International Journal of Research in Pharmacy and Pharmaceutical Sciences
ISSN: 2455-698X
Impact Factor: RJIF 5.22
www.pharmacyjournal.in
Volume 3; Issue 1; January 2018; Page No. 21-27

Evaluation of promethazine tablets available at Libyan markets

[*] Antesar M Boshhiha, Faiza Mosbah Elhssony, Marwa Omar Diryaq
Faculty of Pharmacy, Pharmaceutics Department, Benghazi University, Benghazi, Libya

Abstract
Promethazine hydrochloride tablets commercially available at Libyan market. It is use as antihistaminic tablet, strong seddative, reduce motion sickness, and has antiemetic and anticholinergic properties. It works as competitive histamine (H_1) and alpha - adrenergic receptor antagonist. This study aims to measure the quality of those promethazine tablets and the released active ingredient.
Material and Methods: Promethazine Hydrochloride 25mg tablets purchased from pharma international company (drug distributer of Remedica), Benghazi-Libya. The tests used in this study were the following: hardness, friability, weight uniformity, content uniformity, disintegration, and dissolution test. Those tests certified at the British pharmacopeia (Bp).
Results: The hardness test shows a hardness value of 6.76kg. This means that the tablet meets the pharmacopeial requirements. The promethazine tablet with 0.401cm thickness(h) and 0.820cm in diameter (r) requires a force of 13.465kg\cm (T.s) to be broken. The results obtained comply with the British pharmacopeia1998. The promethazine tablet has friability of 0.032%, which does not comply with the British pharmacopeia1998. The promethazine tablets have weight uniformity of 209.3mg. Which means that the tablet is uniform in weight and accepted according to the pharmacopeial limits. Disintegration test shows that the tablets completely disintegrated after 1.84min. The content uniformity test shows results within a pharmacopeial limit. Additionally, the dissolution test results were out of the pharmacopeial range.
Conclusion: The promethazine tablets deviate from some pharmacopeial tests, which emphasized the need of continuous investigations to the antihistaminic tablets present at Libyan market to ensure the quality of medicines for the Libyan patients.

Keywords: content uniformity, weight uniformity, hardness, disintegration

1. Introduction
Promethazine is a neuroleptic medication and is one of the first-generation antihistamine of the phenothiazine family. The drug has strong sedative and weak antipsychotic effects. It reduces motion sickness and has antiemetic and anticholinergic properties (via its action on the dopamine receptor D2). In some countries, it has prescribed for insomnia when benzodiazepines are contraindicated. Promethazine was developed mid-1940s when team of scientists from Rhone-Poulenc laboratories were able to synthesize it from phenothiazine and a diamine side chain of diphenhydramine [7, 9].

Promethazine is used to relieve the symptoms of allergic reactions such as allergic rhinitis (runny nose and watery eyes caused by allergy to pollen, mold or dust), allergic conjunctive, allergic skin reaction, and allergic reaction to blood or plasma products. Promethazine used with other medications to treat anaphylaxis and the symptoms of the common cold such as sneezing, cough, and runny nose [3, 7, 10, 11].

Promethazine HCL is a racemic compound (Figure 1); empirical formula is C17H20N2. HCL and its molecular weight is 320.88. Promethazine HCL a phenothiazine derivative, is designated chemically as 10H-Phenothiazine-10-ethanamine, N, N-trimethyl-, monohydrochloride, promethazine HCL occurs as a white to faint yellow, practically odorless, crystalline powder which slowly oxidizes and turns blue on prolonged exposure to air. It is freely soluble in water and soluble in alcohol [5].

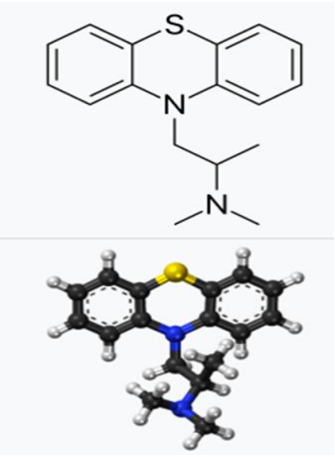

Fig 1: Chemical structure of promethazine HCl [11].

