ORIGINAL RESEARCH

Assessment of the Pharmaceutical Quality of some Brands of Omeprazole Capsules Marketed in Maiduguri Metropolis, Borno, Nigeria.

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ABSTRACT

BACKGROUND: The proliferation of counterfeit, substandard and inferior quality drugs is a major challenge in low- middle income countries like Nigeria where drug regulation and law enforcement are constrained by limited resources.
OBJECTIVES: The aim of the study was to assess the quality parameters of some brands of Omeprazole capsules marketed in Maiduguri Metropolis, Borno State, Nigeria.
METHODS: The uniformity of weight, disintegration test, content uniformity and dissolution rate test were the official tests carried out using Pharmacopoeial methods. Organoleptic tests and other non-official tests were carried out.
RESULTS: Ten brands of omeprazole capsules were assessed for purity using omeprazole sample as standard for comparison. All the ten brands tested passed the visual inspection, organoleptic tests, weight uniformity and disintegration tests. Three (3) brands (OMC 1, 4 and 6) out of the ten (10) brands passed the content uniformity test, while the other seven (7) brands were either below or above the acceptable Pharmacopoeial limit. For the dissolution test, only three (3) brands (OMC 1, 3 and 8) passed the test.
CONCLUSION: The results therefore, indicated that some of the brands of the Omeprazole capsules marketed in Maiduguri Metropolis failed to comply with some Pharmacopoeial standards.

Keywords: Omeprazole; Physicochemical properties; Quality assessment; Pharmacopoeial standards

INTRODUCTION

There is considerable evidence that the incidence of falsified and substandard medicines is increasing, particularly in middle and lower income countries. There have been many well established instances of spurious, falsely labelled, falsified or counterfeit (SFFC) medicines in recent years. In addition, substandard medicines, which are prepared by legitimate manufacturers but fail to meet Pharmacopoeial requirements, also constitute enormous public health problem. On-going and continuous surveillance thus seem essential[1]. Poor quality medications

can be classified into three key categories: counterfeit, substandard, and degraded. Counterfeit medications are produced with intentional fraudulent activity and are "misbranded" with intent. Counterfeiting of medications is clearly a criminal act. Substandard products may occur for many reasons including inadequacies in raw material testing, poor conditions and procedures of manufacture and control, inadequate training of production workers or poor maintenance of production equipment. Inadequate quality procedures may lead to the unintentional release of substandard product onto the market. Intentional fraudulent activity may also result in the release of substandard product. Poor shipping and storage conditions may also contribute to the degradation potential of drug products especially due to the effects of temperature and humidity over time[2]. Substandard medicines, produced by licensed manufacturers, pose a serious public health risk, especially in the developing world. At their very best, these medicines are ineffective; at worst, they cause harm, creating drug-resistant pathogens or resulting in death. Substandard medicines run from products that contain correct ingredients in incorrect proportions to products without active ingredients or with harmful substitutes. Ten categories of substandard medicines have been identified including overconcentration of active ingredient, under-concentration of active ingredient, irregular filling of vials, contamination, mislabelling (not counterfeit), problems with active ingredient, problems with excipients, poor stability, packing problems, and unsatisfactory dissolution profiles. These categories exemplify the diverse number of ways in which medicines may be rendered substandard. Medicines may be rendered substandard at any point along the medical supply chain, from the point of manufacture through the point of distribution. Use of substandard medicines increases mortality and morbidity and may result in harmful side effects or allergies or engender drug-resistant pathogens that limit the therapeutic effectiveness of legitimate medicines. Substandard antimalarials in Africa, for example, engender drug resistance by exposing parasites to sub-lethal concentrations of active ingredients. Substandard medicines also contribute to the spread of infectious diseases and, if contaminated with pathogens (fungi, bacteria, viruses, or parasites) or other toxic elements, can cause further illness or poisoning[3].

