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Perception of Quality about Local Manufacturing of Drugs in Pakistan and Its Qualitative Analysis

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Abstract: The new drug development process is very expensive, so initially when a new drug comes in the market the innovator pharmaceutical company gets the sole rights to manufacture the drug for specific time. But later, other pharmaceutical companies get the rights to manufacture that drug. This increases the number of generic drugs available in the market and decreases the cost of therapy. But this decrease in cost of medicine does not mean poor quality. The objective of this research work was to identify that different generic products from local and multinational firms available in the market are comparable in quality to each other and innovator product and are pharmaceutically equivalent. A comparative qualitative research was carried out on innovator and genetic marketed formulations of atenolol tablets from multinational and local pharmaceutical industries. A total of five products were selected and different in-vitro tests were performed and compared against British Pharmacopoeia standards. All the marketed formulations of atenolol tablets were as per standards of British Pharmacopoeia and complied with the weight variation, dimension, hardness, friability, disintegration, dissolutions tests and assay. All the marketed formulations of atenolol tablets from innovator, multinational and local industry companies were pharmaceutical equivalent and can be used interchangeably.

Keywords: Brand, Generic, Atenolol, Quality

1. INTRODUCTION

Drug development process is very expensive. That is why, when a new drug is developed the treatment of a disease, the innovator company gets the exclusive rights to manufacture that drug for a specific period of time that is about 12 years. During that period the drug is prescribed by its marketed name and only the discovering company gets the financial benefits of the new product. The drug in that duration is said to be patent drug or patent medicine. The other pharmaceutical companies get chance for manufacturing of that new drug after the expiry of patent, and then the drug is said to be generic drug. (Sherwood, *n.d.*)

Generic drug must show the same effects as shown by that of brand name drug and should be pharmaceutically equivalent. Generic drugs necessarily have identical active pharmaceutical ingredient (API), strength, dosage form and route of administration as required by the Food and Drug Administration (FDA). (Davit, *et al.*, 2009)

Manufacturing generic drugs is 80-85% cost effective as compare to its brand name drug, and this increases the number of the generic products in the market. These generic drugs are sold under different marketing names. The advantage of this is that cheaper medicines are available for the public. However, lower price does not mean a poor-quality product.(Davit *et al.*, 2009).

On the other hand, there may be chances of products having poor quality due to increased number of marketed formulations of the same drug. There is also possibility that drug products may not show comparable bioavailability, and drug release pattern may become threat for the patients. (Dharmalingam, *et al.*,2014).

World Health Organization (WHO) in May 2017, defined substandard and falsified pharmaceutical products. When pharmaceutical product is approved by national regulatory authorities but does not meet quality standards or specifications as prescribed by national or international standards it comes under sub-standard pharmaceutical product or out of specification category. On other side, falsified pharmaceutical products intentionally or through fraud, misrepresent identity, composition or source of a drug product. For the investigation of genuine nature of pharmaceutical products many public institutions have reported various surveys. Out of seven regions of the world, it has been reported by Pharmaceutical Security Research Institute in 2015, that drug crime ratio is high in Asia. In 2015, a total of 3002 cases of drug crime were reported in Asia-Pacific region. (Kakio *et al.*, 2018).

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In Pakistan, there is also perception that most of the locally manufactured generics are inferior in quality than the generics manufactured by multinational firms. A study was conducted in Karachi for determination of attitude of medical practitioners about generic and brand name medications. In this study the general practitioner informed that the generic medicines are cheaper than brands (n=188, 91.2%). However, half of the medical practitioners in the study (n=123, 59.7%) thought that the products manufacture by multinational firms were of better quality than the products manufactured by the local firms. More than three-quarters (n=157, 76.2%) of the medical practitioners were reluctant to prescribe low cost pharmaceutical brands. About 35% (n=72) of the medical practitioners were not comfortable to prescribe medicines from local manufacturers and majority of these general practitioners were older. More than 50% (n=109, 52.9%) medical practitioners were having doubts in quality check of locally manufactured pharmaceutical products.(Jamshed *et al.,* 2012).

