https://dx.doi.org/10.4314/jpb.v19i3.4
Vol. 19 no. 3, pp. 153-159 (September 2022)
http://ajol.info/index.php/jpb

Journal of
PHARMACY AND
BIORESOURCES

Quality evaluation of Oral Rehydration Salt (ORS) products marketed in Abuja, Nigeria

Nneka N. IBEKWE[1*], Obiageri OBODOZIE-OFOEGBU[1], Obi P. ADIGWE[2]

[1]Department of Medicinal Chemistry & Quality Control; [2]Office of the Director-General; National Institute for Pharmaceutical Research & Development, Abuja. Nigeria.

Received 23rd May 2022; Accepted 3rd August 2022

Abstract
Medicine security remains one of the public health challenges in Sub-Saharan Africa as the report by World Health Organization (WHO) shows that 10.5% of medicines in low and middle-income countries worldwide are falsified or substandard. The study aimed to evaluate the quality of Oral Rehydration Salt (ORS) products sold in pharmacy outlets in Abuja, Nigeria. Seventeen different commercial brands of WHO recommended low-osmolarity ORS finished pharmaceutical products (FPP) were randomly selected from pharmacy outlets in the Federal Capital Territory (FCT) and Gwagwalada Area Council in Abuja. They were assessed for quality based on physicochemical properties and the content of active pharmaceutical ingredients in accordance with the International Pharmacopeia (IP) guidelines. The shelf lives of all the samples were valid, and they all met the visual inspection test, labelling, pH (7.4–8.0 between 23.3–23.9°C) and moisture content (1–9 mg/g) requirements. The content assay revealed 88.2%, 88.2%, 64.7%, 47.1%, and 35.3% compliance of the samples for glucose, chloride, citrate, sodium and potassium, respectively. Twelve (76.5%) of the brands failed at least one content assay and 8 (47%) had zero potassium content. The study underscores the need for regular, periodic post-market surveillance on essential medicines sold in the Nigerian market.

Keywords: Oral Rehydration Salt (ORS); Diarrhoea; Quality; Substandard and falsified (SF) drugs

INTRODUCTION

Substandard and falsified (SF) medicines remain a global challenge to health care delivery despite the regulatory control measures enforced by individual countries to curtail the menace. The COVID-19 pandemic has further increased the vulnerability of global supply chains to a surge of SF medicines, not just for those directly related to COVID-19 [1, 2]**.** According to a report by WHO, the aggregate failure rate of tested samples of SF medicines in low- and middle-income countries (LMICs) is approximately 10.5% [3]. In a systematic review conducted by Ozawa *et al* in 2018, the results of the meta-analysis showed that Africa had the highest prevalence of SF medicines with 18.7% of the samples substandard or falsified [4]. To underscore the importance of medicine security, Goal 3, Target 3.8 of the United Nations (UN) Sustainable Development Goals for 2030 is aimed to achieve universal access to safe, effective, quality and affordable essential medicines [5]. One of such medicines included in the Essential Medicines List and Priority Medicines for Mothers and Children

*Correspondence. *E-mail*: nnekaibekwe@yahoo.com *Tel*: +234-8058939488. ISSN 0189-8442

and listed as a life-saving commodity by the UN, is the Oral Rehydration Salt (ORS). ORS has been successfully used for more than four decades as an intervention in the management of diarrhoea in infants, children and adults [6]. Nine percent of child deaths worldwide are attributed to diarrhoeal diseases making diarrhoea the second leading cause of mortality in infants and young children under the age of five [7]. ORS solution acts as a rehydration therapy through the replacement of fluid and electrolytes loss due to diarrhoea. The formulation recommended by WHO and the United Nations Children's Fund (UNICEF) is sodium 75 mmol/L, potassium 20 mmol/L, chlorine 65 mmol/L, citrate 10 mmol/L and glucose 75 mmol/L for a total osmolarity of 245 mOsmol/L [8]. The therapeutic values of the substances are as follows; glucose facilitates the absorption of sodium (and hence water) on a 1:1 molar basis in the small intestine, sodium and potassium are needed to replace the losses of these essential ions during diarrhoea (and vomiting) while citrate corrects the acidosis that occurs as a result of diarrhoea and dehydration [9]. Information on the quality assessment of ORS products is sparse. A previous study in India had assessed the quality of five commercial brands of ORS in comparison to a rice-based Oral Rehydration Therapy (ORT) formulated into tablets. The authors reported that there was a wide variation in the content of the essential constituents in the commercial products, although they did not state the exact values [10]. In another study, Mishra and Mahapatra (2011) compared the sodium and potassium contents in two ORS brands by flame photometry, but they did not relate their findings to any pharmacopoeial specifications [11]. Pharmacopeia monographs provide test procedures that confirm the identity, purity, potency and acceptance limits of medicines, and these quality control measures are crucial towards the efforts for the attainment of medicine security. Many different brands of ORS are marketed in Nigeria but so far, there are no reports on the quality assessment. In this paper, we evaluated the quality of ORS sold in pharmacy outlets in Abuja, Nigeria.

