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A Pilot Study to Evaluation of the Level of Knowledge and Quality of Water Used in Drug Reconstitution among Community Pharmacist in Palestine

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Water is widely used as diluents because of its ability to dissolve, absorb, or suspend many different compounds including reconstituted drugs. The quality of water used is important as it may include contaminants that may represent hazards.
Methodology: In this pilot study we evaluated the problems associated with the improper use of water grade used in reconstitution of dry powdered drugs. A self-administered questionnaire was constructed to determine the rate of dispensing drug that needs reconstitution and to evaluate the knowledge of the pharmacists about the type of water that should be used and its specifications. Eight different tests were applied on the collected samples including microbiological an electrolytes tests.

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Results: The results of this study showed a low response rate of the visited pharmacies. Only 47 out of 90 filled the questionnaire and provided water samples for testing. Testing results of the collected samples showed that (33%) of the samples had failed the microbiological test. Most of the samples passed the Sulphate and Calcium tests (85.1%, 74.4%) respectively. However, most of the samples failed the Chloride and Ammonia tests (93.6%, 85.1%) respectively. Moreover, (97.8%) of the tested samples failed the conductivity and pH specified test.
Conclusion: The results of this study show a low level of knowledge among the local community pharmacists regarding the proper type of water and the allowed mineral content in water used for the reconstitution of powdered drugs. The quality tests results of the collected samples showed the unsuitability of the water used by the community pharmacist.

Keywords: Water; powder for reconstitution; community pharmacist.

1. INTRODUCTION

1.1 Background

Water is the most widely used diluent; it has unique chemical properties due to its polarity and its capability of making hydrogen bonds [1]. It is able to dissolve, absorb, or suspend many different compounds including reconstituted drugs. The quality of water used as diluents is important as it may include contaminants that may represent hazards themselves or may react with the product substances, resulting in hazards to health if they are mixed with medication. Water is widely used in pharmaceutical preparation and depending on the type of pharmaceutical dosage form; different grades of water quality are used for different pharmaceutical preparation [2].

With the exception of some nebuliser preparations, purified water is the acceptable grade of water for all non-sterile products [3].

In general, the international pharmacopeia including the European pharmacopoeia provides standards for different grades of water used in pharmaceutical preparation it includes: Water for injections, Purified water, highly purified water [4].

Purified water is the minimum grade that must be used in reconstituting oral powdered preparation. However, highly purified water must be used in the preparation of product where water of high biological quality is needed, except where water for injections is required [5]. The minimum specifications and requirements of purified water are stated in Table 1.

Potable water is the drinking water, its chemical composition may include mineral impurities, which would react with water as calcium carbonate in hard water, and calcium interacts with different antibiotics. For example, Calcium can interfere with the body's ability to absorb Quinolone antibiotics. Calcium can also interfere with the body's ability to absorb tetracycline antibiotics [7,8].

The common type of water used among the community pharmacists in reconstituting drugs is potable water that is boiled then cooled. Boiling the tap water before using it is an advantageous but not a sufficient procedure since boiling water will precipitate most of dissolved calcium and will reduce the microbiological total count [9,10]. Many other hazardous material will remain even after boiling the water. If the incorrect grade of water is used then the medication may clump or crystallize making it unusable for administration. Moreover, if the water is contaminated with certain contaminant it will make the drug unsuitable for use or may render it toxic and will highly affect the stability of the product [11].

Table 1. The main differences between the purified water specification of the USP and EP [4,6]

Specification	USP[1]	EP[2]
Conductivity	< 1.3 µs/cm at 20℃	< 4.3 µs/cm at 20° C
Bacteria	< 100 cfu/100 ml	< 100 cfu/100 ml
Endotoxins	No specification	<0.25 EU/ml
TOC	<500 ppb	< 0.5 mg/l
PH	5-7	5-7
Nitrates	No specification	≤ 0.2 ppm
Heavy metals	No specification	≤ 0.1 ppm
Aluminium	No specification	≤ 10 ppb

[1.] USP=United state pharmacopeia, [2.] EU= European pharmacopeia

The powdered medications are widely available in community pharmacies, or might be kept in a medication system on the nursing unit. The container containing the powdered medications, usually have directions or recipe on the label, on how to properly reconstitute the medication. Proper reconstitution of a medication is important thus the patient is advised to thoroughly read the direction labeled on the container. A pharmacist or other health professional usually reconstitute the medication or consult the patient on how to reconstitute it, so it can be administered properly. Unfortunately, many of health professional including pharmacists are not aware of the type of water they should use in the reconstitution of drugs. Many health professionals as well as patients used tap water or boiled tap water for the reconstitution and this is done as a common behavior. Previous study showed that 75.5% of professional and patients used a boiled tap water after cooling it in order to prepare antibiotic suspension [12].