Atenolol is widely used beta blocker for the treatment of the hypertension. It is a selective beta-I blocker having less effects on CNS. It is also indicated for the treatment of angina and arrhythmia.(Begum, *et al.,* 2019; Whalen, 2015).

ICI Pharmaceuticals(now AstraZeneca) in 1958 started research work on beta blockers and in 1972 atenolol stepped into development. In 1976, ICI pharmaceuticals launched atenolol in the market under the brand name Tenormin. In 1981, Unites States FDA approved its use as anti-hypertensive and for treatment of coronary artery diseases (CAD). (George and Ajit, 2009) Although it was marketed in 1976, it has holding its position in WHO core list of Essential Medicines for many years. (Badawi *et al.,* 2013).

The objective of this study was to determine that whether marketed formulations of atenolol 50mg tablets from local and multinational firms possess the same quality and can be used interchangeably and whether any substandard or falsified pharmaceutical products are present in the market.

2. MATERIALS AND METHODS

A total of five different marketed formulation of atenolol 50mg of local and multinational firms were selected. All five samples were purchased from various pharmacy outlets of local territory of Hyderabad, Sindh, Pakistan. Out of five samples one was an innovator product from a multinational pharmaceutical company, a generic from a multinational company, and three generics from local manufacturers of Pakistan. The collected samples were coded as Sample-01, Sample-02, Sample-03, Sample-04, and Sample-05.The details are mentioned in **(Table 1).**

Table 1: Details of Samples

	Sample	Manufacturing	Expiry
Multinational	Sample-01 (Innovator Product)	07-2018	06-2023
	Sample-02	08-2018	08-2022
Local	Sample-03	10-2018	10-2021
	Sample-04	08-2018	08-2023
	Sample-05	08-2018	08-2021

Method

A comparative qualitative research study was conducted. Specific physical and analytical tests were carried out. The tests performed on each sample were physical appearance test, weight uniformity test, thickness, diameter, friability, hardness and disintegration test. The results obtained were compared against British Pharmacopoeia (BP) standards.

Physical Appearance

By visual inspection color, shape and appearance of the tablets was evaluated. (Akasha, 2016)

Weight Variation Test

For determination of weight variation in the tablets KERN ALS 220-4, UK analytical balance was used. 20 tablets were picked from the final containers and weighed one by one. Then total weight of tablets was calculated by sum of weight of 20 tablets and average weighted was calculated by dividing total weight of tablets by 20. The upper control limit (UCL) and lower control limit (LCL) were defined and compared against the BP standards as given in **(Table 2).** Not more than 2 of 20 tablets should deviate by the allowed percentage deviation and not a single tablet should deviate by double the percentage of allowed deviation.(Ashames, Abushoffa, Tabet, Saidan, & Lagha, 2019)

Table 2: Prescribed Limit of Weight Variation according to British Pharmacopoeia

Dosage Form	Average Mass	Percentage Deviation
Tablets (Uncoated and Film Coated)	≤80mg	10
	>80mg and <250mg	7.5
	≥250 mg	5

Thickness Test

The thickness of tablets was assessed through Neiko 01407A vernier caliper. For performing thickness test, from the final container 10 tablets were taken out. Then each tablet, according to its width was placed in between jaws of the Vernier caliper. After that, the screw of Vernier caliper was made tight and each tablet's thickness was recorded. The tablets pass the test if they show no deviation by ±5% by average thickness of the ten tablets. (Chavan, *et al.,* 2018; Poonguzhali *et al.,* 2014).

Diameter Test

Diameter of the tablets was evaluated through Neiko 01407A vernier caliper. For performing diameter test, from the final container 10 tablets were taken out. Then each tablet, according to its diameter was placed in between jaws of the Vernier caliper. After that, the screw of Vernier caliper was made tight and each tablet's diameter was recorded. (Alnuhait, *et al.,* 2016).

Hardness Test

For the determination of hardness Curio HT-0308 digital hardness tester was used. For performing hardness test, from the final container, that is blister package, 10 tablets were taken out. Along the radial axis in between the two jaws of the hardness tester each tablet is placed. Then hardness tester was started by pressing start button and the force at which the tablet break was displayed at the screen and was noted down.(Beesh, *et al.,* 2017). The hardness of each tablet uncoated tablet must be more than 4-6kg/cm^{2}unless prescribed. (Beesh *et al.,* 2017; Chavan *et al.,* 2018).