Omeprazole ($C_{17}H_{19}N_3O_3S$) was the first proton pump inhibitor to be marketed in the world. It has been marketed in many countries since the early 1980s and has proved to be a reliable therapy for gastric hyperacidity[4]. The substituted benzimidazoles are a class of antisecretory compounds that suppress gastric acid secretion by inhibition of the H+/K+-ATPase enzyme system (Proton pump) at the secretory surface of gastric parietal cells[1]. Omeprazole is a proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer disease (PUD), Gastro oesophageal reflux disease (GORD/GERD), Laryngopharyngeal reflux (LPR) and Zollinger–Ellison syndrome. Decreasing excess stomach acid can help relieve symptoms such as heartburn, difficulty swallowing, persistent cough, and trouble sleeping. It can also prevent serious acid damage to the digestive system (e.g. ulcers, cancer of the oesophagus)[5,6,7,8]. It is a basic compound that is freely soluble in ethanol and methanol, slightly soluble in acetone and isopropanol and slightly soluble in water[9,10]. It is acid-labile, being degraded rapidly in aqueous solution at low pH, thus, an effective enteric coating for oral administration[11] allows the omeprazole core to be specifically released and dissolved in the duodenum (pH > 5) or terminal ileum where the pH is about 6.8 to 7.5[1,12].

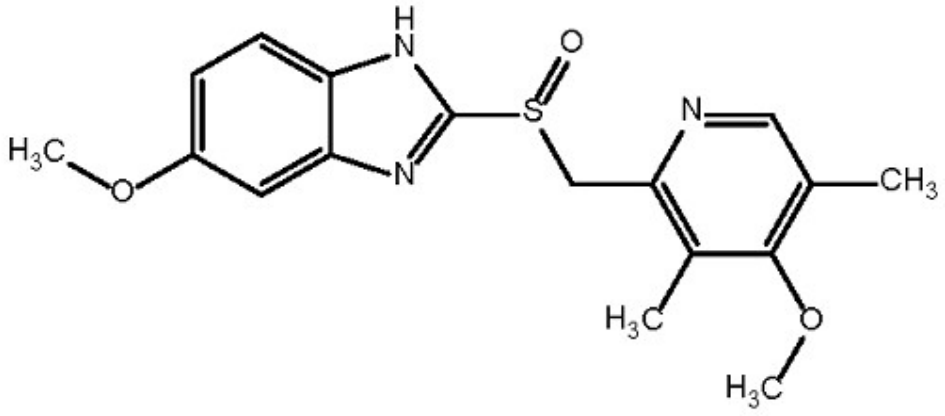

Figure 1: Chemical structure of Omeprazole (Adapted[9])

Omeprazole is useful in combination with the antibiotic clarithromycin and amoxicillin (or metronidazole in penicillin-hypersensitive patients) in the 7-14 day eradication triple therapy for Helicobacter pylori. Infection by H. Pylori is the causative factor in the majority of peptic and duodenal ulcers[5,10].

Omeprazole using coated micro-granules and packaging materials from Asia is most commonly marketed in Nigeria by some pharmaceutical companies. However, the likelihood of variations in the pharmaceutical quality of generic brands of omeprazole can be attributed to several formulation factors like differences in the quality of granule coating and packaging types. Wide variations in prices of marketed omeprazole capsules currently exists, particularly between generic products and the innovator brands.

As reported from previous studies, estimates of the extent of counterfeit medicines in circulation in Nigeria ranged from 25% to 80%[13].

To ensure the requisite quality, drug manufacturers are required to test their products during and after manufacturing and at various intervals during the shelf life of the product. The quality of medicines is an integral part of ensuring that pharmaceutical products are fit for their intended use, comply with the requirement of the marketing authorization and do not expose consumers to undue risks. Many developing countries, Nigeria inclusive do not have an effective means of monitoring the quality of generic drug products in the market. This results in widespread distribution of substandard and/or counterfeit drug products.

There is mounting evidence that counterfeit pharmaceuticals pose a serious threat to public health, especially in developing countries[14]. With numerous reports of fraudulent and counterfeiting activity in pharmaceutical products, and with the potentially increased likelihood of drug degradation during prolonged shipment from an increasing number of manufacturing sites around the world, assessing marketed products seems a reasonable measure to evaluate the frequency of problems and risk to the public[2].

