

## Journal of Coastal Life Medicine

journal homepage: www.jclmm.com



Original article doi: 10.12980/jclm.4.2016J6-101

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## Pharmaceutical evaluation and comparison of different brands of metronidazole available in the local market of Peshawar (Pakistan)

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## ARTICLE INFO

## Article history:

Received 6 Jun 2016

Received in revised form 18 Jul 2016

Accepted 25 Jul 2016

Available online 3 Aug 2016

## Keywords:

Metronidazole

Friability

Hardness

Weight variation

Dissolution

Disintegration

## ABSTRACT

**Objective:** To assess the pharmaceutical quality of different brands of metronidazole manufactured, available and prescribed by the doctors of Peshawar, Pakistan.**Methods:** Different film-coated metronidazole products manufactured by multinational and national pharmaceutical industries and prescribed by the doctors were collected from Peshawar, Khyber Pakhtunkhwa, Pakistan. Their physico-chemical properties were assessed, which included friability, hardness, disintegration, dissolution and weight variation tests according to the United States Pharmacopoeia (USP) standards.**Results:** All the brands showed a average weight of 5.74 g for 13 tablets (products A–M). Product J had the highest weight and products D and E failed the hardness, friability and disintegration time according to USP standards. Products M, K and G, L failed disintegration test and dissolution test, respectively. Weight variation of all the products proved statistically that they were in accordance with the standards of USP.**Conclusions:** The study suggested that products A, F, H and J passed all the tests according to the USP standards while the rest of them did not fulfill the standards specification.

## 1. Introduction

Metronidazole is a nitroimidazole derivative, classified as tissue and luminal amoebocides. It is effective against protozoal infestations and bacterial infections[1]. It is inexpensive with good tissue penetration tendency and produces relatively mild side effects. Metronidazole is available in forms of white to off-white, circular biconvex, film-coated tablets, *i.e.* round or oblong. The International Union of Pure and Applied Chemistry name for metronidazole is 2-(2-methyl-5-nitro-1-H-imidazol-1-y) ethan-1-ol, having molecular formula C<sub>6</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>, molecular mass 171.15 g/mol, while the melting point is 159–163 °C.

It has been used for the treatment of infections for more than 45 years and is still in use for the treatment of amoebiasis, giardiasis, infections during pregnancy, bacterial vaginosis and prophylaxis against anaerobic infection after bowel surgery, wound abscess, antibiotic-associated colitis against *Helicobacter pylori* and

*Giardia lamblia* that can cause travelling diarrhea[2-4]. However, the chances of the development of clinically drug-resistant strains of *Helicobacter pylori* leading to gastro intestinal GI cancer may increase by overusing metronidazole for the treatment of parasitic infections[5].

When metronidazole is administered, it inhibits nucleic acid synthesis by disrupting the DNA of microbial cells[6]. Metronidazole is a well tolerated and safe antibiotic, as it does not cause any serious adverse effects[7]. Metronidazole is available in different formulations of suspension, tablets, creams and infusion of which tablets is widely prescribed products in health care settings[8]. Metronidazole can be administered through different routes like rectal, topical, intravenous, oral and vaginal having different bioavailability percentages, *i.e.* 80% (oral), 60%–80% (rectal), 20%–25% (vaginal)[6]. It is metabolized by liver, excreted through urine, having biological half-life for 8 h. Common adverse drug reactions treated by metronidazole therapy include, nausea, diarrhea, weight loss, abdominal pain, vomiting, headache dizziness, metallic taste in the mouth, thrombophlebitis, hypersensitivity reactions (rash, itch, flushing, fever), glossitis, dark urine, paresthesia, skin irritation; and eye watering (if it's applied near eyes)[8]. Metronidazole may interact with other drugs like alcohol, alprazolam, busulphan, carbamazepine, cimetidine, lithium disulfiram phenytoin, *etc.* These interactions are sometime beneficial and may sometime pose threats

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to life.

