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Detection of Substandard Medicines in Sudanese Market by Assessing Pharmaceutical Equivalences of Five Brands of Lisinopril 10mg Tablets

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Abstract

Counterfeit medicines resemble a silent murderer when used to treat life threatening conditions and people of lower-income segment are at greater risk of purchasing and consuming unsafe counterfeit products. The aim of this study is to examine if substandard medicines are circulating in the regulated supply chain of Sudan and to assess the enforcement of law and regulations by drug regulatory authority taking Lisinopril 10mg brands, fully registered in Sudan, as a model drug. The quality of Zestril, P1, P2, P3 and P4 were evaluated by qualifying tablets for harness, friability, disintegration time, dissolution and assay according to pharmacopoeial methods. All brands have passed the official tests, however two of them failed to pass the friability and hardness tests and Zestril failed to pass only the hardness test. The results might be attributed mainly to the variations in excipients used. The formulation that contains only maize starch as binding agent totally failed to pass both hardness and friability tests and was therefore of substandard quality. The studied showed that circulating pharmaceutical alternatives and equivalence in Sudanese market may need more efficient system to assess their quality before and after circulating on the Sudan's market to safeguard the health of the population.

Keywords: Lisinopril, Official tests**,** Substandard**,** counterfeit

1. Introduction

1.1. Counterfeit and Substandard Medicines.

Counterfeit medicines resemble a silent murderer when they are used to treat life threatening conditions [1,2], and people of lower-income segment who are attracted by the lower price of counterfeit medicines are at greater risk of purchasing and consuming unsafe counterfeit products [3]. WHO defines counterfeit medicine as one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products, and may include products with correct or wrong ingredients, incorrect amount of active ingredients, without active ingredients and fake packaging [4].Very recently the WHO changed the term counterfeit medical products into Substandard, Spurious, Falsely- labelled, Falsified, and Counterfeit medical products (SSFFC) to involve all types of sub standards and to overcome debates that may originate whether it is a counterfeit or only substandard [5].

1.2.Distribution of Counterfeit Medicines.

Counterfeit medicines can be found everywhere with different frequency. In developing countries, medicines are often sold in many uncontrolled situations. Therefore it is easier to sell counterfeit medicines than in countries that can count on more effective control on manufacturing and distribution as well as on more effective law enforcement [3].

The aim of the present study was to collect all registered brands of lisinopril 10 mg available in Sudanese market in February 2015 (5 brands including the originator) to analyze them to fulfill the following; address the problem of SSFFC medicines, to examine if such medicines are circulating in the regulated supply chain, to examine if the originator and generic medicines distributed in the country comply with the approved standards, to assess the compliance of marketing authorization holders with the registration certificates and to assess the enforcement of law and regulations by drug regulatory authority.

2. Materials and Methods

2.1. Brands tested

The branded medicines used in the practical work of this research are listed below in table (2-1) each one with its excipients;

Table (2-1): The labels and excipients used in branded medicines studied

Brand	Label	Excipients
Zestril 10mg tablets	AstraZenica UK Limited. Lot: KV 835. MFG: 4/2014. Exp: 3/2018	calcium hydrogen phosphate dihydrate (123.4 mg), pregelatinized starch (4 mg), mannitol (41.2 mg), maize starch (11 mg), maize starch anhydrous (20 mg), magnesium stearate 1.5 mg, and red iron oxide E 172 (0.268 mg).
P1 10 mg tablets	MFG: 4/2013. Exp: 4/2015.	dibasic calcium phosphate powder (96 mg), mannitol (36 mg), maize starch (40 mg), Croscarmellose (3.8 mg), colloidal anhydrous silica (0.95 mg), magnesium stearate 2.36 mg) and purified water (Q.S.).
P2 10 mg tablets	MFG: 3/2014. Exp.: 3/2017.	calcium hydrogen phosphate anhydrous fine powder (57.675 mg), mannitol (27.5 mg), maize starch (12.5 mg), pregelatinized starch (2 mg), magnesium stearate (1.125 mg), red iron oxide (0.8 mg)).
P3 10 mg tabs	MFG.: 3/2013. Exp.: 3/2016.	microcrystalline cellulose (164.8 mg), sodium starch glycollate (20 mg), colloidal anhydrous silica (2 mg), magnesium stearate (2 mg), and red iron oxide (0.2 mg)).
P4 10 mg tabs	MFG: 7/213. Exp.:7/2015.	dibasic calcium phosphate (98.96), maize starch (74 mg), Povidone K_{30} (11 mg), magnesium stearate (3 mg), purified talc (3 mg), Erythrocin red (0.04 mg), purified water (0.06 ml).