In the light of the aforementioned challenges, this study was carried out to assess the pharmaceutical quality of some brands of omeprazole capsules obtained from registered pharmacy outlets in Maiduguri Metropolis, Borno State, Nigeria.

MATERIALS AND METHODS

Materials

The ten different brands of 20 mg omeprazole capsules were purchased from

registered pharmacy outlets within Maiduguri Metropolitan Council prior to quality assessment studies. Omeprazole reference standard was obtained from National Agency for Food and Drugs Administration and Control (NAFDAC), along Tashan Kano road, Maiduguri, Borno State. Hydrochloric acid, Ethanol, (BDH Chemicals, England), Sodium hydroxide (Surechem, England), and Phosphate buffer (pH 6.8) which was prepared during the analysis. All other reagents used were of analytical grade.

Methods - Physicochemical Analysis:

Packaging and Labelling Inspection

The primary and secondary packages of the different brands were examined carefully to check for required information such as product name, manufacturers address, manufacturing dates, batch numbers, expiry date, amount of active ingredients and NAFDAC Registration number.

Test for organoleptic property

Five (5) capsules from each brand of omeprazole were picked randomly and inspected. The organoleptic properties of the different brands e.g. colour of capsule shell, colour of the drug before and after exposure to light, odour of the drug and texture of the drug were determined by inspection. These properties are directly related to the chemistry of the drug and as such can serve as a non-specific identification test of the drug[15].

Solubility test

The drug content in the capsules of each brand was emptied into a porcelain mortar, crushed and 250 mg each of the resulting powder was weighed and dissolved in 3 beakers containing 25 ml of distilled water, 25 ml of 96 % ethanol (prepared by diluting 24 ml of absolute ethanol up to 25 ml using distilled water), 10 % sodium hydroxide solution (prepared by dissolving 2.5 g of sodium hydroxide pellets in 25 ml of distilled water) respectively, then observed visually for dissolution in the respective solvents. The three beakers were stirred using a glass stirrer for 5 minutes each and allowed to stand for 15 minutes. This test was carried out for all the brands and the results obtained were recorded.[13]

Melting point Determination

Powdered drug from each brand were introduced into different capillary tubes and then inserted into the capillary port of the Gallenkamp melting point apparatus. The process was repeated and the results determined in triplicate.[13]

Methods - Pharmacopoeial Tests:

Weight uniformity

Weight uniformity was evaluated by individually weighing the capsules from each brand and recording their respective weights. 20 capsules from each of the brands were used. The contents of the capsule were removed without altering the integrity of the capsule shell, and the weight of the individual empty capsule shell was determined. The net weight of each capsule content was determined by subtracting the weight of each empty capsule shell from the initial capsule weight. This test was carried out for all the brands and the values obtained were recorded. The mean weight, standard deviation and percentage standard deviation were determined[15].

Uniformity of content

The content of active ingredient of each brand sample was determined using an UV/VIS Spectrophotometer (UV7652 (D) Pec Medical, USA) according to the method described by Kumaraswamy *et al.,* 2013.[16]

Disintegration test

Six (6) capsules of each brand of the omeprazole were used. The capsules were placed in the tubes which were closed at the end with a screen of 2 mm nominal aperture. The temperature of the distilled water was kept at 37 ± 1ºC, the machine was operated, and the tubes were immersed and raised in the media. 1000 ml of 0.1 N Phosphate buffer (pH 6.8) maintained at 37 ± 1°C was used as the immersion fluid. The disintegration time for all the omeprazole capsule brands was determined according

to the United States Pharmacopoeia (2010) method using a disintegration apparatus (Erweka, ZT 71, Germany).