EXPERIMENTAL METHODS

Equipment. Optical rotation was determined using an automatic polarimeter (Biobase BK-P850, China). The estimations of sodium and potassium were done with a flame photometer (Jenway, model PFP7, United Kingdom). Calibrated burette was employed for titrimetric analysis. The pH measurement was carried out with a pH meter (Mettler Toledo, SevenExcellenceTM, Malaysia). Weight measurements were taken on an analytical balance (Mettler Toledo, ME303E, China).

Chemicals. Analytical grades of potassium chloride (Sigma Aldrich, Germany), sodium chloride (99.5%, Loba Chemie Pvt, Ltd) and deionized water (laboratory prepared) were used to prepare standard solutions of sodium and potassium ions to calibrate the flame photometer. Perchloric acid (Sigma Aldrich, Germany) acetic anhydride (Sigma Aldrich, Germany) and glacial acetic acid (BDH laboratory supplies, Poole, England) were used to prepare 0.1 M perchloric acid, and standardized with potassium hydrogen phthalate (Qualigens fine chemicals, Bombay, India) . Silver nitrate (Emsure® Merck, Germany) and distilled water (laboratory prepared) were used to prepare and standardize 0.1 N silver nitrate VS. 1-naphtobenzein solution TS (Molychem, Mumbai, India) and potassium chromate 100 g/L TS (Oxford Lab, Mumbai, India) were used as indicators for citrate and chloride determinations, respectively. Ammonia 100 g/L (35% R, Sigma Aldrich, Germany) and distilled water (laboratory prepared) were used in sample preparation for measurement of optical rotation. Buffer solutions pH 4, 7, 9 (Merck, Germany) were used to calibrate the pH meter prior to analysis.

Sample collection. Five samples each of seventeen (17) different brands of ORS with the same batch numbers were randomly selected and purchased from pharmacy outlets within the Federal Capital Territory (FCT) and Gwagwalada Area Council, Abuja, Nigeria The samples were purchased between January and June 2021, and the study was conducted before their expiry dates.

Product packaging and information. Prior to analysis, the packets of each sample were assessed for label information such as brand name, batch no, manufacturer's name and address, manufacture and expiry dates, National Agency for Food and Drug Administration and Control (NAFDAC) registration no, directions for use/ dosage, storage, caution, content of APIs in grams or millimoles/Litre.

Physicochemical properties

Appearance of solution. A packet of each sample of ORS was dissolved in 1L of water and the appearance was observed.

Seal integrity. To determine leakage or otherwise of the contents, a packet of each sample of ORS was submerged under water in a vacuum desiccator. Negative pressure was drawn to create a vacuum, and held for one minute. Normal pressure was re-established and packets were opened to examine for water penetration.

Determination of pH of samples. Each sample was diluted according to the manufacturer's instruction. Two grams of each sample was dissolved in 50 mL of water. Standard phosphate buffers (pH 4, 7 and 9) were used to calibrate the pH meter and buffer pH 7 was used for verification (Mettler Toledo, SevenExcellence^{TM}, Malaysia). The temperature of the sample solutions was maintained between 23.3–23.9°C with an ice pack, and they were then measured in triplicate determinations on the pH meter and recorded.

Determination of moisture content (loss on drying). One (1) gram of each sample was taken into a pre-weighed and preheated disposable aluminium pan and dried it at 50°C for 2 h [12]. The sample was then transferred to a desiccator and allowed to come to room temperature before triplicate measurements of the final weight was taken (Mettler Toledo, ME303E, China), and the loss in drying calculated.