Promethazine administered parenterally via intravenous or intramuscular injection, promethazine is absorbed by the gastrointestinal tract and is 75% - 93% bound to plasma proteins. Sedation typically occur within 5 minutes of intravenous administration and within 20 minutes of intramuscular administration. When administered orally or rectally, promethazine is also absorbed through the

gastrointestinal tract and is subject to extensive hepatic metabolism [1].

Cyp450 enzymes, primarily cyp2D6 isozymes, facilitate the First-pass hepatic metabolism of the promethazine. Cyp2D6 converts promethazine to its predominant metabolite N-demethylpromethazine and various promethazine sulfoxides. Promethazine distributed widely throughout bodily tissues and organs. The duration of promethazine therapeutic effects reportedly ranges between 2 and 8 hours post-ingestion and is largely contingent upon route of administration [1].

The range of half-lives suggests that promethazine may be eliminated from plasma circulation in as early as 2.1 days and as late as 4.35 days-depending upon the route of administration. A majority of promethazine processed by kidneys and excreted via urine. Less than 1% excreted as unchanged promethazine, while the majority appears as N-desmethylpromethazine and promethazine sulfoxide metabolites [1].

The bioavailability of promethazine hydrochloride is 88% absorbed but after it has been subjected to the first-pass metabolism; its bioavailability reduced to 25% [2].

Promethazine is a phenothiazine derivative, which differs structurally from the antipsychotic phenothiazine by the presence of a branched side chain and no ring substitution [6, 8]. It is thought that, this configuration is responsible for its relative lack (1/10) of dopamine antagonist properties [4, 8].

Promethazine is an H_1 receptor-blocking agent in addition to its antihistaminic action; it provides clinically useful sedative and antiemetic effects. Promethazine is well absorbed from the gastrointestinal tract. Clinical effects are apparent within 20 minutes after oral administration and generally last four to six hours, although they may persist as long as 12 hours. Promethazine metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-demthylpromethazine are the predominant metabolites appearing in the urine [4].

Monoamino-oxidase inhibitors (MAOI)-drug interaction, including an increased incidence of extrapyramidal effect, have been reported when some MAOI and phenothiazine are used concomitantly. This possibility should be considered with phenergan tablets [4].

2. Materials and Methods

Promethazine Hydrochloride 25mgtabletswere purchased from pharma international company at Benghazi-Libya, which originally imported from the Remedca Company. Trade names Phenergan, Promethazine (HCL) Tablets. Each tablet of phenergan present as 12.5mg, 25mg or 50mg promethazine HCL. The inactive ingredients present are lactose, magnesium stearate, and methylcellulose [5].

2.1 Hardness test of promethazine tablet

Measuring tablet hardness (breaking force) plays a vital role in defining dosage form with optimum physical characteristics and testing whether the produced dosage form meets the defined specifications in manufacturing. The hardness test carried out in the hardness tester, which shown in Figure 2. Each tablet of the promethazine tablets placed between two anvils force, which applied to the anvil and the crushing strength that just causes the tablet to break recorded. To compare the mechanical strength of the tablet with different dimensions, another measurement is calculated called Tensile Strength (T.s), which includes hardness, thickness and diameter of tablet in its calculation as by the following formula:

$$T.s = 2F / \pi r h \qquad \text{Equation 1}$$

Where: T.s =Tensile strength in Kg/cm^2, F=Hardness in Kg, r = Diameter in cm. Tablet hardness has been defined, as the force required for breaking a table in diametric compression test.

Fig 2: Hardness tester (pharma test (PTB) company).

