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In Vitro Quality Evaluation of Three Different Br ands of B1, B6 and B12 Tablets Marketed in Two Different Thermal Zones in Yemen

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Abstract:

In Yemen, since medications are often purchased without adequately referenced quality standards and are not routinely evaluated, continuous evaluation of marketed drug products remains essential to ensure that the required quality is maintained post- marketing, which lead to protect public health,, maintain physicians' trust and save time and cost. The current study aimed to compare the quality of three different brands of B1, B6 and B12 tablets that are commercially marketed at two thermally different zones in Yemen. The same patch of the three brands were collected from Dhamar and Al- Hodidah cities and named as brand A, brand B and brand C. The quality control testing were determined through weight variation, hardness, disintegration, dissolution and content uniformity tests. All brands have been evaluated for compliance with United State Pharmacopeia standards. Quality control tests showed that B1, B6 and B12 of all brands were complied with the United State Pharmacopeia limits, except for B1 from Al-Hodidah city, and B6 from Dhamar city did not comply in content uniformity tests with pharmacopeia limits with by ± 2%. The brand B and C were physically and chemically good compared to the original brand A. in-vitro CQ testing of drug products after their marketing should be applied as replacement to in vivo bioequivalence testing under certain circumstances to maintain their safety and effectiveness, and to improve accessibility to health care and save money and time.

Keywords: *B1, B6, B12, quality control, United State Pharmacopeia, Thermal Zone.*

Introduction

The quality of a generic drug product is an important factor to support its commercial marketing, saving money, improving accessibility and delivery to healthcare, and promoting patient's adherence [1-4]. However, general people and healthcare providers, rarely question the quality of marketed generic drug products, which may result in suboptimal use of them [2 -5].

Quality control (QC) is a part of the Good manufacture practice (GMP), and it involves tests of friability, weight variation, disintegration, dissolution, and drug assay [6-8]. It ensures that the drug adheres to the details as per the description and data stated on the drug label [9-10]. Furthermore, QC testing also ensures the safety, and effectiveness of the drug, and checks its purities and impurities, that may lead to potential degradation and alteration of chemical and pharmacological properties of pharmaceutical products, which have a significant effect on drug product quality, safety and efficacy [8-11].

Drug stability means the ability of the pharmaceutical dosage form to maintain the physical, chemical, therapeutic properties during the time of storage and usage by the patient [12,13]. The minor objective of pharmaceutical product stability is to find out the quality assurance that the product will remain at a desirable level of fitness throughout its validity during its existence in the pharmacy or its treatment regimen [14,15]. Therefore, one of the primary reasons for stability testing is to create confidence in the patient who is suffering from a disease and avoid the decomposition of unstable products to yield toxic material or losing its activity which leads to death due to the failure of treatment [15-18]. The second reason is related to the drug manufacturer protecting his brand name which evidenced and proved that it remains with effectiveness. In another way, the stability studies are used by manufacturers during the development of drug formulation to select the suitable excipients, to distinguish the best storage conditions, to determine the claimed drug product shelf life, and finally to verify that the manufacturing method or drug formulation has no changes which can adversely influence the product stability [17-19].

On the other hand, to maintain the activity and integrity of the pharmaceutical products, they should be stored in appropriate conditions to protect their composition, which is sensitive and/or decomposed by environmental factors. High temperature accelerates oxidation, reduction and hydrolysis reaction which lead to drug degradation, acidic and alkaline pH influence the rate of decomposition of most drugs, and moisture can catalyze chemical reactions as oxidation, hydrolysis and reduction reactions and promotes microbial growth, and

light affects drug stability through its energy or thermal effect which lead to oxidation [20-21].

The B1, B6, and B12 vitamin is a micronutrient that comprises three water-soluble vitamins, which form essential and closely interrelated functions [22-24]. Their main physiological regulation processes are the metabolism of carbohydrates, amino acids, and fatty acids, and the synthesis of proteins, cholesterol, neurotransmitters, S-adenosyl methionine, and nucleotide bases [25-27]. They also reduce atherosclerosis-associated secondary outcomes. Moreover, it is known that B1, B6, and B12 vitamin deficiency leads to anemia, digestive and skin problems, infections, peripheral neuropathy, and psychiatric disorders [25-27].

