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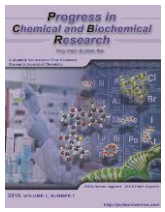

Comparative study of pharmaceutical content of three different cardio vascular system drugs marketed in Tripoli- Libya

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ABSTRACT

Generic drugs have increased in their popularity as the cost of their brand counterparts have arisen. Post-marketing testing of some drugs is used to assure quality, efficacy and safety of those drugs made available for public use. This is to give evidence of their effectiveness.
This study was undertaken to justify the use of generic substitution of metoprolol, spironolactone and verapamil brands marketed in Tripoli-Libya. This evaluation was achieved through QC tests for hardness, disintegration time and chemical content according to British Pharmacopoeial standards. The results of these tests were found to comply with pharmacopoial range indicating their efficiency to be used as a substituent for brands of higher price.

1. Introduction

Pharmaceutical spending has been rising rapidly recently and prescription drugs have been a target to struggle to contain health care costs. Therefore, there is an arising attractive option to use generic drugs which have almost as little as one-third the cost of their brand name products [1].

What are Generic Medicines? A generic drug is identical, or bioequivalent, to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use [2].

The selected drugs are used for treatment of hypertension and other cardiac diseases of three different origins; metoprolol tartarate tablets, verapamil injection and spironolactone tablets. These drugs were chosen because of the need for them to be highly effective leaving no chance for lowered dose or ineffective formula to be administered to patients. Therefore; the substituent must have equal efficacy and safety. The tests performed would be of a greater value if accompanied by tests for bioavailability.

Pharmacopoeial monographs can be used by manufacturers, regulators and other stockholders for quality control of active pharmaceutical ingredients (APIs) and finished products against internationally recommended specifications. Pharmacopoeia requirements in countries form a part of national legislation, defining the specifications which pharmaceutical products circulating on their market must fulfil [3].

Stable tablets retain their original size, shape, weight, and colour under normal handling and storage conditions throughout their shelf life. There are various quality control tests for tablets, the control tests and specifications for the finished product should be such as to allow the qualitative and quantitative determination of the main active constituents [4, 5].

The breakage of tablet into smaller fragments is called disintegration of tablet. The drug is released from a

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disintegrating tablet in a sequence of processes, including Tablet disintegration, drug dissolution and drug absorption. All these processes will affect, and can be rate-limiting step for the rate of drug bioavailability [6].

The degree of hardness of the tablet depends on its physical size and shape together with the characteristics of the chemicals that go into the formulation and the pressure applied during compression. So hardness so important for handling, shipping, and dispensing [7].

The differences in results of these tests can lead to differences between bioavailability of brands compared to generic drug products.

For each proposed drug; two generic products of different origin were analysed. These products are available for patients to be used with lower price compared to a brand.

The following table summarizes the name, pharmacological action and use for each tested drug. The detail for manufacturing names, dates and numbers are kept as a record with the researchers.

Table 1. Pharmacological action and use of tested drugs

No.	Name	Pharmacological action	Uses
1.	Metoprolol-1	Selective beta blocker	Hypertension Angina pectoris Myocardial infarction
2.	Metoprolol-2		
3.	Verapamil-1	Calcium channel blocker	Hypertension Angina pectoris Cluster headach prophylaxis
4.	Verapamil-2		
5.	Spironolactone-1	Aldosterone antagonist	Hypertention Hypokalemia Conn's syndrom
6.	Spironolactone-2		

2. Experimental

2. 1. Hardness

Aim

To determine the suitability of a material for a given application.

Materials

Metoprolol tablets and spironolactone tablets, tablets hardness tester machine (Pharmatest, Germany).

Method

Take 10 tablets from each brand from each drug and measure hardness using the tablet hardness tester machine. A tablet is placed between two anvils. Force is applied to the anvils and the crushing strength that just causes the tablet to break is recorded on the machine **Limits**: For uncoated tablet: 4–8 kg/cm^2. For coated tablet: 10 to 20 kg/cm^2.

2. 2. Disintegration test

Aim

This test determines tablets disintegrate within a prescribed time when placed in a liquid medium under the prescribed experimental conditions.