2.2. Chemicals

Lisinopril working standard (Huahai manufacture ,MFG. date 11/2013. , Expiry date 10/2016. Assay 99.51%. and Water content 8.83%). Analytical grade of Ortho-phosphoric acid, Potassium dihydrogen phosphate, Sodium 1-hexane sulphonate, Acetonitrile, Methanol as well as distilled water.

2.3. Methods

All tests were carried according to BP or USP [6,7].

2.3.1. Hardness test

The test was carried out for random 10 tablets; they were tested using the hardness tester (Erweka, Germany). The test was repeated 3 times.

2.3.2. Friability test

For friability test random 10 tablets were weighed firstly using sensitive balance (Bell Engineering, Italy) and tumbled in friability tester (Erweka, Germany), for 4 minutes at 25 RPM, tablets were then weighed again and percentage loss were calculated.

2.3.3. Disintegration test

The test was conducted using a disintegration apparatus (Copley Scientific, United Kingdom). The apparatus employs a basket of six tubes with a base of metal sieve. A tablet was placed in each tube and held in place by a plastic weight. The six-tube assembly, containing six tablets, was suspended using a hanger with a mechanism of vertical motion at a fixed speed. While hanging the six-tube assembly on the hanger, the assembly was moved in vertical motion in distilled water at 37^0c. The time for disintegration of the six tablets was recorded for each sampled medicine. The test was repeated thrice.

2.3.4. Dissolution test

To determine the amount of lisinopril dissolved, USP apparatus 2 (Erweka, Germany) was used with 900 ml of 0.1N HCl as dissolution medium, each tablet was mounted at 50 rpm and maintained at 37 °c temperature for 30 minutes.

Phosphate solution was prepared by dissolving 4.10 g of monobasic potassium phosphate in 900 ml of water in a 1000 ml volumetric flask then, the pH is adjusted to 2 with phosphoric acid then water was added to volume and the solution is mixed.

Mobile phase was prepared by dissolving 1.0g of sodium 1-hexanesulphonate in 820 ml of phosphate solution. 180ml of acetonitile was added, and then mixed, filtered and degased using sonicator (Hwashin, Japan) for 5 minutes. Diluent was prepared by mixing water and methanol (4:1) volumes respectively.

A standard solution was prepared by dissolving 582.2 mg of lisinopril working standard in diluent to

obtain a solution having a known concentration of about 0.2 mg per ml. 20µl was injected in a chromatographic system (HPLC) which was equipped with a 215-nm detector (Shimadzu, Japan) and a 4.6 mm × 20 cm column (Shimadzu, Japan) that contained packing L7 and was maintained at a temperature of 40 °c. The flow rate was 1ml per minute.

The amount of lisinopril dissolved was determined by the following procedure; equal volumes (20ml) of the filtered solutions of the 6 individual specimens was withdrawn and combined and the pooled sample was used as the test sample for each of the tested brands separately. A volume of the pooled sample was injected into the above chromatographic system, the chromatograph was recorded and the response for the major peak was measured. The quantity of lisinopril dissolved was calculated in comparison with the standard solution having a known concentration in the same medium and similarly chromatographed.

2.3.5. Assay test

It was also carried out by chromatographic method according to both USP and BP. The mobile phases, diluent, standard solution preparation as well as the chromatographic system were as same as those in the dissolution test.

Assay preparation was carried out by transferring, to a suitable size volumetric flask, powdered 10 tablets, diluted with the diluent to yield a solution having a concentration of about0.2 mg/ ml. After adding diluent, sonicated for 5 minutes and then the flasks were shacked by mechanical shaker (Edmund Buhler, Germany) for 20 minutes then diluted with the diluent to volume, then mixed and filtered. Equal volumes from the standard solution and the assay preparations were injected into the chromatograph separately, then the chromatograms were recorded and the area responses for major peaks were measured and recorded.

3. Results and discussion

3.1. Results

Table (3-1): Results of quality control tests for all batches of lisinopril 10mg tablets.

Test type	Non official		Official		
Sample	Hardness (Kp)	Friability (Loss%)	Disintegration (min:sec)	Dissolution (amount released%)	Assay (content %)
Zestril 10mg	3.53	0.03	1:38	96	95.5
P1 10mg	1.25	1.37	2:45	96	96.7
P2 10mg	3.74	1.15	3:40	100	98.2
P3 10mg	17.53	0.06	4:14	102	95.4
P4 10mg	5.17	0.41	5:11	121	102.1

3.2 Discussion

The table (3-2) below which is introduced to ease referring to the formulation details while discussing the results obtained from the different brands and as many excipients are multi-functional, the major role of the excipient is designated as claimed by the manufacturer(s), however when discussing various functions that are performed by the excipient are included.