Dissolution test

The release rate of omeprazole from the capsules was conducted with the basket method in a dissolution apparatus (Erweka DT-700, Germany) in 900 ml of phosphate buffer (pH 6.8) maintained at 37 ± 1°C. The basket speed was set at 100 rpm and the procedure lasted for 60 min. Aliquot portions (5 ml) samples were withdrawn at intervals of 10 min and replaced with the same volume of phosphate buffer. These samples were assayed for drug content using UV spectrophotometric method of analysis (wavelength 305 nm) described by Kumaraswamy *et al.,* 2013)[16].

RESULTS

Tables 1 gives the descriptive details of the Omeprazole capsules assessed. All the omeprazole capsules investigated contained enteric coated pellets labelled to contain 20 mg Omeprazole and were within their shelf lives. They were all certified by the NAFDAC with the exception of OMC 4 which had no NAFDAC registration number. From the ten brands evaluated, seven was produced in India while the remaining three were produced in Oman, Pakistan and Nigeria respectively. Also, seven brands were manufactured according to BP specifications while the other three were manufactured according to USP specifications.

Table 2 gives the physicochemical parameters while Table 3 gives the quality assurance parameters of the omeprazole capsules tested. Figure 1 shows the dissolution profile of the capsules.

DISCUSSION

The solubility profile of the Omeprazole pellets evaluated showed that they were all slightly soluble in water, sparingly soluble in ethanol and soluble in 0.1N NaOH. This conforms to the characteristic of omeprazole which has been reported to be freely soluble in ethanol and methanol, slightly soluble in acetone and isopropanol and very slightly soluble in water[10]. The purity of any compound can be ascertained by its melting point, as such any deviation could mean alteration in mixture, degradation or presence of impurities[13]. The melting point of the omeprazole is 155 °C[9]. None of the brands tested conformed to this specification, as the values obtained were higher than this range (200- 245 °C). The high melting points observed could be due to the presence of the excipients used in the manufacture of the Omeprazole pellets. The variation in melting point between the different brands sampled may have resulted from differences in the quality of excipients used in the formulation or purity of the original omeprazole sample itself considering the source[17].

The acceptance criteria for the B.P. for drug content of capsules is equivalent of not less than 95 % and not more than 105 % of the labelled amount of drug and for USP samples the acceptance rate is between 90 – 110 %. Out of the ten brands only OMC 1, 4 and 6 conformed to the USP and BP specification of content uniformity. The high drug content of OMC 5, 9 and 10 and the low drug content of OMC 2, 3, 7 and 8 could be attributed to non-uniformity in capsule filling during production resulting in weight variation. This will invariably affect dosage uniformity indicative of possible formulation errors and non-compliance to current Good Manufacturing Practice.

The differences in capsule size among the brands may have some negative psychological effects on clinicians and their patients since they could raise some doubts on the general equivalence of the different brands of omeprazole capsules available. The World Health Organization model formulary advises that a patient should be placed on a particular brand, probably due to pharmacokinetic and psychological reasons.