Friability

Curio, FB-0607 friabilator was used to determine percentage lost during transport and handling. For performing friability test uncoated tablets weighing near to 6.5g were taken from the final container as intact form. Firstly, initial weight (W_1) of the tablets was noted by weighing them on the weighing balance. Then in friabilator tablets were placed and tumbled for 100 times. After that, tablets were taken out of the friabilator and dedusted. Final weight (W_2) of the tablets was recorded by weighing the tumbled tablets on weighing balance. Lastly, percentage loss was calculated by using formula given below. Percentage lost should be equal or less than 1%. (Beesh *et al.,* 2017; Dharmalingam *et al.,* 2014).

$$Friability\ \% = \frac{W_1 - W_2}{W_1} \times 100$$

Disintegration Test

Disintegration of tablets was determined using Curio DT disintegration apparatus. The disintegration apparatus was assembled, and baskets of the apparatus were placed in such a manner that it was 15mm below the surface of the distilled water on upward move of the mesh, and 25mm above the bottom of the beaker on descending move of the basket. 6 tablets were taken and placed in each tube. At 28-32 cycles per minute disintegration apparatus was operated and disintegration time was noted. **(Table 3)** shows the disintegration test requirements;

Table 3: Disintegration Test Requirements

Medium	Distilled Water (900m)
Time	Uncoated tablets -5 min Film Coated Tablets – half an hour Sugar Coated Tablets– one hour
Temperature	37ºC ±2ºC

If all tablets show disintegration within time, then this test is passed by the tablets. If not more than one tablet shows deviation from the prescribed disintegration time or if stick to the disks, on 12 additional tablets test is again performed. Now, if out of 18, 16 tablets disintegrate within prescribed time then the test is passed by the tablets. (Beesh *et al.,* 2017).

Dissolution Test

Dissolution test was carried out using Curio, DL-0708 dissolution apparatus. Buffer of pH 4.6 prepared by mixing 44.9 parts (v/v) of 0.1N Sodium Acetate and 55.1 parts (v/v) of 0.1N Acetic Acid solution.900ml of buffer was placed in each vessel of the dissolution apparatus. At 37ºC the temperature of buffer medium was adjusted. The instrument was operated at 50rpm for 30 minutes by placing one tablet in each vessel. At the end of the test dilution was made by taking filtered test solution (about 20ml) to produce 0.0lmg/ml of Atenolol. Reference preparation of known concentration, that is, 0.01mg/ml of atenolol was made by taking spedific quantity of atenolol and then dissolving it in the buffer medium. At 275nm Absorbance of the test solution and reference preparation taken. If 80% of the drug is released from the tablet in 30 minutes, then dissolution test is passed by tablets. (Yasmeen, *et al.,* 2005).

Assay

20 tablets were taken from the final containers for performing assay test. One by one each tablet was weighed, and average weight was calculated. Then all tablets taken were powdered and for analysis, powder equal to average weight of tablet was taken. In a 500ml volumetric flask,300ml of methanol was taken and powder of tablet was added. At 60C this suspension was heated and then shaken for 15 minutes. After that the

suspension was set aside for cooling, then for mark-up up-to 500ml, 200ml of methanol was added. By using fine glass Whatman GF/C suspension was filtered. Dilution was made by adding 50ml of methanol in 5 ml of the filtrate and solution was made that contain 0.01% w/v of Atenolol. By using UV Spectrophotometer (Shimadzu mini 1240). The absorbance of the resulting solution was measured at the maximum at 275 nm. Finally, the content of atenolol was calculated taking 53.7 as the value of A (1%, 1 cm). According to the BP, the tablet must contain 95-105% of the drug as claimed on the label. (Ashames *et al.*, 2019).