Metronidazole is available in white to off-white, circular biconvex or film-coated tablets. Film-coating is a thin layer of an inactive excipient that is applied on tablets to prevent the bitter taste while taking the medicines, protect the tablet from microbial growth moisture, light and color changes or to meet the desired release profile. Polymers employed for these tasks are mostly water-soluble, such as cellulose ethers, *e.g.* hydroxypropyl methylcellulose, polyvinyl acetate or polyvinyl pyrrolidone[9]. Different problems may arise during film coating of metronidazole like scuffing, excessive roughness (orange peel), twinning, surface erosion, discoloration, picking and sticking, logo bridging, breakage film, cracking, film peeling, tablet edge chipping erosion and filling of logos/break lines due to non-technical handling of tablets by untrained personnels, use of non-suitable polymers for coating, lack of following the standard operating procedures for film coating, no control on temperature[10], *i.e.* over drying or over wetting the tablets to be coated[11,12], using high viscous polymers, very sharp tablet edges[13]. So, corrective measures should be taken as a remedy in case of any problem that arises during film coating like to change the tablet's shape, shorten the duration of the film coating process, decrease spray rate[14], make tablet having greater mechanical strength and high flexibility[15] and increase pan speed in the spray zone.

The main objective of the study was to assess the relative quality parameters of 13 brands of metronidazole, which were manufactured and available in Peshawar, Khyber Pakhtunkhwa, Pakistan. The metronidazole treatment protocols commonly employed are three times per day for 3–5 days[16]. It is typically administered to adults in doses of 250 mg three times a day for 5–7 days and 15 mg/kg three times a day for 5–7 days in children. Orally administered drugs induce 90% systemic effect. So dosage form of tablets highlights their extensive importance. Content uniformity and adequate bioavailability are two factors that show the therapeutic effectiveness of the compressed tablets[8]. Excipient's physicochemical properties and active pharmaceutical ingredients are also of great importance during manufacturing processing of the tablet[17].

## 2. Material and methods

In the current study, a total of 13 commercially available registered brands of metronidazole tablets were used. Six different brands were purchased from registered wholesale dealers and seven were collected from the manufacturer companies in Hayatabad, Industrial

State, Peshawar, Khyber Pakhtunkhwa, Pakistan. Out of the 13 brands, one brand was from multinational manufacturer and the rest were national manufacturers. British pharmacopeia and United States Pharmacopeia (USP) were used as standards for quality evaluation.

### 2.1. Physical appearance and weight

Physical appearance of tablets of each brand was seen. Ten tablets were randomly selected for each brand and weighed individually with the help of a weight balance (Model, Chyo JK-180).

### 2.2. Friability test

Tablets friability test apparatus was used for the determination of durability of the tablet at the time of production. Ten tablets were randomly selected and weighed for the purpose of friability test. Tablets were then placed into calibrated friabilator for 4 min at 25 r/min. The differences in weight were calculated as percentage friability by weighing the tablets again. The percentage (%) losses of 10 tablets were calculated as per the following equation:

$$\text{Friability (\%)} = (W1 - W2)/W1 \times 100$$

W1 = Weight of 10 tablets before friability test

W2 = Weight of 10 tablets after friability test

### 2.3. Hardness test

Hardness of 4 tablets from each brand was measured individually by calibrated hardness apparatus. Standards for adjustment of hardness apparatus based on physical appearance of the tablets were given Table 1. The standardized value for hardness ranges from 8–15 kg/cm<sup>2</sup>. After operating the procedure for 4 tablets of each sample, the mean value was calculated.

### 2.4. Disintegration test

The apparatus used for disintegration test was calibrated before carrying out the test. The apparatus contained two beakers of 1000 mL capacity having six basket assemblies with supporting transparent cylindrical tubes. The basket assembly moved upward and downward inside the premises of beaker at 28–32 oscillation/min with equal retention time. Six tablets were taken from each brand and used on the disintegration testing apparatus. Distilled

**Table 1**

Detailed results of all the performed tests of the generic metronidazole tablets of different brands.