2.2 Friability test of promethazine tablet

Friability test carried out in an instrument called a friabilator. A friability testing apparatus should simulate the conditions that the product exposed to during the process of production. This test is a method to determine physical strength of the coated tablet upon exposure to mechanical shock and attrition. This instrument consists of a plastic chamber for placing the tablets, which attached to a horizontal axis. The drum has an inside diameter of 287mm and is about 38mm in depth made of a transparent synthetic polymer with polished internal surface. The commonly used friabilator in the faculty of pharmacy laboratories is the Roche friabilator (pharma test (PTF-E) company) (Figure 3).

The number of promethazine tablet taken depends on the average weight of the tested tablets. A set of pre weighed tablets placed in the plastic chamber revolving at 24-25 rpm for 4 min. [If the unit mass of the tablet is less than 650mg take 10 tablets. Subsequently, if the unit mass of the tablets is equal to or more than 650mg take 20 tablets] [10].

$$\%\text{weight loss} = (\text{Initial weight} - \text{Final weight}) / \text{Initial weight} \times 100 \qquad \text{Equation 2}$$

% Weight loss of coated tablet should be 0.0 % to be considered acceptable according to the USP and BP.

The friability test carried out to determine the fragility of the tablet and its capability of handling the packaging, storage, transporting condition. In this test, the weight of 20 tablets together is calculated and inspected for any increase or decrease in weight after the calculation of the average value from three experiments.

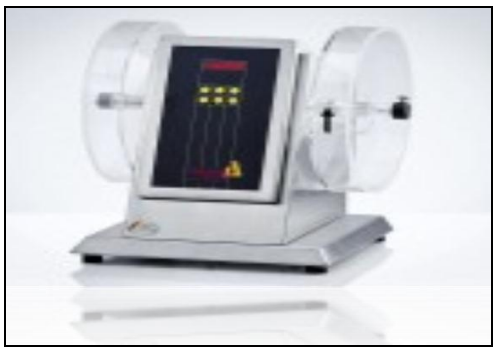

Fig 3: Roche friabilator

2.3 Weight uniformity test of promethazine tablet

The weight uniformity test was carried out at the calibrated sensitive weighter ($KERN^{870}$) shown in Figure 4.

Fig 4: Calibrated weighter ($KERN_{870}$)

The 20 tablets of the promethazine hydrochloride25 mg selected randomly were weighted and then the average weight of those tablets were determined. Percentage deviation in weight of each tablet from the average weight was determined.

Limit

Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the Table 1, and none deviates by more than twice that percentage.

Table 1: The average weight of tablets and percentage deviation limits.

Average weight of tablet (x)	Percentage deviation
80 mg or less	10
More than 80 mg & less than 250 mg	7.5
250 mg or more	5

2.4 Content uniformity test of promethazine tablet

Randomly 20 tablets of promethazine tablet were selected, weighted and powdered. An amount of the powder equivalent to 0.05g of tablet was dissolved in 100 ml of water in a measuring cylinder, filtered, diluted suitably with the same medium and the absorbance was measured at its λmax of 249nm. The average amount of drug per tablet present in each batch calculated with the help of appropriate calibration curve constructed from the absorbance values of promethazine solutions.

2.5 Disintegration test for promethazine tablets

In this test, the water used as an immersion fluid at a temperature of 37°C in the disintegration apparatus shown in Figure 5. One tablet placed in each of the six tubes and, a disc added to each tube. The apparatus operated for the specified period. Then a sample withdrawn and examined to evaluate the state of the tablets. All six tablets should disintegrate to pass the test [2].

Fig 5: Disintegration test (pharma test (PTZ-E) company).

The limit

The preparation examined complies with the test. If all six tablets have not complete disintegration. They considered to be achieved when no residue except fragments of undissolved tablet coating remains on the screen of test apparatus or adhere to the lower surface of the disc used. The tablet disintegrates within 15 minutes unless otherwise justified.