3. RESULTS AND DISCUSSION

All the samples collected were within their shelf-life. In the physical appearance test the tablets were undamaged with no cracks, having smooth surface with no contaminants present visually. Similar results were observed by Siaan *et al*. (2017) while performing quality control tests.(Siaan, *et al.*, 2017).

In the weight variation test, all the samples complied with the specification of BP i.e. 20/20 tablets were within upper and lower control limit of ±7.5% and none of tablet's weight was double than the allowed limitas shown in **(Table 4).** Ashames *et al.* also achieved similar results of weight variation in the Libyan market. (Ashames *et al.*, 2019). The dimensions of the tablets were also within specified limits of ±5%.Comparableoutcomes were observed by Manimala *et al.* (2018) who also reported that all the samples were within the specified limits.(Manimala *et al*, 2018).The results of dimensions and weight variation tests are given in the following table.

Table 4: The Results of Weight Variation, Thickness and Diameter Test

Weight Variation							
Name	**Average Weight (mg)**	**A.L.±7.5%(mg)**	**UCL (mg)**	**LCL (mg)**	**Tablets within Limit**	**S.D.**	**Result**
Sample-01	189.688	14.227	203.91	175.46	20/20	1.885	Complies
Sample-02	118.061	8.854	126.91	109.20	20/20	2.625	Complies
Sample-03	187.05	14.029	201.07	173.02	20/20	3.994	Complies
Sample-04	119.786	8.984	130.45	110.80	20/20	5.117	Complies
Sample-05	189.632	14.222	203.85	175.41	20/20	3.424	Complies
Thickness							
Name	**Average Diameter (mm)**	**A.L. ±5% (mm)**	**UCL (mm)**	**LCL (mm)**	**Tablets within Limit**	**S.D.**	**Result**
Sample-01	3.99	0.200	4.20	3.20	10/10	0.039	Complies
Sample-02	3.23	0.162	3.39	3.07	10/10	0.018	Complies
Sample-03	3.46	0.173	3.63	3.29	10/10	0.063	Complies
Sample-04	2.97	0.148	3.12	2.82	10/10	0.089	Complies
Sample-05	3.72	0.186	3.91	3.53	10/10	0.019	Complies
Diameter							
Name	**Average Diameter (mm)**	**A.L. ±5% (mm)**	**UCL (mm)**	**LCL (mm)**	**Tablets within Limit**	**S.D.**	**Result**
Sample-01	8.09	0.405	8.49	7.69	10/10	0.017	Complies
Sample-02	7.04	0.352	7.39	6.69	10/10	0.031	Complies
Sample-03	8.65	0.433	9.09	8.22	10/10	0.039	Complies
Sample-04	8.04	0.402	8.44	7.64	10/10	0.017	Complies
Sample-05	8.92	0.446	9.37	8.48	10/10	0.012	Complies

A.L.=Allowed Limit; UCL=Upper Controlled Limit; LCL=Lower Control Limit; S.D.=Standard Deviation. The hardness test of the tablets was performed for the uncoated tablets i.e. Sample-02 and Sample-04 and it complied with the standard of minimum 4kg/cm^{2}as described in Table 5. The friability test was also performed for only uncoated tablets and all the samples having uncoated tablets were within specified limits of not more than 1%as given in **(Table 5).** Similar results were observed by Alnuhait *et al.* (2016) while perfirming a study in Riyadh, Saudi Arabia. (Alnuhait et al., 2016)In the disintegration test most of the tablets disintegrated well before specified time showing good disintegration properties and hence were within specified limits as shown in Table 5. Like results were concluded by Dohare *et al.* (2016) in a study that was conducted in India. (Dohare, *et al.,* 2015) In the following table the results of hardness friability and disintegration test of all the samples are given.