No.	Brand	Physical appearance	Weight (g)	Friability (%)	Hardness (Kg/m <sup>2</sup> )	Disintegration time (min)	Assay (%)	Dissolution (%)
1	Product A	Spherical	5.43	0.02	14.80	8.00	92.00	109.00
2	Product B	Spherical	6.21	0.06	7.40	39.00	76.00	99.20
3	Product C	Oblong	6.88	0.03	10.00	2.00	65.40	66.50
4	Product D	Spherical	5.06	1.00	5.40	40.00	89.10	85.70
5	Product E	Spherical	5.84	1.15	17.00	13.00	87.83	80.50
6	Product F	Spherical	5.11	0.02	10.55	11.00	97.20	101.00
7	Product G	Spherical	5.16	0.04	10.47	23.30	106.40	47.60
8	Product H	Spherical	5.26	0.10	13.00	7.90	100.00	109.00
9	Product I	Oblong	6.34	0.05	16.10	12.00	101.89	102.60
10	Product J	Oblong	7.56	0.14	14.70	15.00	101.00	85.70
11	Product K	Spherical	4.69	0.06	13.00	18.00	98.91	97.36
12	Product L	Spherical	5.24	0.13	10.80	15.00	68.00	67.89
13	Product M	Spherical	5.90	0.03	22.30	13.00	97.29	97.10

water thermostated at 37 °C was used as the disintegrating medium. The time taken by each tablet to break up and pass through the mesh screen was recorded. As the samples were coated, the insoluble coating remained on the screen of the test apparatus. To pass the test, all of the six tablets should be disintegrated.

### 2.5. Dissolution of metronidazole

For dissolution purpose “paddle 2 basket method” was used. “Model DL 0298” was used for the detection of dissolution. It contained six beakers of 1000 mL capacity. Concentrated HCl (8.65 mL) was dissolved in distilled water to make the volume up to 1000 mL. The calculated amount of concentrated HCl was taken by using the given formula:

$$\text{Required normality} \times \text{Gram equivalent weight} \times \text{Volume required} = 0.1 \times 36.46 \times 1 = 8.65 \text{ mL}$$

$$\text{Percentage purity} \times \text{Density} = 1.19 \times 0.354$$

Dissolution apparatus was set according to the USP standards (0.1 mol/L HCl, 277 nm, 37 °C). Fifty milligrams of standard pure powdered metronidazole was diluted in 100 mL of 0.1 mol/L HCl in 100 mL flask then second dilution was made by taking 2 mL from this solution and diluted in 100 mL of 0.1 mol/L HCl. Blank solution in 100 mL flask (0.1 mol/L HCl) was taken. After standardizing the apparatus according to the standards of USP, one tablet of metronidazole (sample) of the same brand was put into each beaker containing the media and ran for 60 min. After 60 min, 5.6 mL of this solution was dissolved in 250 mL flask and made the volume by 0.1 mol/L HCL up to 250 mL. The same procedure was applied for the rest five beakers containing metronidazole. The sample was then analyzed by double beam spectrophotometer.

### 2.6. Weight variation test

Ten tablets from each sample were weighed. The average weight was calculated within the composite sample that had an acceptable average weight. The USP provided limits for the permissible variations in the weights of individual tablets expressed as a percentage of the average weight of the sample. The lower limit and upper limit were calculated by the following formula:

$$\text{Upper limit} = \text{Average weight} + 5\%$$

$$\text{Lower limit} = \text{Average weight} - 5\%$$

## 3. Results

In the present study, 13 brands of metronidazole were randomly selected from the Peshawar local pharmaceutical market by using probability-sampling tools. Various tests, *i.e.* weight, weight variation test, hardness, friability, disintegration and dissolution assay were performed by using UV double beam spectrophotometer in accordance with the stated methods and guidelines given in USP. The detailed results of all the tests that were performed were given in Table 1.