Table (3-2): Excipients used in various tested brands

Brands	Diluents	Binder	Disintegrant	Glidant	Lubricant	Colouring agent
Zestril	1/Calcium Hydrogen Phosphate Dihydrate (123.4mg). 2/ Mannitol (41.2mg)	Maize Starch (11mg)	Maize Starch anhydrous (20mg)	Pregelatenized Starch (4 mg)	Magnesium Stearate (1.5mg)	Red Ion Oxide E172 (0.268mg)
P1	1/ Dibasic calcium phosphate powder (96mg). 2/ Mannitol (36mg)	Maize Starch (40mg)	Croscarmellose (3.8mg)	Colloidal anhydrous silica (0.95mg)	Magnesium Stearate (2.36mg)	

P2	1/ Calcium Hydrogen phosphate (anhydrous) fine powder (51.27mg). 2/ Mannitol (24.44mg).	Pregelatenized Starch (2mg)	Maize starch (12.5mg)		Magnesium Stearate (1.125mg)	Red Ion Oxide (0.8mg)
P3	Microcrystalline Cellulose (164.8mg)	MCC	Sodium Starch Glycollate (Primojel) (20mg).	Colloidal anhydrous silica (2mg)	Magnesium Stearate (2mg).	Red Ion Oxide (0.2mg)
P4	1/ Dibasic calcium phosphate powder (98.96mg). 2/ Maize starch (74mg).	Povidone K30 (11mg)		Purified Talc (3mg)	Magnesium Stearate (3mg)	Erythrocin Red (0.04mg).

3.2.1. Hardness of lisinopril 10 mg tablets

The force required to break the tablet is measured in kiloponds and a crushing strength of 4Kp (39.2 N) is usually considered to be the minimum for satisfactory tablets. According to table (3.1.), three brands namely Zestril, P1, and P2 have crushing strength values of less than 4 with P1 results of only 1.25 Kp, Zestril and P2 have values around the minimum acceptable value (3.53 and 3.74), respectively. These values are lower than the minimum force required (4 Kp) and thus especially P1 can be described as soft tablets. If a tablet is described as soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. Easy breakage of tablet may also lead to loss of medicament which eventually leads to sub dosing. Hardness test is not an official pharmacopeial test, however the regular force required to break all 10 tablet samples is an indication of the good quality of the tablet manufacturing process. Tablet hardness depends on the weight of material and the space between the upper and lower punches at the moment of compression. Inconsistent hardness values are likely to result from variation in these parameters [8].

The hardness or crushing strength reflects the function and appropriateness of the type and

quantity of binder and lubricant employed as well as the compression force used in preparing the tablets [9]. Lerk et al. showed that a concentration of 0.2% colloidal silica in a tablet formulation had no effect on tablet crushing strength. However, higher concentrations reduced crushing strength especially when associated with prolonged mixing times [10].

In tablet manufacturing, lubricants such as magnesium stearate act by adsorbing onto the surface of granules and forming a film, thus decreasing the crushing force and ejection force during compression [11]. This may explain the low crushing values of both Zestril, P2 and in addition to that P1 contains also colloidal anhydrous silica as a glidant in its formulation in a concentration slightly more than 0.5%. The binder system for P1 is maize starch, for P2 is both maize starch and pregelatinized starch while for Zestril is all maize starch, pregelatinized starch and maize starch anhydrous. P1 is softer than those having combined starch systems which synergistically improve their hardness despite of the same obstacles discussed above.The mean force required to break P3 and P4 brand of P2 tablets is 17.53 Kp and 5.17, respectively and so they had passed the test.

The hardest tablet was P3 which was formulated by using microcrystalline cellulose as a filler as it known to produce harder tablets with low pressure compression. It acts as an auxiliary wet binder promoting hard granules with fewer fines [12]. Formulations which contain significant concentrations of microcrystalline cellulose (82.44% of tablet weight in our case) typically form good compacts due to its plastic deformation properties [13].

P4 was formulated by maize starch and Povidone K_{30} in a concentration of 5.445% which was slightly more than 5% the upper limit for it as a binder. however, a temporary acceptable daily intake for Povidone has been set by the WHO at up to 25mg/kg body-weight [14]. This combination has yielded tablets of a good hardness.