Content assay. The samples were analysed for the content of the active ingredients; glucose ($C_6H_{12}O_6$), chloride (Cl^-), citrate ($C_6H_5O^{3-}$), sodium (Na^+), and potassium (K^+), according to International Pharmacopoeia guidelines [12]. The techniques adopted and requirements of the monograph for concentrations and limits of acceptance of each of the active substances calculated for the standard weight of 20.5 g dissolved in 1000 mL of water of the samples are summarized in Table 1.

RESULTS AND DISCUSSION

Samples of seventeen different brands of ORS were purchased of which 11 were locally produced (Nigeria) while 6 were foreign produced (India). All of the samples (100%) had the required information and their shelf lives were valid within the period of evaluation. The packaging of all samples was well sealed, and did not show any signs of leakage. The physical characteristics of the samples showed that they were crystalline and when dissolved in distilled water, had a clear appearance. All the samples (100%) also met the requirements for pH and moisture content tests. The product label information and physicochemical properties are shown in Tables 2 and 3, respectively. Moisture content and pH are important test parameters for assessing the stability and thus, the quality of the pharmaceutical product [13]. The analysis of the active pharmaceutical ingredients (API) showed that 15 (88.2%), 15 (88.2%), 11 (64.7%), 8 (47.1%), and 6 (35.3%) samples complied with the International Pharmacopoeia specification for the content of glucose, chloride, citrate, sodium and potassium, respectively (Table 4). A few samples had APIs just outside the limit of specification for glucose (sample 13), sodium (sample 10) and citrate (samples 2 and 17).

Eight samples which constitute 47% of the total (samples 1, 2, 8, 9, 13, 14, 16 and 17) had no potassium content at all, and interestingly, these samples were locally produced brands. One out of 11 (9.1%) of the locally produced and 3 out of 6 (50.0%) of the foreign produced brands passed all the quality tests. In all, only 4 samples (samples 3, 5, 6 and 11) which is approximately a quarter of the products tested passed all the quality evaluation tests and were considered to be of good quality while 1 (sample 13) sample failed the content assay for all substances tested and 12 (76.5%) failed at least one content assay. The samples that failed had amounts that fell below or exceeded the label claims. As defined by WHO, substandard medicines are authorized medical products that fail to meet either their quality standards or specification, or both. Falsified medicines, on the other hand, are defined as medical products that deliberately/fraudulently misrepresent their identity, composition or source [14]. The results from this study show that the term 'substandard' can be justifiably ascribed to the samples whose values did not fall within the pharmacopoeia limits for the content assays. Most drugs are substandard due to poor manufacturing practices, inadequate quality-control processes, incorrect storage or inappropriate packaging, or a combination of these factors [15]. The substandard quality of the ORS products may also be attributed to variations in the quantity of powder used in batch production. A study where rice-based ORS effervescent tablets were formulated was suggested as an alternative to the powder form as the active constituents were found to conform to label claims within the limits specified by IP [10]. The batch to batch invariability was further stressed in a study which evaluated the *in vitro* efficacy of two different batches of antifungal agents against some *Candida* strains where the results revealed that there were different susceptibility patterns for each strain of *Candida* towards the two batches. The authors attributed the findings to the inconsistency in different production batches of the drugs, and which could be overcome by continuous production where all the key characteristics are roughly constant at any time, leading to lower batch-to-batch variations [16, 17]. Inadequate (or excessive amounts) of API will result in underdose (or overdose) medication, leading to poor treatment outcomes. The 8 samples that were devoid of potassium content lend support to the reports on falsified medicines, and in some cases these products have led to treatment failures and in extreme cases, death. An infamous example was the case of the falsified meningitis vaccine administered to over 50,000 people in Niger which resulted in the death of 2,500 persons [18]. In a previous study carried out to determine the effects of low and high doses of sodium and potassium, the results showed that repeated therapy of infants with oral solutions containing inadequate or no potassium would surely increase the risk of significant total body potassium depletion during serial diarrhoea attacks, with associated increased risk of muscle weakness, arrhythmias, ileus, and hypokalemic nephropathy. Potassium depletion leads to loss of muscle tone in the abdominal wall causing the typical distended abdomen of a severely malnourished child [19, 20]. Even as the world gradually returns to normal following the recent COVID-19 pandemic, the propensity for SF medicines in Nigeria has been made worse. This is partly due to the pharmaceutical supply chain challenges and the market gap being experienced globally because of states of emergency and lockdowns declared in many countries as a large percentage of active pharmaceutical ingredients and finished drug products are processed and manufactured overseas.