Table 1: Description of the Omeprazole Capsules Assessed

Product Code	Product Name	Manufacturer Address	Marketing Company	Batch No.	NAFDAC Reg. Number	Manufacture date	Expiry date	Official book claimed
OMC1	JVI Omeprazole	Afirst Life Science, PVT, LTD, India	JVI Pharm. Ltd, India.	603703	B4-3202	Aug, 2016	Jul, 2019	20 mg B.P.
OMC2	Omeflux	MeCure Indsutries Ltd, Lagos.	MeCure Indsutries Ltd, Lagos.	OF155	A4-0048	Aug, 2017	Jul, 2020	20 mg B.P.
OMC3	Prazocap	Syncom Formulations Ltd, India	NCI Pharm Chem, Ind.Ltd, Lagos.	1950	/4-9876	Apr, 2017	Dec, 2020	20 mg B.P.
OMC4	Dr. Omeprazole	Kamla Biochem, Mumbai,India	Kamla Biochem, Mumbai,India	G-17110	NIL	Mar, 2016	Feb, 2020	20 mg B.P.
OMC5	Krishat	Baroque Pharmaceutical PVT Ltd, India	Krishat Pharma Ind, Ltd.	G-015358	B4-5077	Jan, 2016	Dec, 2018	20 mg U.S.P.
OMC6	Labzaole	Brussels Lab, PVT Ltd, India	UGOLAB Productions Nigeria Ltd, Kano	BX-17084	B4-0892	May, 2017	Apr, 2020	20 mg U.S.P.
OMC7	Omester	Sterling Healthcare Ltd, India	Sterling Healthcare Ltd, India	GN-1503X	B4-4930	Dec, 2017	Nov, 2018	20 mg B.P.
OMC8	Rumaprazole	Medisure Laboratories, PVT Ltd, Pakistan	Aliyu Mega Pharmaceuticals, Nigeria Ltd.	RZ-1002	A4-9543	Aug, 2016	Jul, 2019	20 mg U.S.P.
OMC9	Omit	MicroLab Ltd, India.	MicroLab Ltd, India.	OMIH0011	A4-9014	Dec, 2016	Nov, 2018	20 mg B.P.
OMC10	Omezyn 20	Oman Pharmaceutical Product Salalah.	Oman Pharmaceutical Product Salalah.	6DP008B	A4-4007	Jun, 2017	Jun, 2019	20 mg B.P.

Tablet 2: Physicochemical properties of Omeprazole capsule assessed

Product code	Appearance of the drug	Odour	Melting point (°C)	Solubility in water	Solubility in ethanol	Solubility in 0.1N NaOH
OMC1	Enteric coated pellets	Characteristic odour	205	Slightly soluble	Sparingly soluble	Soluble with precipitate
OMC2	Enteric coated pellets	Characteristic odour	200	Slightly soluble	Sparingly soluble	Soluble with precipitate
OMC3	Enteric coated pellets	Characteristic odour	205	Slightly soluble	Sparingly soluble	Soluble with precipitate
OMC4	Enteric coated pellets	Characteristic odour	205	Slightly soluble	Sparingly soluble	Soluble with precipitate
OMC5	Enteric coated pellets	Characteristic odour	210	Slightly soluble	Sparingly soluble	Soluble with precipitate
OMC6	Enteric coated pellets	Characteristic odour	220	Slightly soluble	Sparingly soluble	Soluble with precipitate
OMC7	Enteric coated pellets	Characteristic odour	230	Slightly soluble	Sparingly soluble	Soluble with precipitate
OMC8	Enteric coated pellets	Characteristic odour	245	Slightly soluble	Sparingly soluble	Soluble with precipitate
OMC9	Enteric coated pellets	Characteristic odour	235	Slightly soluble	Sparingly soluble	Soluble with precipitate
OMC10	Enteric coated pellets	Characteristic odour	210	Slightly soluble	Sparingly soluble	Soluble with precipitate

Tablet 3: Quality assurance parameters of Omeprazole capsule assessed

Product code	Uniformity of weight (mg)	Disintegration time (Min)	T_{45} (%)	Content of API (%)
OMC1	267±8.37*	2.56±0.36	85	90±0.00
OMC2	209±7.50	10.56±2.06	65	60±0.00
OMC3	269±4.32	8.36±3.80	100	60±0.00
OMC4	265±5.32	6.94±0.51	65	100±0.00
OMC5	283±6.18	5.06±2.30	170	140±0.00
OMC6	267±9.59	11.29±0.91	123	100±0.00
OMC7	236±3.11	4.23±1.33	120	35±0.00
OMC8	229±5.45	5.95±1.47	100	40±0.00
OMC9	281±8.05	5.41±2.15	45	130±0.00
OMC10	230±4.85	5.64±1.11	150	150±0.00