Materials and instruments

Metoprolol tablets, Spironolactone tablets, disintegrator tester (Pharma test, Germany).

Method

Place one dosage unit in each of the six tubes of the basket and if specified add a disc. Operate the apparatus using water as the immersion fluid unless another liquid is specified and maintain its temperature at 35–39 °C. At the end of the specified time lift the basket from the fluid and observe the dosage units: all of the dosage units have disintegrated completely. If one or two dosage units fail to disintegrate repeat the test on 12 additional dosage units. The requirements of the test are met if not less than 16 of the 18 dosage units tested are disintegrated.

2. 3. Percent of Content using UV-Vis Spectroscopy

Aim

This study aims to find out % of content by using UV-Vis Spectrophotometer according to the British Pharmacopeia 2010 reference range.

2. 3. 1. Metoprolol Tablet

Materials and Instrumental

Ethanol, Distal water, Ultrasound, Filter paper, Balance, Volumetric flask 200 mL and 50 mL, Mortar and pestle, Measuring cylinder L, pipette, dropper, beaker and UV-Vis Spectrophotometer (JENWAY, UK).

Method of Assay

weigh and powder 20 tablets, add to a quantity of the powdered tablets containing 75 mg of metoprolol tartrate 150 ml of absolute ethanol, shake with the aid of ultra sound for 15 minutes, allow to cool, add sufficient absolute *ethanol* to produce 200 mL and filter (whatman GF\C paper is suitable), to 20 mL of the filtrate add sufficient absolute ethanol to produce 50 mL and measure the absorbance of the resulting solution at 274 nm [8].

NOTE:

METOPROLOL (LOPRESSOR) is used as reference standard because the chemical stander are not available. And produced Abs= 0.662.

2. 3. 2. Verapamil Injection

Materials and Instrumental

HCl, Volumetric flack 200 mL, beaker, dropper and UV-Vis Spectrophotometer (JENWAY, UK).

Method of Assay

Dilute a volume containing 5 mg of Verapamil hydrochloride to 100 mL with 0.01 M hydrochloric acid Measure the absorbance of the resulting solution at the maximum at 278nm [8].

2. 3. 3. Spironolacone tablets

Materials and Instrumental

Methanol, mortar and pastel, distal water, balance, glass rode, measuring cylinder, pipette, volumetric flask 100 mL and 250 mL, beaker, dropper and UV-Vis Spectrophotometer (JENWAY, UK).

Method of Assay

Weight and powder 20 tablets. To a quantity of the powder containing 25 mg of spironolactone add 100 mL of methanol and heat just to boiling, with swirling. Cool, add sufficient methanol to produce 250 ml, dilute 10 ml to 100 ml with methanol and measure the absorbance of resulting solution at the maximum at 238 nm [8].

3. Result and Discussion

3.1. Hardness result

3.1.1. Metoprolol tablet

Table 1. Hardness result of Apo metoprolol tablets (Canadian)

Tablet No.	Hardness (N/cm^2)	Hardness (Kg/cm^2)	Tablet diameter (mm)	Tablet Thickness (mm)
1	56.3	5.7	9.60	4.23
2	58.8	6	9.60	4.27
3	57.6	5.8	9.60	4.26
4	61.0	6.2	9.60	4.31
5	59.7	6.0	9.60	4.57
6	55.4	5.6	9.60	4.11
7	57.4	5.8	9.60	4.25
8	54.7	5.5	9.60	4.28
9	66.0	6.7	9.59	4.31
10	47.9	4.8	9.60	4.27

Table 2. Hardness result of lachipres®(Italian)

Tablet No.	Hardness (N/cm^2)	Hardness (Kg/cm^2)	Tablet diameter (mm)	Tablet Thickness (mm)
1	40.0	4	11.15	3.00
2	34.1	3.4	11.14	3.05
3	36.8	3.7	11.14	3.07
4	40.0	4	11.22	3.08
5	36.3	3.7	11.15	3.09
6	39.1	3.9	11.22	3.07
7	32.9	3.3	11.15	3.08
8	47.4	4.8	11.17	3.07
9	34.7	3.5	11.22	3.08
10	23.9	2.4	11.20	3.08