In some countries, quality restricted procedures are not implemented by non-governmental organizations (NGOs) which work during drug purchase [28]. For drug purchase, the registration in resource-limited countries is usually approved under a prerequisite of a stability test; however, the approval of a drug in such countries is registered based on a simple review of documentation [28-30]. Furthermore, the technical assessment of the drug quality monitoring is imitated. Even if the efforts of such drug quality monitoring are being made in developing countries, only simple pharmacopeia test methods for quality confirmation exist and the stability test for generic drug products will not be performed [28-30].

In Yemen, since drugs are often procured without the quality standards of sufficient references and the stability of products not routinely assessed, ongoing evaluation of marketed products, including B1, B6, and B12 vitamins, remains essential to ensure that the desired quality is maintained post-marketing, to protect public health, and to retain general people and healthcare workers confidence. Therefore, this study designed to evaluate quality of two different national brands of B1, B6 and B12 tablets, through in vitro QC testing as per the United States Pharmacopeia (USP) [31-33] and to compare their quality with a foreign product that commercially available on Yemeni pharmaceutical market of two thermally different zones.

Materials and Methods

Study setting

All the analytical tests for the current study were carried out in the QC laboratories of Global Pharma Company, Sana'a, Yemen, from April to August, 2022.

Materials

Chemical agents (B1, B6, and B12 tablets)

The search in literature Supreme Board of Drug and Medical Appliances and the market survey indicated that three different brands of B1, B6,

and B12 tablets were commercially available in retail pharmacies inthe Yemeni pharmaceutical market at the study time. Before purchase, label information of the included brands of B1, B6, and B12 tablets was checked for manufacturing company, the strength of B1, B6, and B12 in tablet, batch number, date of manufacture and expiring dates. Subsequently, the three different commercial brands of B1, B6, and B12 tablets were randomly purchased from different private retail pharmacies in Dhamar and Al- Hodeida cities. Thereafter, the tablets were randomly coded with the letters A1, A2, B1, B2, and C1, C2, as outlined in Table 1.

Table 1: Label information of the included brands of B1, B6, and B12 tablets

Brand	Code	M. Company	Country of origin	Strength		Dosage Form	No. of Batch	*M. Date	*Ex. Date
Neurobion	A	Merck	Austria	B1	100mg	Sugar-coated	339021A	4/2021	3/2023
				B6	200mg				
				B12	200mcg				
Neuromax	B	Global Pharma	Yemen	B1	100mg	Film-coated	21346	6/2021	6/2023
				B6	200mg				
				B12	200mcg				
Three- B	C	Biopharma	Yemen	B1	100mg	Film-coated	379T	11/2021	4/2023
				B6	200mg				
				B12	200mcg				

*M. date: Manufacturing date *Ex. Date: Expiry date

Equipments

Table 2: Equipments

No.	Name of equipment	Company	Country of origin
1.	Hardness tester	Pharmatest	Germany
2.	Analytical balance	Mettler Toledo	Germany
3.	Disintegration tester	Pharmatest	Germany
4.	Dissolution tester	Pharmatest	Germany
5.	HPLC	Waters	USA

Study design

The current study was designed as in vitro comparative study, where the three brands of B1, B6, and B12 tablets that are commercially

available in the Yemeni pharmaceutical market were subjected to the QC tests procedures.

Quality control tests and calculations

All brands were subjected to the QC tests, that included method assay tests, hardness, weight variation test, disintegration time, and dissolution tests, according to United States Pharmacopoeia (USP) [31-33].

1. Non-official test methods

Hardness test

The crushing strength of the tablet was measured using an automatic hardness tester (Pharmatest, Germany). At first 6 tablets were picked randomly from 20 tablets. Force has been applied with the screw thread and pressed until the tablets have been fractured [22, 34-38].

2. Official test methods

2.1. Weight variation test

Twenty tablets were randomly selected from each brand and individually weighed using an analytical balance (Mettler Toledo, Germany). The mean and standard deviation (SD) were calculated for the tablets [22, 34-38]. Then the percentage of weight variation was calculated by using the following formula:

$$\% \text{ weight variation} = \frac{\mathbf{w1 - w2}}{\mathbf{w2}} \times \mathbf{100}$$

Where, w1 = individual weight of the tablet, and w2 = average weight of tablets.