2.6 Dissolution test for promethazine tablets

Dissolution testing is the test, which monitors the impact of environmental storage conditions and manufacturing process upon the rate of drug release from a tablet. Firstly, the volume of the dissolution medium placed in the vessel. Then the apparatus assembled and placed in a water-bath. The temperature of the dissolution medium allowed reaching 37 ± 0.5°C in the dissolution tester, which shown in the Figure 6. In this experiment, a promethazine tablet allowed to sink to the bottom of the vessel before starting the rotation of the blade. Taking care that no air bubbles are present on the surface of the dosage form. In order to stop the dosage form from floating, anchor it to the bottom of the vessel using a suitable device such as a wire or glass helix. Immediately the rotation of the blade started at the specified rate, (which is determined after the first experiment and it was approximately 1hr).

Fig 6: Dissolution tester (ERWEKA (DT_{600}) Company).

The volume of dissolution medium replaced with a volume equal to that of the liquid removed. For filtration of the removed liquid, an inert filter with a suitable pore size used.

3. Results and Discussion

The *in vitro* study of the promethazine hydrochloride tablets done using the quality control tests. Those tests repeated three times to each test.

3.1 Hardness test of promethazine tablet

Testing tablet hardness is more than ensuring the mechanical integrity of produced tablets during subsequent processes. Because the hardness of a tablet directly relates to all other physical parameters.

3.1.1 Hardness calculation 1

In the hardness test the average of the tablet hardness, thickness, and diameter of 10 promethazine tablets have calculated and then repeated twice to calculate the tensile strength (T.S). Tensile strength defined as a stress, which measured as force per unit area. From this calculation, estimation of the force required to break the tablet done via using an Equation (1).

Table 2: Hardness results of the first hardness experiment.

Tablet number	Diameter (mm)	Thickness (mm)	Hardness (N)
1	8.21	4.03	70.0
2	8.23	4.00	64.9
3	8.22	4.00	71.4
4	8.20	4.02	65.6
5	8.22	4.02	61.2
6	8.24	4.01	72
7	8.23	4.03	85.9
8	8.22	4.03	62.6
9	8.22	4.00	63.9
10	8.23	4.00	67
Mean	8.222	4.014	68.45

Tablet thickness (h) = 4.014mm/ 10 = 0.401cm
Tablet diameter(r) = 8.222mm/10= 0.8222cm
The required force to break (f) = 68.45N /9.8 = 6.984kg
T.s = 2F/ r h
T.s = 2*6.984/ 3.14*0.822 *0.401
T.s = 13.495kg/cm

3.1.2 Hardness calculation 2

Tensile strength (T.S) = $2F/\pi$ r h

Table 3: Hardness results of the second hardness experiment.

Tablet number	Thickness (mm)	Diameter (mm)	Hardness (N)
1	8.20	4.01	60.50
2	8.18	4.02	55.80
3	8.22	4.02	68.30
4	8.19	4.00	59.50
5	8.21	4.02	62.90
6	8.21	4.02	61.50
7	8.20	4.01	63.20
8	8.19	4.00	61.20
9	8.25	4.03	63.20
10	8.19	4.01	59.20
mean	8.20	4.01	61.53

h = 4.01cm /10 =0.401mm
r = 8.204cm /10= 0.820mm
f = 61.53N/9.8 =6.27kg
T.s = 2(6.72) / 3.14*0.820*0.401
T.s = 13.02kg/cm

3.1.3 Hardness calculation 3

Tensile strength (T.S) = $2F/\pi$ r h

Table 4: Hardness results of the third hardness experiment.

Tablet number	Thickness (mm)	Diameter (mm)	Hardness (N)
1	8.20	4.00	77.10
2	8.21	4.03	70.20
3	8.20	4.03	69.30
4	8.20	4.02	65.20
5	8.23	4.00	64.10
6	8.19	4.02	62.60
7	8.19	4.03	71.30
8	8.20	4.01	70.30
9	8.20	4.00	68.20
10	8.22	4.03	70.10
Mean	8.20	4.02	68.84

h = 4.02cm /10 = 0.402mm
r = 8.20cm /10 = 0.820mm
f = 68.84N/9.8 =7.02kg
T.s = 2(7.02) / 3.14*0.820*0.402
T.s = 13.88kg/cm

From the results obtained above the promethazine tablet have a hardness value of 6.76kg, which mean that the promethazine tablet with 0.401cm thickness (h) and 0.820cm in diameter (r) require a force of 13.465kg/cm (T.s) to be broken? The results obtained from this test comply with the British pharmacopeia 1998, which means that those tablets meet the pharmacopeial requirements and satisfy the patient needs at the Libyan pharmaceutical market.

