaluated and compared equivalence of five different generic products of Nitazoxanide 500 mg tablets manufactured by different manufacturers in Bangladesh. We observed different parameter including, diameter, thickness, hardness, friability, disintegration time and dissolution time. All parameters matched acceptable limit as per BP or USP specified ideal specification. Since Nitazoxanide 500 mg tablets is one of the prescription drugs which is used as an antiprotozoal agent worldwide. To conserve the trade secrecy, we did not disclose the name of manufacturers. We shall not disclose the faults or mistake of any manufacturers' products studied by us.

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Conflict of Interest: The authors declare no conflict of interest.

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