Table 3: Weight Variation Limit

IP/USP	Limit [tablet]
< 130mg	±10
130 - 324 mg	±7.5
> 324 mg	±5

The result be accepted for the product if not more than two tablets which under the test be deviate from the limit of average weight [22, 34-38].

2.2. Disintegration test

Six tablets were randomly selected from each brand and placed in the disintegration apparatus (Pharmatest, Germany), which is filled with 900 mL of distilled water as disintegration medium, and 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 [22, 34-38].

2.3. Dissolution test (only Pyridoxine and Thiamine):

Preparation of mobile Phase

Methanol 700: Buffer 300: Triethylamine 1. adjust with H_3PO4 to a pH of 4.3

Buffer: Dissolve 0.234 g of NaH_2PO4 and transfer 0.1 ml of H_3PO4 to 300 ml of water.

Table. 4: Dissolution parameter

Dissolution parameter	
Medium	900 ml of 0.1M HCl.
apparatus	2
time	60 min.
speed	75 rpm

Preparation of the standard

Weigh accurately equivalent to 50 mg of Thiamine RS and equivalent to 50 mg of Pyridoxine RS into 100 ml V.F, dissolve and dilute to volume with 0.1 M HCL and mix well. Transfer 5 ml of this solution to 50 ml V.F dilute to volume with medium and mix. (0.05 mg/ml of Thiamine and 0.05 mg of Pyridoxine).

Preparation of sample solution

Use the direct filtrate solution (0.05556 mg/ml of Pyridoxine & 0.05556 mg of Thiamine).

HPLC conditions for Thiamine

Column	**C8, 25 cm hypersil**			**Wavelength**	**280**	**Flow rate**	**2**
						End Time	**4**
Limit	**NLT**	**75**	**%(Q)**				

HPLC conditions for Pyridoxine

Column	**C8, 25 cm hypersail**			**Wavelength**	**280**	**Flow rate**	**2**
limit	**NLT**	**75**	**%(Q)**			**End Time**	**5**

3. Assay methods

3.1. Method:- HPLC Reference:- Thiamine HCLPreparation of mobile Phase: -

(Methanol: Buffer: Triethylamine) (700: 300: 1). adjust with H3PO4 to a pH of 4.3 Buffer: Dissolve 0.234 g of NaH2PO4 and transfer 0.1 ml of H3PO4 to 300 ml of water.

Preparation of the standard

Weigh accurately equivalent to 50 mg of Pyridoxine RS and equivalent to 50 mg of Thiamine RS into 100 ml V.F, dissolve and dilute to volume with 0.1 M HCL and mix well. Transfer 5 ml of this solution to 50 ml V.F dilute to volume with medium and mix. (0.05 mg/ml of Pyridoxine & 0.05 mg of Thiamine).

Preparation of sample solution

Use the direct filterate solution (0.05556 mg/ml of Pyridoxine &0.05556 mg of Thiamine).

HPLC conditions

Column-	**C18,15 cm hypersail**			**Wavelength**	**280**	**Flow rate**	**2**
limit	**NLT**	**90% to**	**120**			**End Time**	**4**

3.2. Method :- HPLC Reference :- Pyridoxine HCLPreparation of mobile Phase: -

(Methanol: Buffer: Triethylamine) (700:300:1). Adjust with H3PO4 to a pH of 4.3 Buffer: Dissolve 0.234 g of NaH2PO4 and transfer 0.1 ml of H3PO4 to 300 ml of water.

Preparation of the standard:

Weigh accurately equivalent to 50 mg of Pyridoxine RS and equivalent to 50 mg of Thiamine RS into 100 ml V.F, dissolve and dilute to volume withmobile phase and mix well.

Preparation of sample solution

Grind not less than 10 tablets and weight equivalent to one tablet into100 ml V.F dissolves with mobile phase and sonicates for ten minutes, thenlet cool and complete to volume with the mobile phase.