The water that should be used in reconstitution of drugs is clearly stated in many countries; for example the Australian therapeutic good administration has adopted the European Union quality guidelines, published in 15 Feb2007. This guideline recommended purified water as the minimum acceptable quality of water for reconstituting oral preparations.

It is very important that the pharmacist give intensive counseling for patient on how to reconstitute the drug and make it clear for the quality of water used. Unfortunately, directions on the bottles as well as leaflets are not stated clearly and the patient ask pharmacist for advice on how to reconstitute. In a recent study it clearly demonstrated almost half of the reconstituted drugs are prepared by pharmacist and the rest are done by the patient himself [12].

There are limited data about the problems associated with the use of improper type of water in the reconstitution of antibiotics worldwide, among the community of pharmacists. Therefore, it is important to evaluate this problem to determine the risk of this practice and to prevent the misuse of medication that might lead to treatment failure. Moreover, most of people who need to reconstitute medications by themselves are not aware of the problems that may arise if they did not stick to the instructions labeled on the bottle.

The aim of this study is to evaluate the problems associated with the improper reconstitution of dry powder antibiotics and to assess the pharmacist's practice in consulting patients regarding how to reconstitute drug. We also assessed the pharmacist's knowledge regarding water quality that should be attained.

2. MATERIALS AND METHODS

2.1 Materials and Reagents

All the reagents that were used in water testing were of at least of analytical grade (AR) and all of them were purchased from reliable sources; these reagents include: Tryptic soy agar, barium chloride, nitric acid, silver nitrate, mercuric potassium iodide, ammonium oxalate.

2.2 Instrumentation

All the following instruments were used in different quality tests of the collected water samples; these instruments include: Conductivity Meter Model (LF538) manufactured by Wissenschaftlich–Technische was used to test the conductivity of the water samples. The pH of the samples was tested using pH Meter Model (691), manufactured by Ω Metrohm. The microbial testing of the samples was performed in Binder Incubator Model No BD-240 manufactured by Binder GmbH. Water Bath Model NO 800316 manufactured by PolyScience was used in different quality testing.

2.3 Questionnaire

Data collection tool was a self-administered questionnaire which was divided into three parts based on the field the study to be covered. The first part was collecting general information about the pharmacy itself, its location and the qualification of the one who filled the questionnaire. The second part was intended to conduct information about the rate of dispensing of reconstituted powdered medications. The last part was a set of questions in order to measure the knowledge of the person who filled the questionnaire; these questions include the type of water used for reconstitution and the materials that are allowed to be present in the water. The detailed questionnaire is attached as an appendix at the end of this report.

2.4 Samples Collection

The sample collection plan was designed in order to cover the northern and middle region of

the West Bank. Samples were collected from five different cities (Ramallah, Nablus, Tulkarm, Qalqelia and Jenin). The samples were collected in a rational way according to the population of each city. Sample collection was done by the research team themselves and the pharmacists were asked to fill the self-administered a questionnaire before the team collected the sample. The samples were collected in sterilized cups, opened just before collection, and immediately kept in refrigeration at 8℃.

2.5 Testing Procedure

The collected water samples were tested in the quality control lab of Jerusalem Pharmaceutical Company- Ramallah. The tests were performed by a well qualified team and in accordance with GLP rules. The tests were performed according to the Pharmacopeial procedure.

2.5.1 The microbiological test

The microbiological test was performed using Tryptic Soy Agar dishes, prepared by constituting 40g of Tryptic soy agar powder with a liter of water in a water bath. In each Petri dish, 20 ml of agar solution were added and left to cool. One ml of each sample was transferred into the petridishes; swirl the petridish cover & incubate at 32.5±2.5℃ for 48 hr's. The colonies were then counted and the test is considered pass if the count does not exceed 100 cfu/ml.