3.1.2. Spironolactone tablet

Table 3. Hardness result of spironolactone®(UK)

Tablet No.	Hardness (N/cm²)	Hardness (Kg/cm²)	Tablet diameter (mm)	Tablet Thickness (mm)
1	57.4	5.8	8.65	3.72
2	54.5	5.5	8.65	3.68
3	61.1	6.2	8.74	3.67
4	54.5	5.5	8.70	3.75
5	53.2	5.4	8.70	3.72
6	62.0	6.3	8.62	3.90
7	57.7	5.8	8.72	3.77
8	60.2	6.1	8.68	3.76
9	55.8	5.6	8.64	3.65
10	53.2	5.4	8.67	3.73

Table 4. Hardness result of aldactone tablets (Egyptian)

Tablet No.	Hardness (N/cm²)	Hardness (Kg/cm²)	Tablet diameter (mm)	Tablet Thickness (mm)
1	52.7	5.3	8.82	3.51
2	51.1	5.2	8.82	3.59
3	51.7	5.2	8.85	3.60
4	47.9	4.8	8.82	3.57
5	41.8	4.2	8.83	3.56
6	47.3	4.8	8.82	3.59
7	49.3	5.0	8.82	3.58
8	47.9	4.8	8.82	3.63
9	48.7	4.9	8.83	3.60
10	43.8	4.4	8.83	3.59

3.2. Disintegration result

3.2.1. Metoprolol tablet

Table 5. Disintegration time of apo metoprolol (Canadian)

Tablet No.	Disintegration Time Hours:minutes:seconds
1	0 : 08 : 52
2	0 : 09 : 26
3	0 : 08 : 22 (minimum)
4	0 : 09 : 10
5	0 : 09 : 28
6	0 : 10 : 54 (maximum)
Average disintegration time	0 : 09 : 22
Standard Deviation (SD)	0 : 00 : 51

Table 6. Disintegration time of Lachipres (Italian)

Tablet No.	Disintegration Time Hours : minutes : seconds
1	0 : 09 : 36
2	0 : 10 : 48
3	0 : 12 : 00 (maximum)
4	0 : 06 : 09
5	0 : 04 : 45 (minimum)
6	0 : 06: 13
Average disintegration time	0 : 08 : 15
Standard Deviation (SD)	0 : 02 : 56

Table 7. Disintegration time of spironolactone Tablets (UK)

Tablet No.	Disintegration Time Hours : minutes : seconds
1	0 : 03 : 50
2	0 : 6 : 48 (maximum)
3	0 : 03 : 18(minimum)
4	0 : 06 : 04
5	0 : 06 : 00
6	0 : 03 : 32
Average disintegration time	0 : 04 : 55
Standard Deviation (SD)	0 : 01 : 31

Table 8. Disintegration time of aldactone (Egyptian)

Tablet No.	Disintegration Time Hours : minutes : seconds
1	0 : 01 : 31
2	0 : 01 : 27 (minimum)
3	0 : 01 : 59
4	0 : 02 : 47
5	0 : 02 : 25
6	0 : 03 : 29 (maximum)
Average disintegration time	0 : 02 : 16
Standard Deviation (SD)	0 : 00 : 47

3.3. Percent content result and calculations

The percentage content was calculated using the following equation

$$\% \text{ content} = \frac{actual concentration\ (gmL{-}1)}{theoretical concentration\ (gmL{-}1)} \times 100$$

The actual concentration was calculated using the following equation

$$standard \text{ concentration (g mL}^{-1}) \times \text{actual concentration} = \frac{absorbance of sample}{absorbance of standard}$$

3.3.1. Percent content of metoprolol tablet

3.3.1.1. Sample calculation for the assay of Lachipres metoprolol (Italian)

$$0.00015 = 0.00015 \text{ g /mL} \times \text{Actual concentration} = \frac{0.6632}{0.662}$$

$$= 0{,}00015 \text{ g /mL} \qquad \text{Theoretical concentration} = \frac{0.075\text{g} \times 20\text{ml}}{200\text{ml} \times 50\text{ml}}$$

$$\mathbf{100.1\%} = 100 \times \text{Content} = \frac{0.00015}{0.00015}\%$$

Table 9. % content of Lachipres metoprolol (Italian)