HPLC conditions

Column:-	**C8, 25 cm hyper sail**			**Wavelength**	**280**	**Flow rate**	**2**
limit	**NLT**	**75**	**%(Q)**			**End Time**	**5**

3.3. Method :- HPLC Reference :- Cyanocobalamin Preparation of mobile Phase: -

Methanol and water (7:13)

Preparation of the standard:-

5 µg/mL of cyanocobalamin from USP Cyanocobalamin RS in water.

Preparation of sample solution: -

Finely powder NLT 20 Tablets. Transfer a portion of the powder, equivalentto 500 µg of cyanocobalamin, to a100-mL volumetric flask, add 60 mL of water, and sonicate for 5 min. Dilute with water to volume, and filter.

HPLC conditions:-

Column:-	**C18, 15 cm hyper sail**	**Wavelength**	**361**	**Flow rate**	**2**
Limit	**NLT 90% to 120%**			**End Time**	**8**

3.4. Content uniformity test

The active ingredient uniformity test of the tablets was carried out using HPLC (Waters, USA). Active ingredient chemical identification and content uniformity tests were carried out according to the USP [31-33].

Data analysis

Weight uniformity, weight variation, hardness, dissolution, and disintegration times of B1, B6, and B12 tablets of each brand were analyzed by calculating the mean ± standard deviation (SD) for each parameter using the Excel program for Windows.

Ethical consideration

This study was carried out after approval of ethical committee, faculty of medical sciences, Al-Saeeda University. Although the study did not involve human or animal subjects, informed consent was obtained before the collection of specimens.

Results and Discussion

Ongoing evaluation of the quality of generic drug products remains crucial to protect public health,, improve the confidence of clinicians and public and save money. QC involves specific instruments to ensure the quality of drug testing as per set guidelines [2 -5]. We assessed the pharmaceutical quality of an original brand and tow generic brands of thiamine, pyridoxine, and cobalamin tablet, that were commercially available on the Yemeni pharmaceutical market at the period of this study. All brands passed *in-vitro* quality testing like weight variation, drug assay, friability, disintegration, and dissolution tests, according to USP [31-33].

1. Non-official test results

Hardness test

Tables.5: Hardness test results for different brands of B1, B6 and B12 tablets

Hardness kg/cm^2 (Mean ± SD)				
	City			
Brand	**Dhamar**	**Al-Hodidah**	**Limit**	**Conclusion**
A	11.41±1.175	9.98±2.74	5-10 kg/cm^2	Unconformity
B	14.5±5.74	15.96±6.1		
C	9.1±1.06	8.21±0.94		Conformity

If the tablet is too hard, it may disintegrate in the required period and if it is too soft, it will not with stand the handling during subsequent processing such as coating or packaging and shipping operations[22, 34-38].Hardness was monitored using an automatic tablet hardness tester and the results were tabulated Table 5. Hardness range specification is 5 to 10 kg [31-33]. Therefore, the generic brand C was within the USP quality specification, where it passed the hardness test and was within the acceptable range in Dhamar and Al-Hodidah cities. However, the generic brands A and B in Dhamar and Al-Hodidah cities not fulfill the USP quality specification of

hardness test by the average value that were not within the acceptable range. These findings are not similar to those of previous studies conducted in Albania [22].

2. Official tests results

2.1. Weight Variation test

Tables. 6: Weight Variation test results for different brands of B1, B6and B12 tablets from Dhamar City

Weight of Tablet (mg)				Deviation in weight From average (%)			Conclusion
N0.	**A1**	**B1**	**C1**	**A1 %**	**B1 %**	**C1 %**	
1.	744.6	634.6	598.7	6.6	1.2	-2.4	**Conformity**
2.	704.8	635.7	625.2	0.9	1.3	1.8	
3.	674.6	632.9	619.5	-3.3	0.9	0.9	
4.	665.1	615	599.4	-4.7	-1.9	-2.3	
5.	691.4	618.6	607	-0.9	-1.3	-1.07	
6.	696.1	625.9	625.2	-0.3	-0.1	1.8	
7.	647.2	625.9	617.4	-7.2	-0.1	0.6	
8.	683.3	590	612.5	-2.1	-5	-0.1	
9.	683.2	635.2	608.3	-2.1	1.3	-0.8	
10.	708.1	630.9	622.5	1.4	0.6	1.4	
11.	713.4	648.3	621.8	2.1	3.3	1.3	
12.	684.3	616.5	616.3	-1.9	-1.6	0.4	
13.	703.3	619.8	617	0.7	-1.1	0.5	
14.	721.3	622.3	602.7	3.3	-0.7	-1.7	
15.	728.3	620.8	620.4	4.3	-0.9	1.1	
16.	683	632.4	612.1	-2.1	0.8	-0.2	
17.	719.5	636.2	613.2	3	1.4	-0.06	
18.	711.6	636.3	611.3	1.9	1.4	-0.3	
19.	706.2	627.2	607	1.1	0.03	-1.07	
20.	693.8	636.4	616.2	-0.6	1.4	0.4	
Average Wight (mg)	698.1	627	613.6				
Limit	**More than 324**			**±5%**			