2.5.2 Elemental testing

The Sulphate test was performed adding (0.2 ml) of Barium chloride test solution (TS) to 10 ml of the collected water sample. The test will be considered pass if the mixture remains clear. Chlorine test was done by adding one drop of nitric acid (2M) and 0.1 ml of silver nitrate (0.1M) was added to 10 ml the water sample. The test will be considered pass if the mixture remains clear. Testing for Ammonia was done by adding (0.2 ml) mercuric potassium iodide TS to 10 ml of the water sample. The test will be considered pass if the mixture remains clear. Calcium test was performed by adding (0.2 ml) ammonium oxalate TS to 10 ml of the water sample. The test will be considered pass if the mixture remains clear.

2.5.3 Color and appearance

This test is checked by visual examination. The water should be clear free of any visual impurities and should be transparent.

2.5.4 Conductivity test

The conductivity was measured using Conductivity Meter Model: LF538 without temperature compensation and the temperature of water was fixed at 20℃, the purified water meets the requirements of EP and BP2013 if the measured conductivity at 20℃ was less than 4.3 µs/cm [13].

2.5.5 pH test

The pH was measured using pH Meter Model: 691, the purified water meets the requirements if the pH is between 5.0 – 7.0.

2.6 Statistical Analysis

Statistical analysis was performed by using statistical package for social sciences (SPSS version 17). Descriptive analysis was performed; it includes frequencies (percentages) and cross tabs analysis. They were used to calculate categorical variables. The categorical variables were compared using Chi square test. Any p-value of less than 0.05 was considered statistically significant for all the performed analyses.

3. RESULTS AND DISCUSSION

3.1 Questionnaire Results

The data analysis results of the study showed a low percentage in response; out of 90 pharmacies visited only 47 filled the questionnaire and provided water samples for testing. The low responses of the pharmacists reflect their worries that the water they use in reconstitution may fail the quality control and specification tests. Thus, we believe that our study may suffer some sort of bias due to this low response.

To evaluate the knowledge and the behavior pharmacist we mainly targeted the pharmacist in our study; thus the majority who filled the questionnaire were pharmacist (85.1%) while the rest were assistant pharmacist (12.8%).

Most drug-related errors are caused by lack of understanding of the instructions on the label. Therefore, consulting the patient on how to prepare the suspension will definitely make a change, concerning the consultation. In this study we asked the pharmacist about their consultation regarding drug reconstitution and the result revealed that 46 out 47 said they

always tell the patient how to reconstitute the suspension.

Our study revealed that there is a majority among pharmacists who believe that water filtration system is sufficient to produce proper water that can be used for reconstitution of drugs. Thus the result show that (31.9%) of visited pharmacies had a filtration system. When the pharmacists were asked about the type of water they use; majority of them answered they either use boiled water or mineral water (31.9%). However, only few pharmacists used distilled water for reconstitution (8.5%) but none of them used purified water; the percentages for each type of water used in reconstitution is illustrated in Table 2. These results clearly demonstrate the lack of knowledge among the local pharmacists about the proper type of water that should be used in drug reconstitution.

The Table 2 shows that most of the pharmacist use either boiled or mineral water. The data analysis result revealed a statistical significant (p= 0.016) difference between pharmacy location and the typed of water used for reconstitution.

Many pharmacists keep the water specified for reconstitution stored for a long period of time; this could cause microbial contamination of water. In this study we asked the pharmacists about water changing rate (in days). Pharmacist (25.5%) responded that they change the water for reconstitution every 3 or 4 hours during the day. However, the majority (46.8%) of pharmacist change the water once daily, while (6.3%) of pharmacists said they change the water every 2 days, (6.3%) of pharmacists change the water every 3 days, (4.2%) of pharmacists change the water every 4 days; (4.2%) of them change the water every 5 days, (2.1%) of pharmacists changing water every week, and (4.2%) of pharmacist change the water every 20-30 days. Statistical data analysis showed that there was no significant difference between rates of changing the water and the microbiological test result (p-value =0.69).