Table 5: Results of Hardness Friability and Disintegration Test

Name	Hardness	Friability	Disintegration Time
Sample-01	NA	NA	7 minutes and 16 seconds
Sample-02	4.45 kg/cm^2	0.37%	7 minutes and 50 seconds
Sample-03	NA	NA	3 minutes and 53 seconds
Sample-04	4.35 kg/cm^2	0.51%	9 minutes and 01 seconds
Sample-05	NA	NA	2 minutes and 46 seconds

In the dissolution test all the marketed products were within the specified limits of not less than 80% drug dissolved in 30 minutes. However, it was observed that the dissolution of two of the local generic tablets was better than the multinational brand and generic formulations as shown in **(Table 6).** Similarly, all the atenolol tablets were within the specified limits of content i.e. 95-105%, however the content of two of the locally manufactured formulations was more than the multinational brand and generic formulations as given in Table 6. On the contrary, Poonguzhali *et al.* 2014) in study in India after studying five marketed formulations of atenolol one product failed in assay while other in dissolution.(Poonguzhali et al., 2014)Similar study was also carried out by Beesh and associates in Syria in which one product failed in assay, one in dissolution and one in both assay and dissolution.(Beesh *et al.*, 2017) The results of assay and dissolution are graphically represented in **(Fig. 1and Fig. 2)** respectively.

Table 6: Results of Assay and Dissolution

Name	Dissolution (%; SD)	Assay (%)
Sample-01	90.47%; 4.66	98.69%
Sample-02	93.30%; 2.87	102.38%
Sample-03	95.86%; 2.50	100.58%
Sample-04	94.70%; 2.50	104.28%
Sample-05	86.57%; 4.20	96.82%