Table 1. Substance concentration per dose, pharmacopoeia methods and specifications

Substance	Analytical method	Concentration in mmol/L per dose (243.6 mmol/L)	Acceptable limit (in mmol/L)	Acceptable limit (in percent)
Glucose	Optical rotation	74.9	67.4 - 82.4	(90% - 110%)
Chloride	Titrimetry	64.6	58.1 - 71.1	(90% - 110%)
Citrate	Titrimetry	9.9	8.9 - 10.9	(90% - 110%)
Sodium	Flame photometry	74.1	66.7 - 81.5	(90% - 110%)
Potassium	Flame photometry	20.1	18.1 - 22.1	(90% - 110%)

Table 2. Label information on ORS products*

Sample Code	Batch No	Date of manufacture	Date of expiry	NAFDAC No.	Country of Manufacture
ORS 1	AX07	02/2019	02/2022	A4-2289	Nigeria
ORS 2	DRP0746	02/2020	05/2023	A4-8788	Nigeria
ORS 3	GP20371	07/2020	06/2023	B4-3170	India
ORS 4	GP20516	09/2020	08/2023	B4-4549	India
ORS 5	601559Z	03/2020	02/2023	B4-0245	Nigeria
ORS 6	NO8269	09/2018	08/2021	B4-2426	India
ORS 7	GP20445	08/2020	07/2023	B4-5400	India
ORS 8	005	11/2020	10/2023	B4-1389	Nigeria
ORS 9	21200201	02/2021	01/2024	B4-3236	Nigeria
ORS 10	V0610	26/2/21	25/2/23	A4-2080	Nigeria
ORS 11	FK04	10/2020	09/2023	B4-6893	India
ORS 12	003	03/2021	02/2024	04-8096	Nigeria
ORS 13	0127221	03/2021	02/2023	A4-6704	Nigeria
ORS 14	KT 0694	06/2021	05/2024	A4-1555	Nigeria
ORS 15	GP20564	10/2020	09/2023	B4-5641	India
ORS 16	00600	01/2021	01/2024	A4-2565	Nigeria
ORS 17	ORS 015	04/2021	03/2024	A11-1154	Nigeria

*The weight of all the samples was labeled as 20.5 g

Table 3. Physicochemical properties of ORS products

Sample Code	Appearance of product	Appearance of solution	pH @ 23.3-23.9°C (SD)*	Loss on Drying (in mg/g) @ 50°C (SD)
ORS 1	Crystalline	Clear	7.6 (0.04)	8.1 (0.06)
ORS 2	Crystalline	Clear	7.8 (0.08)	8.0 (0.12)
ORS 3	Crystalline	Clear	7.7 (0.06)	8.3 (0.00)
ORS 4	Crystalline	Clear	7.5 (0.04)	5.3 (0.12)
ORS 5	Crystalline	Clear	7.7 (0.06)	8.2 (0.06)
ORS 6	Crystalline	Clear	7.7 (0.01)	5.0 (0.06)
ORS 7	Crystalline	Clear	7.9 (0.08)	6.8 (0.00)
ORS 8	Crystalline	Clear	7.8 (0.03)	1.1 (0.06)
ORS 9	Crystalline	Clear	7.8 (0.03)	4.0 (0.06)
ORS 10	Crystalline	Clear	7.8 (0.09)	4.9 (0.06)
ORS 11	Crystalline	Clear	7.4 (0.03)	2.2 (0.12)
ORS 12	Crystalline	Clear	7.6 (0.04)	7.8 (0.00)
ORS 13	Crystalline	Clear	7.5 (0.02)	1.4 (0.06)
ORS 14	Crystalline	Clear	7.6 (0.02)	1.2 (0.00)
ORS 15	Crystalline	Clear	7.4 (0.03)	8.9 (0.06)
ORS 16	Crystalline	Clear	7.6 (0.40)	3.4 (0.10)
ORS 17	Crystalline	Clear	8.0 (0.04)	1.8 (0.06)
Pharmacopoeia specification			7.0-8.8	NMT 20mg/g**