*standard deviation

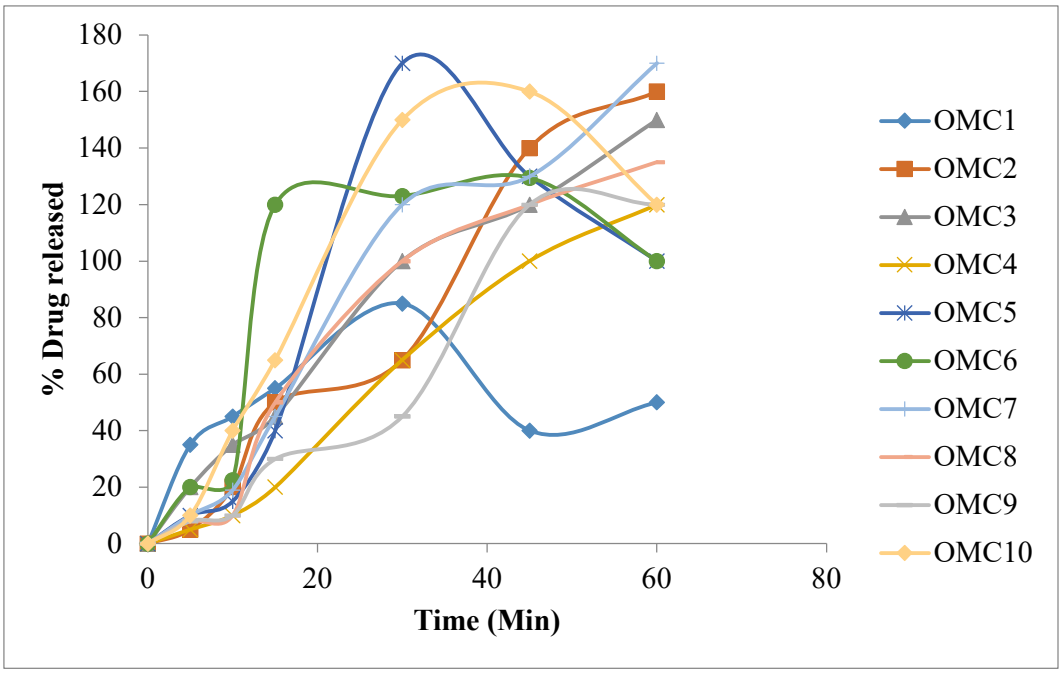

Figure 1: Dissolution Profile of some brands of Omeprazole Capsule

In Nigeria where the availability of a particular brand for the patient concerned is never guaranteed at all times, it would be advisable that manufacturers of this product formulate equivalent sizes of capsules in order to assuage patients' worry regarding the identity and efficacy of the different brands because of the wide differences in capsule sizes[18]. The disintegration time of all the brands were satisfactory, because they fall within the BP specification (less than 30 minutes) for hard capsules. Even though some brands disintegrate much more rapidly than the others, variation in the disintegration time among the various brands may be due the different types and concentration of excipients employed during formulation and manufacturing differences[13].

According to USP, not less than 75% of the labelled omeprazole must be released from the 20mg capsule in 45 minutes. Dissolution of a drug in solid dosage form into an aqueous medium is critical to its absorption, which has an impact on its bioavailability and hence therapeutic efficacy. Variables such as uniformity of weight and percentage purity also play important roles in efficient release of the active ingredient of the drug for systemic absorption[19]. The dissolution profile showed that OMC 1, 3, and 8 had attained a percentage dissolution of > 75% whereas OMC 2, 4, & 9 were below compendial specification while OMC 5, 6, 7 and 10 were above. Most omeprazole capsules are found to have high failure rate in Pharmacopoeial tests, especially dissolution test[1]. The correlation between the disintegration time and dissolution profile of the capsules was also noted. There was a positive correlation between the disintegration time and dissolution profiles for all the brands of omeprazole studied with the exception of OMC 4 and 9 where, despite the fast disintegration times observed; only 65 and 45 % respectively of the drugs could be released.

CONCLUSION

It can be concluded that omeprazole capsules marketed in Maiduguri Metropolis vary in their physicochemical quality assurance parameters. Since there was much variation in their physicochemical properties, it is an indication that bioavailability might differ to a large extent. Thus, in clinical practice, caution is of essence when brand substitution is being done. The importance of continuous quality control and post-marketing analysis of drugs by regulatory agencies cannot be over-emphasized.

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