The results showed that the tablets were in limit of weight variation test which is not more than two tablets deviate from the average ≥ 5 [31-33].

Tables. 7: Weight Variation test results for different brands of B1, B6 andB12 tablets from Al-Hodidah City

	Weight of Tablet (mg)			Deviation in weight From average (%)			Conclusion
N0.	**A2**	**B2**	**C2**	**A2 %**	**B2 %**	**C2 %**	
1.	718.7	635.5	628.9	1.2	1.03	2.5	
2.	719.4	644.1	614.8	1.3	2.4	0.2	
3.	689.6	627.7	615.4	-2.8	-0.2	0.3	
4.	678.6	624	619.4	-4.3	-0.7	0.9	
5.	705.5	614.1	604.7	-0.5	-2.3	-1.4	
6.	693.5	632.8	602.2	-2.2	0.6	-1.8	
7.	705.5	647.7	604.9	-0.5	2.9	-1.4	
8.	700.7	589.5	602.4	-1.2	-6.2	-1.8	**Conformity**
9.	731.5	627	621.4	3.1	-0.3	1.2	
10.	669.5	605.7	609.4	-5.6	-3.7	-0.6	
11.	710.8	618.7	617.3	0.1	-1.6	0.6	
12.	709.7	622.7	616.4	0.01	-1	0.4	
13.	714.6	634.5	613.5	0.7	0.8	0.008	
14.	739.5	633.4	619.5	4.2	0.6	0.9	
15.	733.2	628.3	610.7	3.3	-0.1	-0.4	
16.	735.2	616.9	601.8	3.6	-1.9	-1.9	
17.	746	646.6	614.7	5.1	2.7	0.1	
18.	699	641.4	609.3	-1.4	1.9	-0.6	
19.	705.7	643.2	616.4	-0.5	2.2	0.4	
20.	686.9	646.2	626	-3.1	2.7	2	
Average Wight (mg)	709.6	629	613.5				
Limit	**More than 324**			**±5%**			

The results showed that the tablets were in limit of weight variation test which is not more than two tablets deviate from the average ≥5%. Although the uniformity of weight does serve as a pointer to GMP, and the amount of the active pharmaceutical ingredients, especially for reproducibility of the product which is very essential for mass production ofany product [31-33]. Tables 6 and Table 7. show the average weight and weight variation of the different brands of tested B1, B6 and B12 tablets. Where, all brands A, B, and C in Dhamar and Al-Hodidah Cities conform to USP standards [31-33]. Therefore, all brands were within the USP quality specification. These results are consistent with those of previous studies carried out in Albania [22]

2.2. Disintegration test

Tables. 8: Disintegration test results for different brands of B1, B6 andB12 Vitamin tablets

		Disintegration (min)				
	City		Differences Time (min)	Dosage form	Limit	Conclusion
Brand	Dhamar	Al-Hodidah				
A	30:32	32:35	2.3	Sugar coated	<60 min	Conformity
B	10:30	15:30	5	Film coated	<30 min	
C	10:03	9	1.03	Film coated	<30 min	

Disintegration test plays an important role in a tablet's dissolution. Therefore, the type, concentration, and efficiency of disintegrating to a large extent affected the dissolution [22, 34-38]. As per USP standards, the disintegration time limit for coated tablets is 30 minutes for film coated tablets and 60 minutes for sugar coated tablets. As per the QC tests performed in this study, the disintegration time in Dhamar City for brand A1 was 30.23 minutes, while it was 10.30 and 10.03 minutes for brand B1 and C1 respectively. On the other hand, the disintegration time in Al-Hodidah city for brand A2 was 32.35 minutes, while it was 15:30 and 9 minutes for brand B2 and C2 respectively, as shown in Table 8. Subsequently, the disintegration times of all brands A, B and C were under the USP limit [31-33], therefore, all brands in the current study conform to the disintegration test In addition, although the brand C had the faster disintegration time compared to brands A and B, all brands were within the USP quality specification [31-33]. These findings are in the line to those of previous studies conducted in Albania [22].