* standard deviation, ** not more than

Table 4. Concentration of active substances per dose (in mmol/L)*

Sample code	Glucose	Chloride	Citrate	Sodium	Potassium
ORS 1	72.1 (0.03)	71.1 (0.27)	7.4 (0.00)	98.2 (0.94)	0.0 (0,00)
ORS 2	69.2 (0.02)	66.1 (0.14)	10.2 (0.38)	100.7 (0.61)	0.0 (0.00)
ORS 3	68.6 (0.02)	65.9 (0.33)	8.9 (0.26)	77.2 (1.22)	19.6 (0.17)
ORS 4	71.5 (0.02)	67.2 (0.72)	10.1 (0.19)	91.0 (2.0)	14.7 (0.84)
ORS 5	72.8 (0.02)	64.3 (0.41)	10.7 (0.26)	68.8 (0.36)	18.7 (0.55)
ORS 6	69.4 (0.03)	58.5 (0.42)	10.1 (0.19)	81.5 (0.00)	18.9 (0.30)
ORS 7	74.4 (0.02)	71.8 (0.48)	7.6 (0.44)	67.1 (0.71)	19.0 (0.64)
ORS 8	72.4 (0.02)	65.8 (1.82)	9.4 (0.33)	113.0 (0.97)	0.0 (0.00)
ORS 9	70.5 (0.03)	64.4 (0.55)	10.3 (0.19)	81.3 (0.72)	0.0 (0.00)
ORS 10	83.8 (0.01)	50.3 (0.36)	7.9 (0.07)	63.2 (0.85)	4.9 (0.00)
ORS 11	74.4 (0.02)	68.5 (0.30)	10.6 (0.04)	81.3 (0.36)	20.0 (0.31)
ORS 12	74.1 (0.02)	63.9 (1.11)	10.1 (0.38)	81.2 (0.71)	15.8 (0.31)
ORS 13	67.1 (0.11)	68.5 (0.30)	13.9 (0.25)	127.0 (1.56)	0.0 (0.00)
ORS 14	72.2 (0.01)	69.2 (1.11)	9.2 (0.07)	89.7 (0.71)	0.0 (0.00)
ORS 15	68.6 (0.01)	69.2 (0.56)	7.8 (0.14)	74.7 (0.71)	19.2 (0.00)
ORS 16	72.2 (0.01)	69.9 (0.48)	10.1 (0.30)	107.5 (1.6)	0.0 (0.00)
ORS 17	75.0 (0.01)	69.8 (0.60)	8.7 (0.07)	101.9 (0.62)	0.0 (0.00)

*Values are expressed as the mean (standard deviation) of triplicate determinations.

Conclusion

This is the first report on the quality evaluation of ORS marketed in Nigeria. The study is revealing as it clearly shows that a large percentage of ORS marketed in Abuja, Nigeria are of substandard quality. All the samples tested conformed to the product labeling and packaging requirements. All the samples passed the pH and moisture content tests but most failed in one or more content assays. The results also showed that approximately half of the samples tested had no potassium content demonstrating the preponderance of falsified ORS with the locally manufactured product. The study heightens the concerns on poor quality drugs marketed in the country and the attendant negative impact on medicine security. As the COVID-19 pandemic persists, this study underscores the need to strengthen the post-market surveillance and regulatory measures to ensure the provision of good quality medicines and to avert the risk of a parallel pandemic of SF medicines in Nigeria.

Acknowledgements

The authors wish to thank Mrs. C.E Onanuga, Mrs. E. Oyedele, Mrs. M. Ibe, Mr. T. Ache, and Mrs. G. Adelodun for their technical assistance.

REFERENCES

1. Borse NN, Cha J, Chase CG, Gaur R, Koduri CK, Kokai-Kun JF *et al*. Responding to the surge of substandard and falsified health products triggered by the Covid-19 pandemic [Internet]. United States Pharmacopeia; 2020. Available from https://www.usp.org/sites/default/files/usp/document/our-impact/covid-19/surge-of-substandard-and-falsified-health-products (Accessed 2022 Jan 28).
2. Newton PN, Bond KC. COVID-19 and risks to the supply and quality of tests, drugs, and vaccines. Lancet Glob Health 2020; 8(6: e754–55. doi.org/10.1016/ S2214-109X(20)30136-4.
3. World Health Organization. A study on the public health and socioeconomic impact of substandard and falsified medical products [Internet]. Geneva, Switzerland: WHO; 2017. Available from https://apps.who.int/iris/handle/10665/331690 (Accessed 2022 Feb 22).
4. Ozawa S, Evans DR, Bessias S, Haynie DG, Yemeke TT, Laing SK, *et al*. Prevalence and estimated economic burden of substandard and falsified medicines in low- and middle-income countries: A systematic review and meta-analysis.