### 3.1. Physical appearance and weight

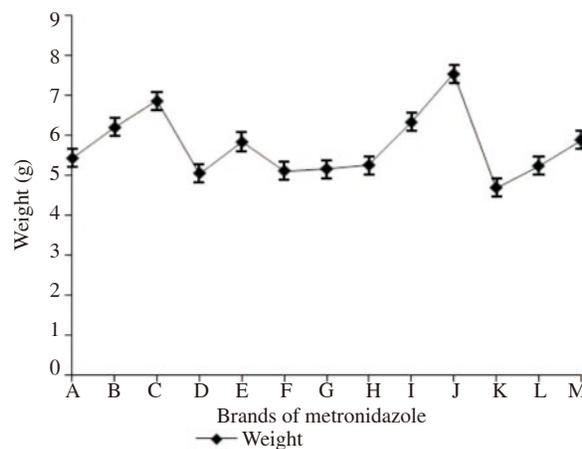
Table 2 shows the physical appearance of the selected brands of metronidazole available in market and USP standards for adjustment

of the hardness apparatus, which included initial position value, slow limit value and force limit value. Products C, I and J were oblong in shape while the rest are spherical. Figure 1 shows that product J brand has the maximum weight as compared to the other weights of the selected brands. There was no significant difference between the weights of the products F, G and H. Product K has the lowest tablet weight.

**Table 2**

USP standards for adjustment of hardness apparatus based on physical appearance of the tablets.

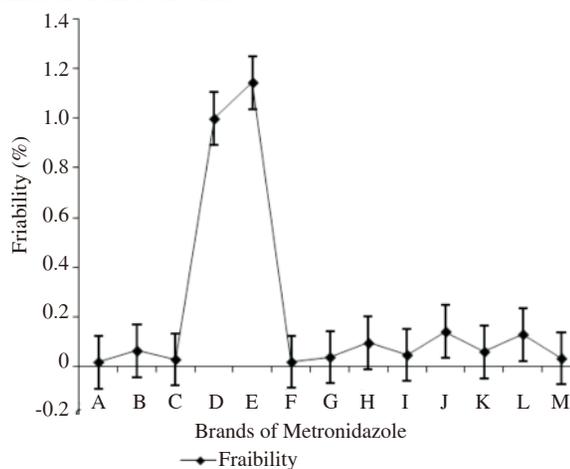
Physical appearance	Initial position value	Slow limit value	Force limit value
Round	20 mm	16 mm	20 kg
Oblong	22 mm	18 mm	25 kg



**Figure 1.** Weight of tablets of different brands (products A–M) of metronidazole.

### 3.2. Friability

Figure 2 shows the friability in percentage of all the selected brands from different markets of Peshawar region. Product F had the highest friability value and product A showed the lowest friability value. All the friability percentage of the samples were significantly different from each other.