The disintegration time provides an idea of when the tablet will disintegrate and reach dissolution. The tablet disintegration time of brand C is less as compared to brand B, this can be attributed to that the powder blend of tablet C could have less binder excipient or there could be less force during tablet compression [22, 34-38].

2.3. Dissolution test

Tables.9: Dissolution test results for different brands of B1, B6 and B12 tablets

		Dissolution (%)			
		City		Differences ratio	Conclusion
Brand	Vitamin	Dhamar	Al-Hodidah	%	
A	B1	96.9±0.72	94±0.56	2.9%	Conformity
	B6	117.5±2.03	115.6±1.13	1.9%	
	B12	-	-		
B	B1	90.5±0.66	88.9±027	1.6%	
	B6	117.9±4.57	120.1±0.43	2.2%	
	B12	-	-		
C	B1	88.1±0.99	87.6±0.69	0.5%	
	B6	117.8±2.61	117±1.33	0.8%	
	B12	-	-		
Limited		Not less than 75%			

The bioavailability and therapeutic effectiveness of oral conventional tablets of the drug depend completely on the dissolution rate of the drug. Therefore, it is very important to estimate the dissolution rate and compare the dissolution profiles of different marketed drug products. Dissolution test measures the extent of solution formation. In the current study, the rate of drug release was confirmed by the dissolution tests of brands of B1, B6 and B12 tablets. It was found that more than 80% of film and sugar coated tablets of all brands that collected from Dhamar and Al-Hodidah cities released within 30 and 60 minutes respectively, as outlined in Table 9. This means all brands meet USP quality specification [31-33] and was satisfactory from the dissolution point of view. Furthermore, this findings are in the line to those of previous studies that conducted in Albania [22].

2.4. Content uniformity test

Tables 10: Content uniformity test for different brandsof B1, B6 and B12 tablets.

		Content uniformity %			
		City		Differences ratio	Conclusion
Brand	Vitamin	Dhamar	Al-Hodidah	%	
A	B1	92.64	97.28	4.64%	Conformity
	B6	111.36	105.47	5.89%	
	B12	105.4	97.6	7.8%	
B	B1	106.78	90.1	16.68%	
	B6	114.65	103.99	10.66%	
	B12	101.20	96.1	5.1%	
C	B1	110.85	88.32	22.53%	Unconformity
	B6	122.81	96.07	26.74%	
	B12	108.50	95.5	13%	
Limit		Not less than 90-120%			

The brands A and B of the B1, B6 and B12 tablets, which marketed in both Dhamar and Al-Hodidah city, complied to USP limits [22-33]. These results indicate a uniform distribution and an excellent quantity, as shown in Table6. However, thiamine of brand C, that marketed in Al- Hodidah city, and pyridoxine of brand C, that marketed in Dhamar city, did not comply with USP limits [31-33]. This can be attributed to a weak mixing process. These findings are not similar to those of previous studies carried out in Albania [22].

Conclusion

It can be concluded that thiamine, pyridoxine, and cobalamin tablets in all brands that marketed in two different thermal regions of Yemen during period of this study were within the USP limits regarding all QC-related tests, except thiamine and pyridoxine of brand C, that respectively collected from Dhamar city, and Al-Hodidah cities, did not comply with USP limits in content uniformity test. Therefore, in-vitro CQ testing of drug products after their marketing should be applied as replacement to in vivo bioequivalence testing under certain

circumstances, and it must be performed from time to time in order to ensure that the quality of generic drug products within pharmacopeia standards and to maintain their safety and effectiveness, that lead to improve accessibility to health care and save money and time.