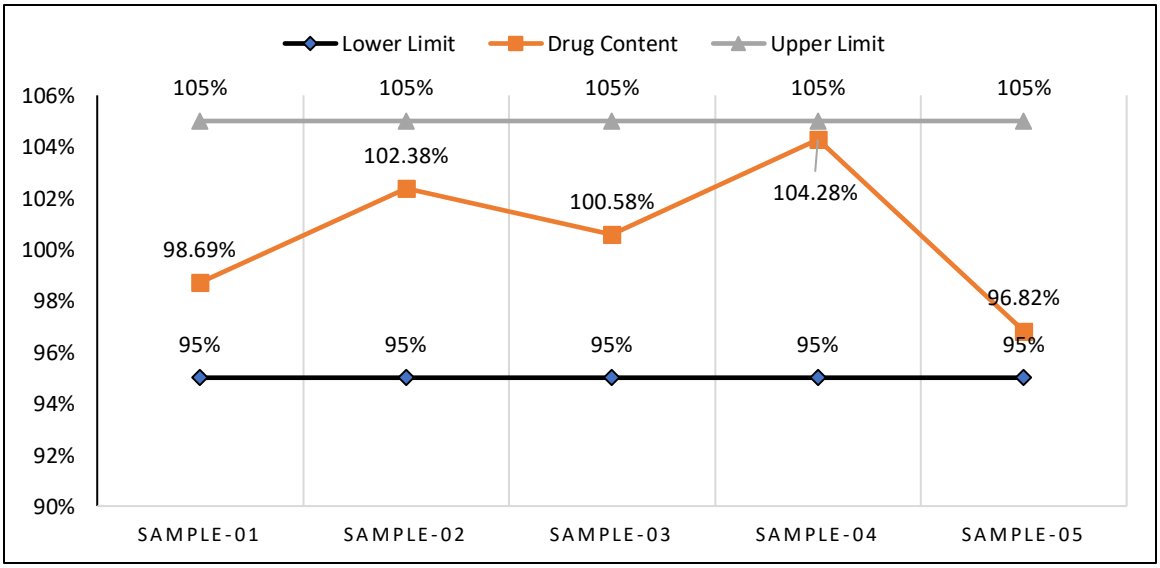

Fig. 1: Assay Test of All Brands

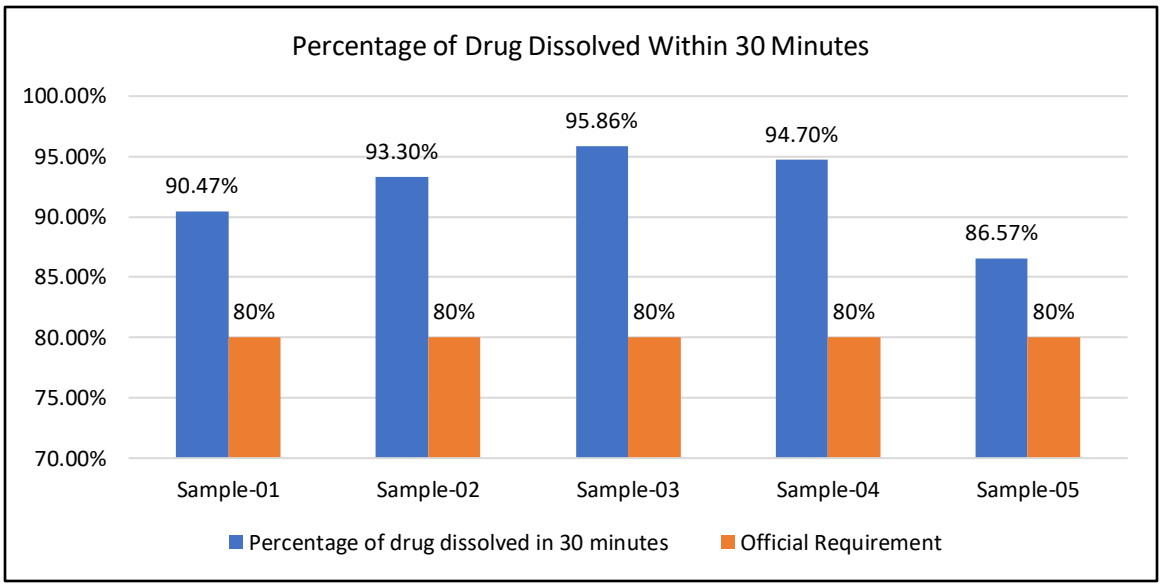

Fig. 2: Percentage of Drug Dissolved Within 30 Minutes

In the year 2015, Pharmaceutical Security Research Institute reported that the crime ratio is more in Asia and about 3002 cases of drug crime were reported in Asia-Pacific region.(Kakio *et al.,* 2018) However, in this study no substandard or falsified product was observed.

The quality of locally manufactured drugs contrary to the questionnaire base study by Shazia *et al.* (2012) who reported perception of decrease in the quality of locally manufactured drugs than the innovator products and productions from multinational firms. (Jamshed *et al.*, 2012) and any observation of significant decrease in quality of generic products as compare to innovator product (Jamshed *et al.*, 2012; Shrank *et al.*, 2011). The results of this study, though different in figures but were similar to study conducted by Naveed *et al.* 2014) in Karachi who reported that all the products were of same quality, pharmaceutical equivalents and could be used interchangeably.(Naveed, *et al.*, 2014).

4. CONCLUSION

All the products collected from the market were within the specified limits of British Pharmacopoeia when weight variation, dimension, hardness, friability, disintegration, dissolution tests and assay was performed. During the study no substandard or falsified product was found. It was noted that dissolution profiles of two of the generic products manufactured locally were better than the innovator and multinational products. The products from innovator, multinational and local firms are pharmaceutical equivalents and can be used interchangeably.

RECOMMENDATIONS:

Marketed formulations from innovator and multinational firms should not be given preference based on the perception that the products from local manufacturers are of low quality. The products from local manufacturers are cheaper but are of quality comparable to multinational generic products and should be used for cost effective treatment. The government should support the local manufacturing of the drug to help the people and boost the economy.

REFERENCES:

Akasha, A. A. (2016). Comparative physical studies of atenolol brands available in libyan drug market. Innoriginal: International Journal of Sciences, 3(1),1-3.

Alnuhait, M. A., A. S. A. Shammari, M. E. Ahmed, and A. A. Obaidat, (2016). In-vitro evaluation of some generic products of atenolol commonly sold in the Saudi market. Journal of Innovations in Pharmaceuticals and Biological Sciences, 3(2), 12-19.

Ashames, A., A. Abushoffa, M. Tabet, R. B. Saidan, and B. Lagha, (2019). Impact of the Libyan Conflict on Quality of Medicines Available in the Local Market. Journal of Chemical and Pharmaceutical Research, 11(1), 20-27.