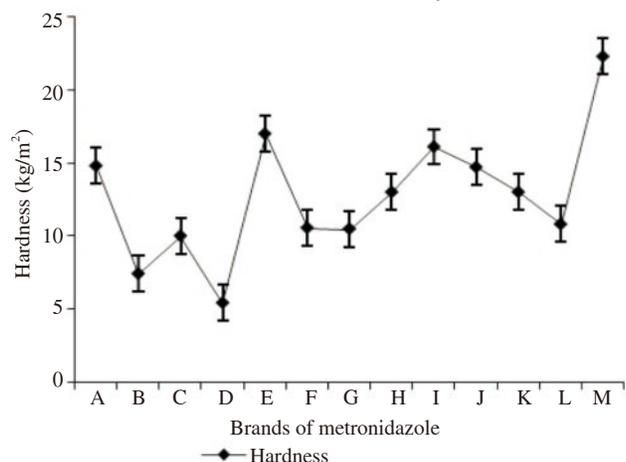


**Figure 2.** Fraibility (%) of different brands (products A–M) of metronidazole.

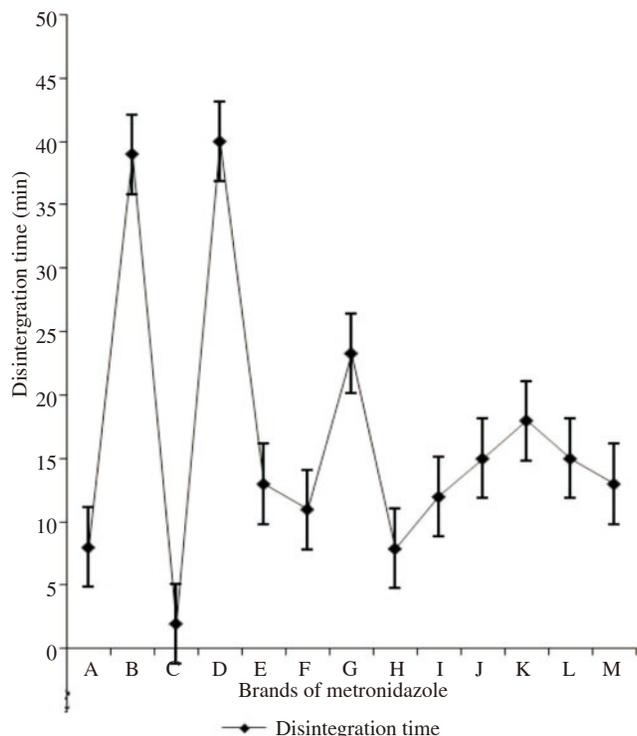
### 3.3. Hardness test

Figure 3 shows the hardness test results and clearly indicates that the results of all the samples significantly differ from each other. The

friability value of product M brand was higher than all of the brands. Products G and F brands were not significantly different from each other. Product D brand had the lowest friability value.



**Figure 3.** Hardness (Kg/m<sup>2</sup>) of different brands (products A–M) of mteronidazole.



**Figure 4.** Disintegration time (min) of different brands (products A–M) of mteronidazole.

**Table 3**

Weight variation calculations.

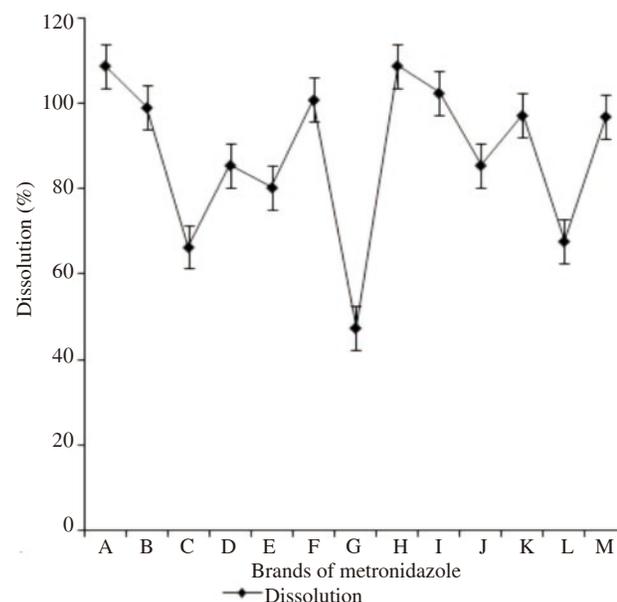
No.	Brands	Average weight of 10 tablets (W)	Limit value (W × 5%)	Upper limit value (W + Limit value)	Lower limit value (W – Limit value)
1	Product A	548.50	27.43	575.93	521.08
2	Product B	602.60	30.13	632.73	572.47
3	Product C	698.60	34.93	733.53	663.67
4	Product D	507.50	25.38	532.88	482.13
5	Product E	580.30	29.02	609.32	551.29
6	Product F	508.40	25.42	533.82	482.98
7	Product G	512.50	25.63	538.13	486.88
8	Product H	511.90	25.60	537.50	486.31
9	Product I	634.70	31.74	666.44	602.97
10	Product J	756.60	37.83	794.43	718.77
11	Product K	450.70	22.54	473.24	428.17
12	Product L	531.70	26.59	558.29	505.12
13	Product M	595.30	29.77	625.07	565.54