3.2 Friability Test of the promethazine tablets

The percentage of Weight loss of the coated tablet should be 0.0 % to be considered acceptable according to the BP. The following are the results of three successive friability tests carried out for the promethazine tablets.

3.2.1 Friability calculation 1
Wt. of one tablet = 0.207g = 207mg, this value is less than 650
The total weight of the 20 tablets are, W0 of 20 tablet = 4.204g

%F = Wo – W1/ Wo * 100

Where %F is the friability percent.
%F = 4.204 – 4.203 / 4.203 * 100
%F = 0.024 %

3.2.2 Friability calculation 2
Wt. of one tablet = 0.207g =207mg
Wo of 20 tablet = 4.198g

%F = Wo –W1 / Wo * 100
%F = 4.198 – 4.196 / 4.1.98 * 100
%F = 0.047%

3.2.3 Friability calculation 3
Wt. of one tablet = 0.207g = 206mg
Wot0 of 20 tablet = 4.204g

%F = Wo – W1 / Wo * 100
%F = 4.204 - 4.203 / 4.204 * 100
%F = 0.024%

The results obtained from the friability test show that the promethazine tablet have 0.032%, which mean that the promethazine tablet does not comply with the (Bp1998), and the tablet affected by the stress occurs during production and transportation process.

3.3 Weight uniformity test of the promethazine tablets
The British pharmacopeia 1998 states: Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table 1, and none deviates by more than twice that percentage.

3.3.1 Weight uniformity calculation 1

$$\% \text{ of deviation} = \frac{X^- - X}{X^-} * \mathbf{100} \quad \text{Equation 3}$$

Where the X^- is the average weight $(X^-) = \Sigma X^-/n$
Weight of tablet = 0.210g =210mg
% of deviation = -2.38

Table 5: The average weight of tablet and percentage deviation

Tablet number.	Tablet weight (g)	Percentage deviation
1	0.208	0.95
2	0.213	-1.43
3	0.209	0.48
4	0.209	0.48
5	0.207	1.43
6	0.210	0
7	0.207	1.43
8	0.211	-0.48
9	0.213	-1.43
10	0.211	-0.48
11	0.207	1.43
12	0.213	-1.43
13	0.215	-2.38
14	0.209	0.48
15	0.209	0.48
16	0.213	-1.43
17	0.211	-0.48
18	0.208	0.95
19	0.209	0.48
20	0.211	-0.48

3.3.2 Weight uniformity calculation 2

$$\% \text{ of deviation} = \frac{X^- - X}{X^-} * \mathbf{100}$$

Where the X^- is the average weight $(X^-) = \Sigma X^-/n$
Weight of tablet = 0.209g =209mg
% of deviation = -7.15

Table 6: The average weight of tablet and percentage deviation

Tablet No.	Tablet weight (g)	Percentage deviation
1	0.209	0
2	0.208	0.48
3	0.211	-0.95
4	0.213	-1.91
5	0.207	0.95
6	0.208	0.48
7	0.209	0
8	0.209	0
9	0.213	-1.91
10	0.209	0
11	0.207	0.95
12	0.209	0
13	0.211	-0.95
14	0.213	-1.91
15	0.215	-2.87
16	0.208	0.48
17	0.208	0.48
18	0.207	0.95
19	0.211	-0.95
20	0.208	0.48

3.3.3 Weight uniformity calculation 3

$$\% \text{ of deviation} = \frac{\bar{X} - X}{\bar{X}} * 100$$

Where the $\bar{X}$ is the average weight ($\bar{X}$) = $\Sigma \bar{X} / n$
Weight of tablet = 0.210g = 210mg
% of deviation = -7.58