3.2.2. Friability of lisinopril 10 mg tablets

From the results of this study as showed in table (3-1), it was noticed that regarding friability testing two of the three brands that did not pass the hardness test ,namely (P1 and P2), also failed to pass the friability test ,while the others has passed the test successfully. The reason of this incompliance with the specification lies within the following factors; these include granulation moisture content, type and amount of granulating agent, type of binder, lubricants and fillers [15]. Zestril succeeded to pass this test because of the combined triple binding system discussed in the hardness section whereas, P1 and P2 binders of maize starch alone in case of the former or maize starch with pregelatinized starch had not qualified them to pass the test.

Also, microcrystalline cellulose (MCC) and Povidone combined with maize starch showed a success to provide tablets with acceptable friability values. Punch geometry -Tablets compressed with extra deep concave punches result in lower friability compared with tablets compressed with standard concave or deep concave punches. Therefore, punch geometry and formulation considerations should be made to reduce tablet friability and their effect on in vitro dissolution. Particle size distribution also affects friability of tablets. Moisture content during storage affects friability as moisture may bring about the disruption of interparticulate bonds and increase porosity to alter the tablet strength and thus cause changes in hardness and friability. All of these factors should be investigated to indicate the reasons for this in-compliance with the approved specifications.

3.2.3 Disintegration times of Lisinopril tablet brands

All samples of Lisinopril tablets were passed the disintegration test (table 3-1). The British Pharmacopoeia [6] stated that, for uncoated tablets, disintegration should occur within 15 minutes, 4 brands disintegrated in less than five minutes and 1 brand, namely P4 disintegrated in slightly more than 5 minutes. For tablets that are bitter in taste or that possess unpleasant smell or taste, a very quick disintegration time is not the best since it can lead to the tablets disintegrating in the mouth of the patient. However this does not affect the therapeutic efficacy of the medication in any way. Moreover, exposure of these tablets to moisture, prior to administration may lead to disintegration and therefore storage conditions of these tablets must be satisfactory in order to maintain the integrity of the tablets.

The hardest tablets according to the hardness test passed the disintegration test. This was due to the formulator used Sodium starch glycollate (Primojel) (super disintegrant) as disintegrating agent in a concentration of 10% while the usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient according to. But, it is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful [14]. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling [15, 16] although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate was not impaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time [17, 18].

3.2.4. Dissolution tests of Lisinopril 10 mg tablets

The results showed in table (3-1) indicated that all studied brands of lisinopril 10 mg tablets

complied with the specification set by U.S.P and BP pharmacopeia with respect to the amount of the drug release from the tablet despite that these brands were formulated from different type of excipients and showed some differences in other tests. As the bioavailability is greatly affected by the dissolution in the site of administration, these brands of lisinopril10mg tablets might suggest to have the same bioavailability.

3.2.5. Percentage content of Lisinopril 10mg tablets using HPLC (Assay)

The USP stated that Lisinopril 10mg tablets contain not less than 90.0% and not more than 110.0% of the amount of the labelled amount while B.P (92.5 to 105.0%). According to these standards, all the tested brands of Lisinopril were formulated with appropriate content of lisinopril as shown in table (3-1).

Official standards for the evaluation of tablets are given by the U.S. Pharmacopeia (USP) and other compendia which include uniformity of dosage units (weight variation, content uniformity), dissolution and disintegration tests. Unofficial tests include those for mechanical strength (hardness, crushing strength) and resistance to abrasion (friability) [19]. From the results shown in table (3-1) we noticed that the tested samples passed all official tests. However, brand 3 did not pass the hardness test and brand 2 failed to pass the friability one. If only official tests are carried out in the regulatory laboratories, this necessitate the close follow up from the concerned departments within the regulatory body for the investigations regarding compliance with cGMP as well as cGDP as these can detect such incompliances and lead to the commitment to the best corrective action courses that should be done by manufacturers and distributors.

4. Conclusion

The study showed that the marketed brands of lisinopril 10 mg in Sudan were formulated with different excipients and manufacturing conditions. This lead to some differences in the unofficial quality control tests whereas the official ones were not affected. The results of this study showed that the interchangeability between the tested brands is possible as the results were comparable between the originator and other tested generic brands. However, this can only be assured when bioavailability studies are carried out. The incompliance results lie within the unofficial tests necessitate the assurance of tight implementation of cGMP and/ or cGDP at manufacturing sites. This should be carried out by both manufacturers and the regulatory body.

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