### 3.4. Disintegration time

Figure 4 shows the disintegration time of all the samples. Graphical representation of the data showed that product C had the lowest disintegration time as compared to the other samples. While product D has the highest disintegration time followed by product B. There was no clear significant difference between products L, J and I brands. The graph also suggested that no clear significant difference could be seen between product M and K.

### 3.5. Dissolution test

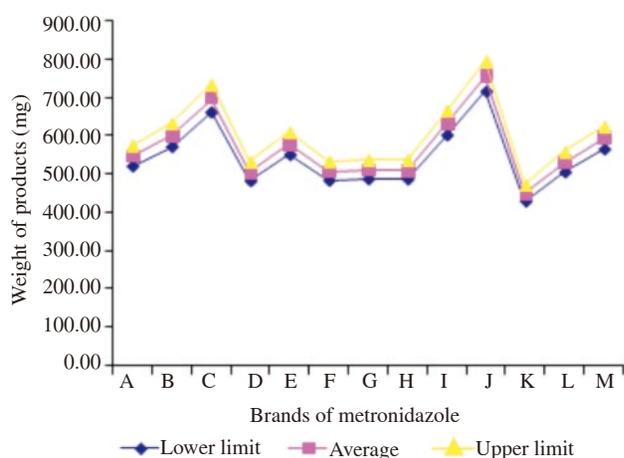
Figure 5 shows the dissolution of each sample. Products M and K did not show significant differences. Product G brand showed the lowest dissolution time as compared to the others.



**Figure 5.** Dissolution (%) of different brands (products A–M) of mteronidazole.

### 3.6. Weight variation test

Figure 6 shows the weight variation results of all brands of metronidazole. The data suggested that the tests were positive for all the products as their average weight ranged within the lower limit and upper limit according to the standards of USP. Table 3 gives detailed calculations of weight variation test.



**Figure 6.** Weight variation of different brands (products A–M) of metronidazole.

## 4. Discussion

### 4.1. Friability

Friability is the measure of the tendency for a tablet to chip, crumble or break, during handling, tumbling motion, transportation, coating, packaging and storage[18]. It can be caused by a number of factors including poor tablet design (too sharp edges), low moisture content, insufficient binder, *etc.* For obvious reasons, tablet is formulated to withstand such stresses without damage but friable enough that it can disintegrate in the gastrointestinal tract. According to USP, the friability value of tablets should be less than 1%[19-21], and as such all the brands of metronidazole tablets had passed this friability specification except brands of products D and E. These 2 brands of metronidazole failed the friability test. As products A and C had low values of friability than all of the brands so it showed that they had higher durability than other brands (Figure 2). All the brands had shown their friability variation within  $\pm 1\%$  range specified by USP. Standard deviation was calculated among all the brands which were very close to individual percentage friability of all the brands.

### 4.2. Hardness

Tablet hardness has been defined as the force required breaking a tablet in a diametric compression test. Hardness test is an important process in assessing whether the tablets being produced are firm enough to withstand breakage, chipping or crumbling, consumer handling and yet not so hard as to delay disintegration and dissolution time[22]. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications. Again, if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The USP states that the friability value of tablets should be in 8–15 kg/m<sup>2</sup> limit. In the present study, among the 13 brands of metronidazole tested, products B and D showed comparatively lower hardness (7.4 and 5.4 kg/m<sup>2</sup>, respectively) than other brands (Figure 3). However, products E, I and M showed higher hardness values than the rest of the brands (17.0, 16.1 and 22.3 kg/m<sup>2</sup>, respectively from each). Hardness value of products