EXP.	abs5	abs4	abs3	abs2	abs	average	content%	STDEV
Exp1	0.652	0.668	0.657	0.675	0.664	0.6632	100.15106	1.342628
Exp2	0.66	0.646	0.646	0.651	0.651	0.6508	98.187311	
Exp3	0.653	0.64	0.644	0.641	0.653	0.6462	97.583082	
						Content%	**98.6 % ± 1.3**	

Since all the results of % content was rounded to 1 significant figure, the final results was reported 100.1%. The same calculations were carried out for other two runs where the % content of runs 2 and 3 were 98.1% and 97.5%, respectively. The final reported result was the average % content, which equals 98,6% ± 1.3%. The 1,3% is the sample standard deviation.

3.3.1.2. Sample calculation for the assay of Apo-metoprolol (Canadian)

$$0.00015 = 0.000147 \text{ g /mL} \times \text{Actual concentration} = \frac{0.651}{0.662}$$

$$= 0{,}00015 \text{ g /mL} \qquad \text{Theoretical concentration} = \frac{0.075\text{g} \times 20\text{ml}}{200\text{ml} \times 50\text{ml}}$$

$$100 = \mathbf{98.3\%} \times \text{Content} = \frac{0.000147}{0.00015}\%$$

Table 10. %content of Apo metoprolol (Canadian)

Exp.	abs1	abs2	abs3	abs4	abs5	average	content%	STDEV
Exp1	0.65	0.65	0.649	0.651	0.655	0.651	98.33837	0.982841
Exp2	0.665	0.661	0.662	0.664	0.671	0.6646	100.3021	
Exp3	0.657	0.657	0.658	0.659	0.663	0.6588	99.39577	
						Content % = 99.3 % ± 0.9		

Since all the results of % content was rounded to 1 significant figure, the final results was reported 98.3%. The same calculations were carried out for other two runs where the % content of runs 2 and 3 were 100.3% and 99.3%, respectively. The final reportedresult was the average % content, which equals 99.3% ± 0.9%. The 0.9% is the sample standard deviation.

3.3.2.1. Sample calculation for the assay of Verapamil vatiopharm (Germany)

$$0.01 = 0.0000545\text{g /mL} \times \text{Actual concentration} = \frac{0.6434}{118}$$

$$= 0.00005 \text{ g /mL} \qquad \text{Theoretical concentration} = \frac{0.005\text{ g}}{100\ ml}$$

$$100 = \mathbf{108.9\%} \times \text{Content} = \frac{0.0000545}{0.00005}\%$$

3.3.2. Percent content of VerapamilInjection

Table 11. % content of Verapamil vatiopharm (Germany)

EXP.	Abs1	Abs2	Abs3	Abs4	Abs5	Average	Content%	STDEV
Exp1	0.642	0.643	0.64	0.644	0.648	0.6434	108.9831	0.169492
Exp2	0.642	0.646	0.641	0.642	0.643	0.6428	108.8136	
Exp3	0.64	0.642	0.64	0.643	0.642	0.6414	108.6441	
						content % = 108.8 % ± 0.1		

Since all the results of % content was rounded to 1 significant figure, the final results was reported 108.9%. The same calculations were carried out for other two runs where the % content of runs 2 and 3 were 99.2% and 108.6%, respectively. The final reported result was the average % content, which equals 108.8 % ± 0.1 %. The 0.1% is the sample standard deviation.