JAMA Netw Open 2018; 1(4): e181662. doi:10.1001/jamanetworkopen.2018.1662.

5. United Nations General Assembly. Transforming our world: The 2030 Agenda for Sustainable Development [Internet]. 2015. Available from http://www.un.org/ga/search/view_ doc.asp?symbol=A/RES/70/1&Lang=E (Accessed 2022 July 6).
6. Oyetunde O, Williams B. Community pharmacists' views of the use of oral rehydration salt in Nigeria. Int J Clin Pharm 2018; 40: 659-67. doi:10.1007/s11096-018-0616-x.
7. Melese B, Paulos W, Astawesegn FH, Gelgelu TB. Prevalence of diarrhoeal diseases and associated factors among under-five children in Dale District, Sidama zone, Southern Ethiopia: a cross-sectional study. BMC Public Health 2019; 19: 1235-44. doi.org/10.1186/s12889-019-7579-2.
8. World Health Organization. Oral rehydration salts (ORS): a new reduced osmolarity formulation [Internet]. New York, USA: WHO; 2002. Available from https://apps.who.int/iris/handle/10665/67322 (Accessed 2022 Feb 20).
9. World Health Organization. (2006) . Oral rehydration salts: production of the new ORS [Internet]. Geneva, Switzerland: WHO; 2006. Available from https://apps.who.int/iris/handle/10665/69227 (Accessed 2022 Jan 26).
10. Krishna GA, Nagavi BG. Evaluation of commercial and formulated Oral Rehydration products. Ind J Pharm Sci 1996; 58(6): 256-57.
11. Mishra P, Mahapatra MK. Comparison of sodium and potassium content in ORS powders by flame photometric method. Res J Pharm Bio Chem Sci 2011; 2(3): 262.
12. World Health Organization. The International Pharmacopoeia. 9th ed. Geneva, Switzerland: WHO; 2019.
13. Bajaj S, Singla D, Sakhuja N. Stability Testing of Pharmaceutical Products. J App Pharm Sci 2012; 2: 129-38. doi:10.7324/JAPS.2012.2322.
14. World Health Organisation, WHO Global Surveillance and Monitoring System for substandard and falsified medical products [Internet]. Geneva, Switzerland: WHO; 2017. Available from https://apps.who.int/iris/handle/10665/326708 (Accessed 2022 Feb 22).
15. Johnston A, Holt DW. Substandard drugs: A potential crisis for public health. Br J Clin Pharmacol 2013; 78(2): 218-43. doi:10.1111/bcp.12298.
16. Ogunshe AAO, Adepoju AA, Oladimeji ME. Clinical efficacy and health implications of inconsistency in different production batches of antimycotic drugs in a developing country. J Pharm Bioall Sci 2011; 3(1): 158-64. doi:0.4103/0975-7406.76501.
17. Lee SL, O'Connor TF, Yang X, Cruz CN, Chatterjee S, Madurawe RD *et al*. Modernizing pharmaceutical manufacturing: from batch to continuous production. J Pharm Innov 2015; 10: 191-99. doi:10.1007/s12247-015-9215-8.
18. Kelesidis T, Kelesidis I, Rafailidis PI, Falagas ME. Counterfeit or substandard antimicrobial drugs: a review of the scientific evidence. J Antimicrob Chemother 2007; 60: 214–36. doi:10.1093/jac/dkm109.
19. Nalin DR., Harland E, Ramlal A, Swaby D, McDonald J, Gangarosa R, *et al*. Comparison of low and high sodium and potassium content in oral rehydration solutions. J Pediatr 1980; 97(5): 848–53. doi:10.1016/s0022-3476(80)80287-3.
20. Leung AKC, Darling P, Auclair C. Oral Rehydration therapy- a review. J R Soc Prom Health 1987; 107: 64-67. doi:10.1177/146642408710700210.