F and G did not differ much from each other, *i.e.* 10.55 and 10.47 kg/m<sup>2</sup>, respectively. Products H and K hardness value were same (13 kg/m<sup>2</sup>). Reasons for more hardness of tablets are addition or deletion of binder, over weight granules, over dried granules, small but dense particles, excessive lubrication. Hardness is a problem of lower punch. Hardness is adjusted within 2.5–10 kg by adjusting the upper punch and high speed of machine. Hardness can be controlled by adjusting the parameters like force of compression, By adjusting the upper punch of compression machine, particle size and die filled ratio is very important, and speed of compression machine must be adjusted, Proper ratio of binders and lubricants and diluents were used.

### 4.3. Disintegration time

This test provides tablets disintegration within prescribed time when they are placed in liquid medium. The disintegration time test measures the time for a tablet into smaller particles in physiological media. This parameter is a basic step prior to the release of the active ingredient for the desired biological activity. Standard limits for disintegration time of coated tablets are 15–30 min while for uncoated tablets its limit is less than 15 min as per USP standards[23]. Disintegration could be related to dissolution and similarly availability of drug to body (absorption), and finally the therapeutic efficacy of product[8]. As all our samples were coated tablets, so we followed the standard limits of disintegration time for coated tablets. Product D showed higher disintegration time (40 min) and failed the test. Product I, J and L did not show differences in disintegration time which was 15 min. Similarly, Products M and K disintegration time was 18 minutes. Products C, E and F failed the test as they were below the USP standards (2, 13 and 11 min, respectively.) The rest of metronidazole brands passed the test.

### 4.4. Dissolution test

Dissolution is the rate of mass transfer from the product to the bulk of solution[24]. One aim of dissolution testing is to guarantee the quality of the pharmaceutical product and prove consistency from one batch to another and no important change occurs during the stability study. Any change in dissolution could impact the efficacy of the pharmaceutical product. In order to detect inconsistencies and changes, the retained conditions (basket or paddle for tablets, medium type, rotation speed, volume, pH, sampling times, use of sinker or not, *etc.*) should be discriminant. That means that the dissolution test should highlight a change when it occurs. The best way to prove discriminance is to have “bad batches” vs. “good batches”, which may help to prove this discriminance. A dissolution test that goes too fast (100% dissolved within 5 or 10 min) will certainly mask potential differences between a “bad batch” and a “good batch”. The limits for dissolution test according to the standards of USP should not be less than 80%. And all the samples of our study were in accordance with the standards of USP except products C, G and L whose values were below the standards of USP. All the positive dissolution test samples are significantly different from each other.

#### 4.5. Weight variation

With a tablet designed to contain a specific amount of drug in a specific amount of formula, the weight of tablet being made is routinely measured to ensure that the tablet contains the proper amount of drug. The weight variation test would be a satisfactory method of determining drug content uniformity of tablets to ensure good manufacturing practices[25]. The tablets meet the USP test if no more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit[26]. The weight variation test is clearly not sufficient to ensure uniform potency of tablets of moderate or low-dose drugs, in which excipients make up the bulk of tablet weight.

Over all the study revealed the different qualitative and quantitative pharmaceutical tests for the 13 brands of metronidazole taken from local market of Peshawar, KP, Pakistan, according to the USP standards. It is concluded that products A, F, H and J full filled all the standard pharmaceutical parameters defined by USP for best biological and chemical activity of metronidazole except products B, C, D, E, G, I, K, L and M which failed either one or all the stated tests.

#### Conflict of interest statement

We declare that we have no conflict of interest.

#### Acknowledgments

This research was supported by Department of Pharmacy, Sarhad University of Science and Technology, Peshawar. We thank to the Quality Assurance Inspector and the supporting staff of Stanley Pharmaceuticals, Peshawar, for their guidance in performing all the practical work, encouragement and cooperation throughout the research work.

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