Table 7: The average weight of tablet and percentage deviation

Tablet No.	Tablet weight (g)	Percentage deviation
1	0.215	-2.38
2	0.213	-1.42
3	0.213	-1.42
4	0.208	0.95
5	0.207	1.42
6	0.215	-2.38
7	0.209	0.48
8	0.209	0.48
9	0.215	-2.38
10	0.208	0.95
11	0.213	-1.42
12	0.208	0.95
13	0.209	0.48
14	0.213	-1.42
15	0.215	-2.38
16	0.207	1.42
17	0.209	0.48
18	0.208	0.95
19	0.209	0.48
20	0.213	-1.42

The results obtained from the weight uniformity test show that, the promethazine tablets have a 209.6mg ± 5.70 weight, which means that the promethazine tablet is in the average weight of tablet of 80-250mg or less which shown in Table 1. Indicates that the promethazine tablets have a percentage of deviation, which equal to 7.5. Subsequently, all the tablets in this experiment are uniform in weight and accepted according to the pharmacopeial requirements.

3.4 Content uniformity test of the promethazine tablets

The tablet passes the content uniformity test if 9 of the 10 tablets contains not less than 85% and not more than 115% of the labeled drug content and the 20th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions do not meet, remaining 10 tablet assayed individually and none may fall outside of the 85 to 115% range.

Wt of 20 Tablet = 5.3 g→5300mg
Practical value (X1)
Y = a + bx
Absorbance = a + bx
X= abs –a /b ×5×100
X = 0.95 –1.41 / 4.99 × 5× 100 = 0.000184mg
0.000184→50mg
Xmg→5300mg
X=× 5300mg / 50mg
X = 0.0195 mg
210mg→X
20mg →0.000184
Active per tablet = 210 × 0.000184 /20 = 0.001932 mg
Theoretical value (X2)
Y= absorbance nm at 249nm
Dilution factor (DF) = 5 Final volume (fv) = 100
Intercept (a) = 1.41 slope (b) = 4.99

X2= Y-a /b × df ×fv= mg

% of content = practical value / theoretical value×100
% of content = 0.001932 – 25 / 25 ×100 = -0.0099
% variation not more than ± 15 %
The results obtained above show that, the promethazine tablets percentage of content of the drug is within the limit (85% and not more than 115% of the labeled drug). This means that this drug complies with the pharmacopeial content uniformity test.

3.5 Disintegration test of the promethazine tablet

3.5.1 Disintegration test calculation 1

Table 8: Disintegration time and its average

No of tablet	Disintegration time
1	1.27
2	1.47
3	1.55
4	1.47
5	2.00
6	1.52
Mean	1.54min

3.5.2 Disintegration test calculation 2

Table 9: Disintegration time and its average

No of tablet	Disintegration time
1	2.14
2	1.47
3	2.12
4	2.14
5	2.23
6	2.15
Mean	2.04min

3.5.3 Disintegration test calculation 3

Table 10: Disintegration time and its average

No of tablet	Disintegration time
1	2.00
2	2.12
3	2.14
4	1.55
5	1.59
6	2.24
Mean	1.94min

From the results obtained above the promethazine tablets completely disintegrated after 1.84 min.

3.6 Dissolution test of the promethazine tablet

The quantity of the active ingredient dissolved in the specified time limit was determined equation 4, 5, 6 (not less than 75%). The results expressed as a percentage of the content.

3.6.1 Dissolution test calculation 1

Calculation of the practical value of the active ingredient in the solution at each time interval (15, 30, 45, 60 minutes) using the following equation

$$y = a + bx$$

Where: a is the intercept = 1.41
b is the slop = 4.99
y is absorbance = 249nm
x is concentration in 25mg
Concentration of drug (×) = y-a/b Equation (4)
% released = amount released / Dose × 100 Equation (5)
% Drug released = Conc of drug × DF × Volume of medium / Stated amount of drug (mg) Equation (6)

Table 11: Parameters of the drug release.