Badawi, M., E. Wagdy, M. Nasr, M. Etman, L. El-Khordagui, and S. Khalil, (2013). Postmarketing pharmacokinetic and pharmacodynamic equivalence of generic and brand atenolol in Egypt/Étude d'équivalence post-commercialisation des propriétés pharmacocin-

étiqueset pharmacodynamiques de l'aténolol en générique et sous son nom de marque en Égypte. Eastern Mediterranean Health Journal, 19(3), S166.

Beesh, M., M. Isbera, K. Aboud, and A. Mohammad, (2017). Quality analysis of different marketed brands of atenolol (50 mg) available in syria and comparing with the reference drug. World Journal of Pharmaceutical Research, 6(14), 61-68.

Begum, R., M. Z. Sultan, J, A. Chowdhury, and M. S. Amran, (2019). In vitro Pharmaceutical Equivalence Study of Three Brands of Atenolol Tablets Available in Bangladesh. Dhaka University Journal of Pharmaceutical Sciences, 18(1), 43-48.

Chavan, H., C. Gurmeet, G. Nayan, and J. Anil, (2018). Comparative study of in-process and finished products quality control test for tablet and capsules according to pharmacopoeias. Asian Journal of Pharmaceutical Research and Development, 6(3), 60-68.

Davit, B. M., P. E.. Nwakama, G. J. Buehler, D. P. Conner, and J. Woodcock, (2009). Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. Annals of Pharmacotherapy, 43(10), 1583-1597.

Dharmalingam, S. R., M. Azizi, S. Shanmugham, V. S. Meka, and P. S. Wong, (2014). Comparative quality control evaluation of atenolol tablets marketed in Kuala Lumpur, Malaysia. British Journal of Pharmaceutical Research, 4(13), 1688.

Dohare, S., V. Shrivastava, U. Jain, (2015). Development and evaluation of fast dissolving tablets & comparative in-vitro dissolution study of various marketed brands of atenolol tablets. Panacea Journal of Pharmacy and Pharmaceutical Sciences, 4(4), 817-841.

George, T., and M. Ajit, (2009). Atenolol in Hypertension. Supplement of Journal of The Association of Physicians of India, 57, 22-25

Jamshed, S. Q., M.I.M. Ibrahim, M. A. A. Hassali, I. Masood, B. Y. Low, and A. A. Shafie, (2012). Perception and attitude of general practitioners regarding generic medicines in Karachi, Pakistan: a questionnaire based study. Southern med review, 5(1), 22Pp.

Kakio, T., H. Nagase, T. Takaoka, N., Yoshida, J. Hirakawa, S. Macha, and K. Kimura, (2018). Survey to identify substandard and falsified tablets in several asian countries with pharmacopeial quality control tests and principal component analysis of handheld raman spectroscopy. The American Journal of Tropical Medicine and Hygiene, 98(6), 1643-1652.

Naveed, S., H. Dilshad, and S. Aziz, (2014). Comparitive study of different brands of atenolol available in karachi. Mintage Fournal of Medical and pharmaceutical Sciences, 3(3), 17-19.

Poonguzhali, S., K. Anusha, T. Mounica, P. M. Niharika, and R. Nadendla, (2014). Comparative InVitro Evaluation of Commercial Atenolol Tablets. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 5(6), 30-35.

Sherwood, T. (n.d.). Generic Drugs - Center for Drug Evaluation and Research FDA.1-40.

Shrank, W. H., J. N. Liberman, M. A. Fischer, C. Girdish, T. A. Brennan, and N. K. Choudhry, (2011). Physician perceptions about generic drugs. Annals of Pharmacotherapy, 45(1), 31-38.

Siaan, M. M., M. A. S. Anwair, F. Sadek, and A Elhamili, (2017). Comparative in Vitro Evaluations of Different Brands of Atenolol Tablets in Libyan Market. Journal of Chemical, Biological and Physical Sciences, 7(4), 857-867.

Whalen, K. (2015). Pharmacology: Lippincott illustrated reviews: Lippincott Williams & Wilkins.

Yasmeen, R., M. H. Shoaib and H. Khalid, (2005). Comparative study of different formulations of atenolol. Biochem. Biophys. Acta, 577, 346-359.