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References

1. Ahuja SS. Assuring quality of drugs by monitoring impurities. *Advanced drug delivery reviews.* 2007; 59(1): 3-11. https://doi.org/10.1016/j.addr.2006.10.003.
2. Keatley KL. A review of the FDA draft guidance document for software validation: guidance for industry. Quality assurance. 2000; 7(1): 49-55. https://doi.org/10.1080/105294100277723.
3. Asan A., Dewan SAR., Ahamed SK., Kai MM. Quality control studies oncetirizine hydrochloride tablets available in Bangladesh drug market. *International Journal of Pharmacy and Biological Sciences*. 2013; 3(1): 349-354.
4. Hammami M.M, Al-Swayeh R., Hussein R.F. Pharmaceutical quality of seven brands of diclofenac tablet on the Saudi market. *BMC Res Notes*. 2020; 13:548. https:// doi.org/ 10.1186/s13104-020-05385-8.
5. Hammami M., Hussein R., Al-Swayeh R., Alvi S. Eight enteric-coated 50 mg diclofenac sodium tablet formulations marketed in Saudi Arabia: in vitro quality evaluation. *BMC Res Notes*. 2020; 13:428. https://doi.org/10.1186/s13104-020-05270-4
6. Gupta, M. M., Khoorban, A., Ali, A., Ramlogan, O., Talukdar, D. Comparative quality control study of different brands of diclofenac sodium tablet available in local and government pharmacies by in-vitro testing. *Cureus.* 2020; 12(11): e11348. DOI 10.7759/ cureus.11348. .
7. Mohan G.M., Madhulika G. Comparative pharmaceutical quality control testing of different brands of paracetamol tablets available in Trinidad and Tobago, West Indies. *Int J Pharm Sci Res.* 2016; 7(7): 2830 - 2836. .
8. Osei-Yeboah F., Sun C., Validation an application of an expedited tablet friability method. *International journal of pharmaceutics.* 2015; 484(1-2):146-155. https://doi.org/10.1016/j.ijpharm.2015.02.061.
9. Bari S B., Jain PS., Shirkhedkar AA., Sonawane LV., Mhaske AJ., Gawad JB. Impurities in pharmaceuticals: A review. *World Journal of Pharmaceutical Research*. 2015; 4(10): 2932-2947.
10. Misra B., Thakur A., Mahata P.P. Pharmaceutical Impurities: A Review. *IJPC.* 2015; 05 (07): 232-239.
11. Ayre A., Varpe D., Nayak R., Vasa N. Impurity profiling of pharmaceuticals. *ARPB.* 2011; 1(2):76-90.