Time (min)	Absorbance (nm)	Amount released (mg)	% drug released
15	0.368	10.86	43.4
30	0.333	9.44	37.76
45	0.313	8.63	34.5

3.6.2 Dissolution calculation 2

Table 12: Parameters of the drug release.

Time (min)	Absorbance (nm)	Amount released (mg)	% drug released
15	0.315	10.86	43.33
30	0.326	9.16	36.64
45	0.337	9.6	38.4

Concentration of drug (×) = y – a / b Equation (4)
% released = amount released / dose × 100 Equation (5)
% Drug released = Conc of drug × DF× volume of medium / stated amount of drug (mg) Equation (6)

3.6.3 Dissolution calculation 3

Table 13: Parameters of the drug release.

Time (min)	Absorbance (nm)	Amount released (mg)	% drug released
15	0.384	11.5	46
30	0.346	9.97	39.88
45	0.315	8.71	34.89

Concentration of drug (×) = y – a / b Equation 4
% released = amount released / dose × 100 Equation 5
% Drug released = Conc of drug × DF× volume of medium / stated amount of drug (mg) Equation 6

Dissolution test carried out by calculation of the percentage of drug release 1000ml volume of water and the calculation of the concentration of the drug from the previous linear relationship multiplied by the dilution factor to obtain the final value. This value will be the value of first sample then the concentration of next sample has been calculated as before and add correction factor which is the concentration of the drug multiplied by dilution factor of the first sample. Lastly, the percentage of drug release of each sample after 15, 30 and 45 minutes from starting experiment time calculated.
From the calculation of this test the concentration of the drug decreases with time (Table 11,Table 12,Table 13), but the % released of the drug shows a small value which is less than the pharmacopeial limit (not less than 70%) and the promethazine tablet was dissolved after 15 minutes from starting time. Those results prove that the promethazine tablet used in this study have not meet the pharmacopeial requirements, and this presents many questions about this promethazine tablet imported to our country at this time period and the bioavailability and the action of this drug with the Libyan patients.

4. Conclusion

The promethazine tablets show good parameters, whereas the hardness, weight uniformity and disintegration tests were in the acceptable limits of the British pharmacopeia. On the other hand, the promethazine tablet has not complied with some of the specified quality control tests (friability and dissolution) certified in the British pharmacopeia.
The promethazine tablets have not shown a good dissolution profile which means it might not give the expected therapeutic effect & reduce patient complaint (this could be authorized due to the absence of the quality control department role during the importing process of such drugs at this time).
This study emphasized the need of continuous investigations to the antihistaminic tablets present at Libyan market to ensure the quality of medicines for patients in Libya.

5. References

1. How long does promethazine stay in your system/https://pubchem.ncbi.nlm.nih.gov/compound/promethazine. 2015.
2. Laura C, Strenkoski-Nix, James Ermer, Sheryl Decleene, William Cevallos, and Philip R. Mayer. Pharmacokinetics of Promethazine Hydrochloride After Administration of Rectal Suppositories and Oral Syrup to Healthy Subjects.Am J Health Syst Pharm. 2000; 57(16).
3. Okubo K, Kurono Y, Fujieda S, Ogino S, Uchio E, Odajima H, Takenaka H. Japanese Guideline for Allergic Rhinitis. Allergology International. 2011; 60:171-189.
4. Paul A Glare, Tanya Nikolova. Management of nausea and vomiting in patients with advanced cancer. Supportive oncology J, 2011, 258-273.
5. Phenergan FDA prescribing information's. https://www.drugs.com/pro/phenergan.htm, cited 2016.
6. Promethazine HCl and codeine sulphate oral solution https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/promethazine.pdf
7. Promethazine drug facts and side effects. http://www.medicinenet.com/promethazine/article.htm, cited, 2016.
8. Promethazine hydrochloride tablet. https://dailymed.nlm.nih.gov/dailymed/lookup.cfm. Cited 2017.
9. United States pharmacopeia USP, 2010.
10. United States pharmacopeia USP, 2011.
11. Wikipedia open access, cited 2017.