3.3.2.2. Sample calculation for the assay of Verapamil lsoptin (American)

$$0.01 = 0.00005228\ g/mL \times \text{Actual concentration} = \frac{0.617}{118}$$

$$= 0.00005\ g/mL \qquad \text{Theoretical concentration} = \frac{0.005\ g}{100\ ml}$$

$$100 = \mathbf{104.5\ \%} \times \text{Content} = \frac{0.00005228}{0.00005}\%$$

Table 12. % contentof Verapamil lsoptin (American)

EXP.	Abs1	Abs2	Abs3	Abs4	Abs5	Average	Content%	STDEV
Exp1	0.612	0.618	0.62	0.618	0.617	0.617	104.5763	0.508475
Exp2	0.608	0.61	0.613	0.616	0.608	0.611	103.5593	
Exp3	0.616	0.613	0.619	0.611	0.613	0.6144	104.0678	
						content % = 104.0 % ± 0.5		

Since all the results of % content was rounded to 1 significant figure, the final resultswas reported 104.5%. The same calculations were carried out for other two runs where the % content of runs 2 and 3 were 103.5% and 104.0%, respectively. The final reported result was the average % content, which equals 104.0% ± 0.5%. The 0.5% is the sample standard deviation.

Table 13. % content of Spironolactone Aldactone (Egyptian)

EXP.	Abs1	Abs2	Abs3	Abs4	Abs5	average	content%	STDEV
Exp1	0.47	0.463	0.458	0.469	0.467	0.4654	99.02	1.405879
Exp2	0.465	0.465	0.467	0.463	0.473	0.4666	99.2766	
Exp3	0.455	0.452	0.455	0.455	0.456	0.4654	96.7234	
						Content % = 98.3 % ± 1.4		

3.3.3. Percent content of spironolactone tablet

3.3.3.1. Sample calculation for the assay of spironolactone Aldactone

$$0.01 = 0.0000099\ g/mL \text{ Actual concentration} = \frac{0.4654}{470}$$

$$= 0.00001\ g/mL \qquad \text{Theoretical concentration} = \frac{0.025g*10ml}{250ml*100ml}$$

$$100 = \mathbf{99.0\ \%} \times \text{Content} = \frac{0.0000099}{0.00001}\%$$

Since all the results of % content was rounded to 1 significant figure, the final results was reported 99.0%. The same calculations were carried out for other two runs where the % content of runs 2 and 3 were 99,2% and 96.7%, respectively. The final reported result was the average % content, which equals 98.3% ± 0.4%. The 0.4% is the sample standard deviation.

3.3.3.2. Sample calculation for the assay of spironolactone Birstol

$$0.01 = 0.0000102.g/mL \times \text{Actual concentration} = \frac{0.4804}{470}$$

$$= 0.00001\ g/mL \qquad \text{Theoretical concentration} = \frac{0.025g*10ml}{250ml*100ml}$$

$$100 = \mathbf{102.1\ \%} \times \text{Content} = \frac{0.0000102}{0.00001}\%$$

Table 14. % content of spironolactone Birstol

EXP.	Abs1	Abs2	Abs3	Abs4	Abs5	Average	Content%	STDEV
Exp1	0.48	0.477	0.482	0.482	0.481	0.4804	102.1277	0.767139
Exp2	0.471	0.477	0.47	0.481	0.476	0.475	101.0638	
Exp3	0.472	0.474	0.472	0.474	0.473	0.473	100.6383	
						Content % = 101.2 % ± 0.7		

Since all the results of % content was rounded to 1 significant figure, the final results was reported 102.1%. The same calculations were carried out for other two runs where the % content of runs 2 and 3 were 101.0% and 100.6%, respectively. The final reported result was the average % content, which equals 101.2% ± 0.7%. The 0.7% is the sample standard deviation.

4. Comments

4.1. Metoprolol Tablets

According to BP limit (95.0% to 105.0%)-

The results of two brands that used in these research conceder within the BP limit. The precision of APOMETOPROLOL brand higher than LACHIPRES.

4.2. Verapamil Injection

According to BP limit (90.0% to 110.0%)-

The results of two brand that used in these research conceder within the BP limit. The precision in VATIOPHARM higher than ISOPTIN.

4.3. Spironolactone Tablets

-According to BP limit (95.0% to 110.0%)

The results of two brand that used in these research conceder within the BP limit. The precision in BRISTOL higher than EYGPTION ALDACTONE.

5. Conclusion

This study should provide the possibility for these generic drugs to be prescribed to patients as they have a lower price compared to a brand. There must be many such study to provide a good evidence for using generics. Also Authorized bodies must have a clear policy to evaluate generic drugs carefully before marketing to ensure safety and efficacy of such products.

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