12. McGinity J W. Drug stability: Principles and practices. *Journal of pharmaceutical sciences*. 1991, 80 (1): 98. https://doi.org/10.1002/jps.2600800127.
13. Jessica C, Timothy G, Philip L, Joseph S. stability studies. *Separation Science and Technology*. 2011; 10: 459-505.
14. González-González, O. et al. Drug Stability: ICH versus Accelerated Predictive Stability Studies. *Pharmaceutics* 2022, 14, 2324. https://doi.org/10.3390/pharmaceutics14112324.
15. Kaur M., Kaur G., Kaur H., Sharma S. Overview on stability studies. *International journal of pharmaceutical, chemical, biological sciences*. 2013; 3(4):1231- 1241.
16. Amruth K.N, Thiruvengada R.V.S. A review on stability studies an overview. *International journal of review in life science*. 2011; 106-111.
17. Blessy M., Patel RD., Prajapati PN., Agrawal YK. Development of forced degradation and stability indicating studies of drugs- A review. *Journal of pharmaceutical analysis*. 2014; 4(3): 159-165.
18. Bajaj S., Singla D., Sakhuja N. Stability Testing of Pharmaceutical Products. *Journal of Applied Pharmaceutical Science*. 2012; 02 (03): 129-138.
19. Singh S., Bakshi M. Guidance on conduct of stress test to determine inherent stability of drugs. *Pharm Technol Asia.* Special Issue, 2000; 24-36.
20. Nguyen, L. T., Tay, A., Balasubramaniam, V. M., Legan, J. D., Turek, E. J., & Gupta, R. Evaluating the impact of thermal and pressure treatment in preserving textural quality of selected foods. *LWT-Food Science and Technology*. 2010; 43(3), 525 - 534.
21. Kumar A., Rajan T. A review on stability studies an overview. *International journal of research in Phytochemistry and pharmacology*. 2016; 6(2): 41-45.
22. Xhafaj, D., Malaj, L. Comparison of quality control of two different B-complex tablets and their legislative issues on the albanian pharmaceutical market. *European scientific journal*. 2014; 10 (30): 149-155. e - ISSN 1857-7431.
23. Huang et al. The Efficacy and Safety of Multivitamin and Mineral Supplement Use To Prevent Cancer and Chronic Disease in Adults: A Systematic Review for a National Institutes of Health State-of-the-Science Conference. *Annals of InternalMedicine*. 2006; 5;145(5):372.
24. Hoad K.E. Vitamin B1 and B6 method harmonization: Comparison of performance between laboratories enrolled in the RCPA Quality Assurance Program. *Clinical Biochemistry*. 2013; 46: 772–776. http://dx.doi.org/10.1016/j.clinbiochem.2013.01.020.
25. Xie, C., et al. In situ fortification of vitamin B12 in wheat flour and wheat bran by fermentation with Propionibacterium freudenreichii. *Journal of Cereal Science*. 2018; 81, 133–139. https://doi.org/10.1016/j.jcs.2018.05.002.
26. Piro A, Tagarelli G, Lagonia P, Tagarelli A, Quattrone . A. Casimir Funk: his discovery of the vitamins and their deficiency disorders. *Ann Nutr Metab*. 2010; 57(2):85–8.
27. Hung S.C., Hung S.H., Tarng D.C., Yang W.C., Chen T.W., Huang T.P. Thiamine deficiency and unexplained encephalopathy in hemodialysis and peritoneal dialysis patients. *American Journal of kidney diseases*. 2001; 38(5): 941–947. https://doi.org/ 10.1053/ajkd. 2001.28578.
28. Damle MC et al., Development and Validation of Stability Indicating HPTLC Method for Determination of Ofloxacin and Ketorolac Tromethamine in Combination, *J. Adv. Sci. Res.* 2011; 2 (3): 77-82.
29. The USP, 32nd ed. General chapters: <1058> Analytical instrument qualification. Rockville, MD, 2009.
30. WHO, The International Pharmacopoeia: General Methods of Analysis, vol. 1, 3rd Edition, 1979.
31. The United States Pharmacopeia 37th – Ed., 2014.
32. Pharmacopeia online. USP32. https ://www.uspbp ep.com/usp32/pub/data/v32270/usp32 nf27s 0_m2497 2.html#usp32 nf27s 0_m2497 2. Accessed 6 Sept 2020.
33. Monographs, O. United States Pharmacopeia-National Formulary (USP25-NF 20). Rockville, Maryland: United States Pharmacopoeial Convention Inc., 2002.
34. Ukwueze S. E., Nkangwung M. J., Odigie J. Comparative study of the quality of some brands of diazepam tablets available in Nigeria. *World Journal of Pharmaceutical Research*. 2021; 10(5): 1970-1980.
35. Senjoti F., Mahmood S., Jaffri J., Mandal U. Design and in vitro evaluation of sustained release floating tablets of metformin HCL based

on effervescence and swelling. *Iran J pharm Res*. 2016; 15(1): 53-70.

36. Dimple B., Vinodh M., Vinayak M. Development and validation of RP-HPLC METHOD for the estimation of clopidogrel bisulphate. *Malaysian journal of analytical sciences*. 2013; 17(3): 387-393.
37. Modasiya M.K., Lala I.I., Prajapati B.G., Patel V.M., Shah D.A. Design and Characterization of Fast Disintegrating Tablets of Piroxicam. *Int.J. PharmTech Res*. 2009 ; 1(2): 353-357.
38. Bhalerao AV, Deshkar SS, Shirolkar SV, Gharge VG, Deshpande AD. Development and Evaluation of Clonazepam Fast Disintigrating Tablets Using Superdisintigrates and Solid Dispersion Technique. *Research J. Pharm. and Tech.2(2): April.-June.2009,;Page 375-377.*