To examine the pharmacist knowledge about the water grades and quality of water that is used in pharmaceutical preparation; the visited pharmacists were asked a set of questions; one of these question was about the purest pharmaceutical water grade; (63.8%) of the participants answered correctly that distilled water is the purest type of water. However, only (6.8%) of them used it for the reconstitution of medications. The lower percentage of using distilled water could be explained by the unavailability of distilled or purified water in the local market. Further examination of the pharmacist knowledge was done by asking them a set of questions about the material that is allowed in the water used for reconstitution. The results are summarized in Table 3. The results obviously illustrate the huge defect in the pharmacist knowledge. Most of pharmacists allowed certain percentage of the listed material to be present in water for reconstitution and some of them answered yes for very toxic substance to be allowed in the water used in the reconstitution; for example the cyanide and mercury.

3.2 Water Testing Results

At first the collected water were examined for general appearance and 2 of the samples (4.2%) were turbid and consequently are considered as failed samples.

The microbiological test was applied on all the 47 collected samples. The results showed that 9 of the samples were classified as TMTC, which mean that 19.15% of the samples have exceed the limit of colony forming unit allowed to be existed in water used for the reconstitution of antibiotic according to Current USP XXIII [14]. This is an alarming result and should be considered by the regulatory affair to make microbial check of the water used in reconstitution as one of the inspection parameters they do in their routine procedure. The microbial testing result also show that (44.4%) of the samples which failed the microbiological test were from pharmacists who used mineral water. This result show that there was no statistical significant difference between the type of water used in reconstitution and the microbiological test results (p-value = 0.44). On the other hand, none of the tape water samples failed; this result could be explained by the fact that when tape water is used it is always boiled before reconstitution.

Table 2. Types of water used for water reconstitution

Tap water	Boiled water	Mineral water	Distilled water	No reconstitution
2	15	15	4	11
4.2%	31.9%	31.9%	8.5%	23.4%

Table 3. The pharmacist opinion, what materials are allowed in water used for reconstitution

Test type	Answered yes	Answered no
Calcium	34 (72.3%)	13 (27.6%)
Nitrate	19 (40.4%)	28 (58.3%)
Chloride	34 (72.3%)	13 (27.6%)
Cyanide	2 (4.2%)	45 95.7%)
Silver	3 (6.3%)	44 (93.6%)
Mercury	5 (10.6%)	42 (98.3%)
Lead	1 (2.1%)	46 (97.8%)
Bacteria	1 (2.1%)	46 (97.8%)
Fungus	1 (2.1%)	46 (97.8%)

The results of the elemental quality control test done on the 47 samples are shown in Table 4. The results clarify the number of samples failed/ passed in the four listed tests. The result clearly illustrate that majority of the tests were failed.

Table 4. Sulphate, chloride, ammonia and calcium tests for the collected water samples

Test type	Pass	Fail
Sulphate	40 (85.1%)	7 (14.8%)
Chloride	3 (6.3%)	44 (93.6%)
Ammonia	7 (14.8%)	40 (85.1%)
Calcium	35 (74.4%)	12 (25.5%)

Conductivity test is one of the quality control tests that must be monitored for the water used in pharmaceutical preparation. This test is generally done to monitor electrolytes that are present in the water sample and the increased conductivity is an indication of increased electrolytes. According to the last update of the USP XXIII. The minimum accepted measurement of conductivity of purified water is ≤ 4.3 µs/cm at 25ºC. The conductivity test was performed on 27 of the 47 samples collected and wasn't done for all samples due to shortage in water quantity needed for this test. The test results show that 26 out of 27 (97.8%) of the collected sample has failed the conductivity test. This result is expected when the electrolytes tests (mentioned previously) also failed.

Water is also checked for it pH value as acidity or alkalinity of water is an indication of water contamination. PH measurements were performed on 27 of the 47 samples collected and were not done for all samples due to shortage in water quantity needed for this test. According to USP specification; the PH of purified water should be between 5 – 7. The result showed that 25 of the 27 sample (92.6%) failed the test and were out of the specification in general the pH of the tested samples were in the alkaline range (96.2%).

4. CONCLUSION

This study clearly demonstrate a low level of knowledge among the local pharmacists regarding the proper type of water and the allowed content that must be used for the reconstitution of powdered drugs. The tests results of the collected samples showed the unsuitability of the water used by the community pharmacist. This reflects the lack of regulatory enforcement and awareness programs among the public as well as the pharmacists regarding the proper water used in reconstitution of drugs. Thus it is highly recommended to make awareness program in corporation with the pharmacy association and the ministry of health about the water used in reconstitution of drugs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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